3. The role of *Staphylococcus aureus* in atopic eczema

Donald Y. M. LEUNG

Staphylococcus aureus infection plays an important role in atopic eczema (AE) because of its ability to produce virulence factors such as superantigens. Epicutaneous application of superantigens induces eczema. Super-antigens also induce corticosteroid resistance, and subvert T-regulatory cell activity, thereby increasing AE severity. Increased binding of S. aureus to skin is driven by underlying AE skin inflammation. This is supported by studies demonstrating that treatment with topical corticosteroids reduces S. aureus counts on atopic skin. AE has also been found to be deficient in antimicrobial peptides needed for host defence against bacteria. The reduced production of antimicrobial peptides in AE appear to be an acquired defect resulting from increased T-helper type 2 cell (Th2) cytokine production. A vicious cycle of skin barrier dysfunction, skin infection and Th2 cell immune activation therefore occurs in AE. Effective strategies for controlling AE require combination therapy that reduces skin inflammation and controls S. aureus colonization and infection.

INTRODUCTION

Atopic eczema (AE), also referred to as atopic dermatitis (AD), is a chronic inflammatory skin disease commonly presenting in infants and young children, with a point prevalence of 10–20% of the population (1). Pruritic skin lesions evolve from complex interactions between IgE-bearing antigen-presenting cells, T-cell activation, mast cell degranulation, keratinocytes, and eosinophils that can be triggered by irritants, foods, aeroallergens and infection (2, 3). Recent studies demonstrating that AE is associated with a defective skin barrier provide evidence of a genetic basis to the disease. Patients are predisposed to selective skin inflammation via enhanced permeability of allergens and microbes, resulting in high-level allergen sensitization and the atopic march leading to respiratory allergy (4, 5). This review focuses on the role of *S. aureus* in the pathogenesis of AE. An understanding of the mechanisms underlying enhanced *S. aureus* colonization and infection in AE, and identification of the molecules involved in triggering atopic skin inflammation, has important implications in our current approach to the management of AE.

S. AUREUS IN ATOPIC ECZEMA

S. aureus colonizes the skin of most patients with AE (6). The number of *S. aureus* on atopic skin depends on the type of skin lesion: *S. aureus* can be isolated from 55–75% of unaffected AE skin, 85–91% of chronic lichenified lesions and 80–100% of acute exudative skin lesions. The density of *S. aureus* can reach 10^7 organisms per cm^2 on acute exudative AE skin lesions. Thus, atopic skin provides a favourable environment for the colonization and proliferation of *S. aureus*. Secondarily infected patients show greater clinical improvement to combined treatment with anti-staphylococcal antibiotics and topical corticosteroids, compared with topical corticosteroids alone, supporting the concept that *S. aureus* contributes to skin inflammation in AE (7, 8).

MECHANISM(S) LEADING TO *S. AUREUS* COLONIZATION

The mechanism(s) leading to increased *S. aureus* colonization in AE are an active area of investigation. The increased *S. aureus* colonization probably results from a combination of processes. These include, in addition to defective skin barrier function, the loss of certain innate anti-bacterial activities as a result of changes in antimicrobial peptide (AMP) levels or reduced immune responses necessary for defence against bacteria. There has also been much interest in the potential role of lipid deficiencies, since lipids have antimicrobial effects (9), and reduced lipid content in AE skin leads to increased transepidermal water loss as well as dry, cracked, brittle skin, which predisposes to *S. aureus* colonization (3, 4). These factors are not mutually exclusive. Indeed, all probably play a role in *S. aureus* colonization of AE skin, varying according to the patient's genetic predisposition and environment.

Increased S. aureus adherence

The initial step in colonization or infection requires attachment of *S. aureus* to skin surfaces. The skin of patients with AE has been demonstrated to have increased adherence for *S. aureus* (Fig. 1). The reason for increased binding of *S. aureus* to AE skin is probably related to the underlying skin atopic inflammation (Table I).

This concept is supported by the following studies. First, acute AE skin lesions are colonized with greater numbers of *S. aureus* than chronic skin lesions, unaffected atopic skin or normal non-atopic skin (6). Secondly, it has been found that treatment with anti-inflammatory medications such as topical corticosteroids or calci-
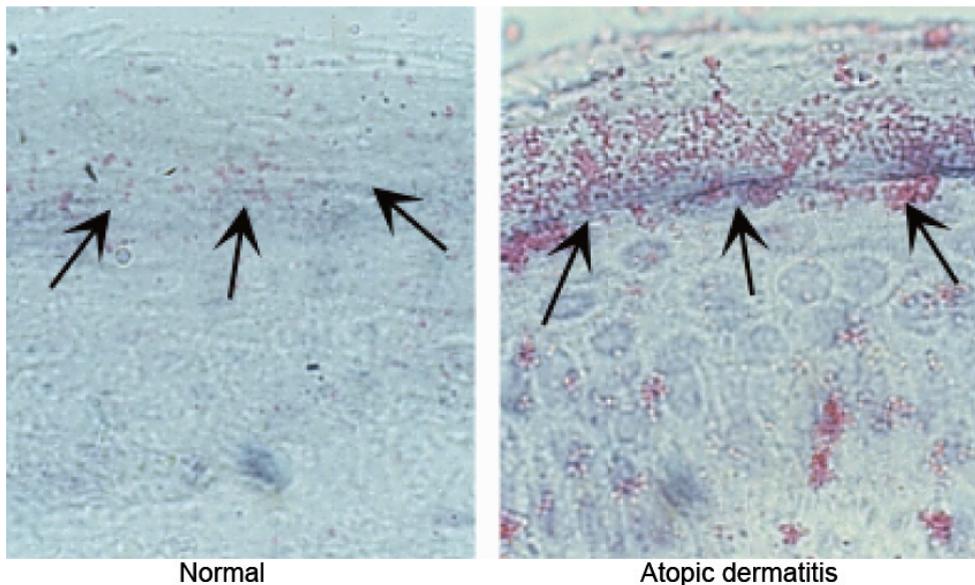
Fig. 1. Atopic skin, compared with normal skin is associated with increased adherence of *S. aureus*. © 2001 Elsevier, reproduced with permission from: Cho S-H, et al. J Allergy Clin Immunol 2001; 108: 269–274 (17).

neurin inhibitors significantly reduces the numbers of *S. aureus* found on atopic skin (10–12). Thirdly, bacterial binding was found to be significantly greater at mouse skin sites with T-helper type 2 cell (Th2)-mediated inflammation than at skin sites with T-helper type 1 cell (Th1)-mediated inflammation (13). This increased bacterial binding did not occur in interleukin (IL)-4 gene knockout mice, suggesting that IL-4 plays a critical role in the enhancement of *S. aureus* binding to skin. In contrast, when normal skin was incubated with IL-4 or with interferon-γ, increased *S. aureus* binding occurred only to skin explants treated with IL-4.

Staphylococcal cell surface molecules termed "adhesins", which are responsible for the adherence of *S. aureus* to the skin, have been identified. These include fibronectin-binding proteins A and B, fibrinogen-binding proteins, and collagen adhesins (14, 15). Relevant to atopic inflammation, IL-4, but not interferon-γ, is known to induce fibronectin production by skin fibroblasts (16). Recently, we found that fibronectin and fibrinogen are involved in the binding of *S. aureus* to Th2-induced inflammatory skin lesions (17). Thus, IL-4 induced fibronectin synthesis, in combination with plasma exudation of fibrinogen, could provide a mechanism by which the atopic/inflammatory environment mediates enhanced *S. aureus* attachment to the skin.

Table I. *Factors contributing to S. aureus colonization/infection in atopic eczema*

- Impaired skin barrier function
- Reduced skin lipid content in atopic eczema
- Increased skin adherence to *S. aureus* due to increased fibronectin and fibrinogen
- Decreased production of endogenous antimicrobial peptides (beta-defensins, LL-37) by keratinocytes

Decreased innate immune response

The density of *S. aureus* on acutely inflamed AE lesions is generally more than 1000-fold higher than on non-lesional AE skin. As increased *S. aureus* adherence can account only for a several-fold increase in *S. aureus* on AE skin, other local host defence mechanisms must also be defective. Using electron microscopy, Morishita et al. (18) found colonies of *S. aureus* distributed on the surface of the epidermis as well as growing between layers of keratinocytes in the absence of an active antimicrobial response. This observation suggests that an exponential increase in *S. aureus* could result from failure of the innate immune response to restrict the growth of microorganisms. Indeed, a direct comparison of AE and psoriasis showed that about 30% of patients with AE suffered from clinical infections, whereas only 6.7% of patients with psoriasis had this complication (19), despite the fact that both skin diseases have defective skin barrier function (20). It is thought that the reduced prevalence of infections in psoriasis may be associated with the increased production of AMPs (21).

Two major classes of AMPs have been found in mammalian skin: beta-defensins (22, 23) and cathelicidins (LL-37) (24, 25). They have been shown to have antimicrobial activities against bacterial, fungal and viral pathogens (26). In the skin, keratinocytes are the primary producer of these peptides. We have compared the expression of AMPs in AE vs. psoriasis to determine if the increased susceptibility to infection in AE is due to a deficiency in AMPs (27, 28). We found that there was abundant LL-37, human beta-defensin (HBD)-2 and HBD-3 in the skin of all patients with psoriasis. In AE lesions, however, immunostaining of LL-37, HBD-2, and HBD-3 was significantly decreased. HBD-2 and LL-37 mRNA was also lower in AE lesions than psoriasis lesions. The combination of LL-37 and HBD-2

showed synergistic antimicrobial activity by effectively killing *S. aureus* more than either AMP alone. Thus, a deficiency in AMP expression could account for the ability of *S. aureus* readily to infect skin from patients with AE.

To examine the potential mechanism for this defect, we examined the ability of cultured AE keratinocytes to produce AMP. We found that after the keratinocytes were removed from the inflammatory milieu of AE skin, they produced normal levels of AMP, suggesting that the defect was acquired (29). As acute AE skin lesions are associated with marked overexpression of IL-4 and IL-13, we studied the effects of IL-4 and IL-13 on tumour necrosis factor-alpha (TNF-α-induced HBD-2 and HBD-3 expression in keratinocytes). IL-4 alone or in combination with IL-13 significantly suppressed TNF-α-induced expression of HBD-2 and HBD-3 in keratinocytes (30). This data suggest that the low expression of AMP expression in AE may be acquired as the result of allergic immune responses (31–33).

Skin inflammation induced by S. aureus

The exact mechanisms by which *S. aureus* induces skin inflammatory responses in AE are being investigated. A number of staphylococcal products, including protein A, lipoteichoic acid and various toxins have been observed to induce activation of cells involved in the pathogenesis of AE including mast cells, T cells, keratinocytes and macrophages (3). An important strategy by which *S. aureus* induces skin inflammation in AE is by secreting a group of toxins known as superantigens (Fig. 2).

Superantigens bind directly to constitutively expressed human leukocyte antigen D-related (HLA-DR) molecules on professional antigen-presenting cells such as macrophages or dendritic cells, and to gamma interferon-induced HLA-DR molecules on non-professional antigen-presenting cells such as keratinocytes (34). This results in the release of pro-inflammatory cytokines by these HLA-DR+ cells, or via the subsequent activation of T cells. The stimulation of T cells by superantigens results in the activation of lymphocytes expressing specific T-cell receptor V-beta regions (35).

A variety of observations support a role for superantigens in triggering AE (Table II). First, the majority of patients with AE have *S. aureus* cultured from their skin that secrete superantigens such as enterotoxins A (SEA), B (SEB) and toxic shock syndrome toxin-1 (TSST-1) (33, 36, 37). Analysis of the peripheral blood skin-homing T cells expressing cutaneous lymphoid antigen (CLA) from these patients as well as their skin lesions reveals that they have undergone a T-cell receptor V-beta expansion within both their CD4+ T cells and their CD8+ T cells, indicative of superantigen stimulation (38, 39).

Secondly, most patients with AE make specific IgE antibodies directed against superantigens found on their skin (36, 37). Basophils from patients with IgE to superantigens release histamine on exposure to the relevant superantigen, but not in response to superantigens to which they make no specific IgE. These data suggest that superantigens induce specific IgE in AE and chronic mast cell degranulation *in vivo* when the superantigens penetrate their impaired skin barrier. This promotes the itch–scratch cycle, thereby contributing to
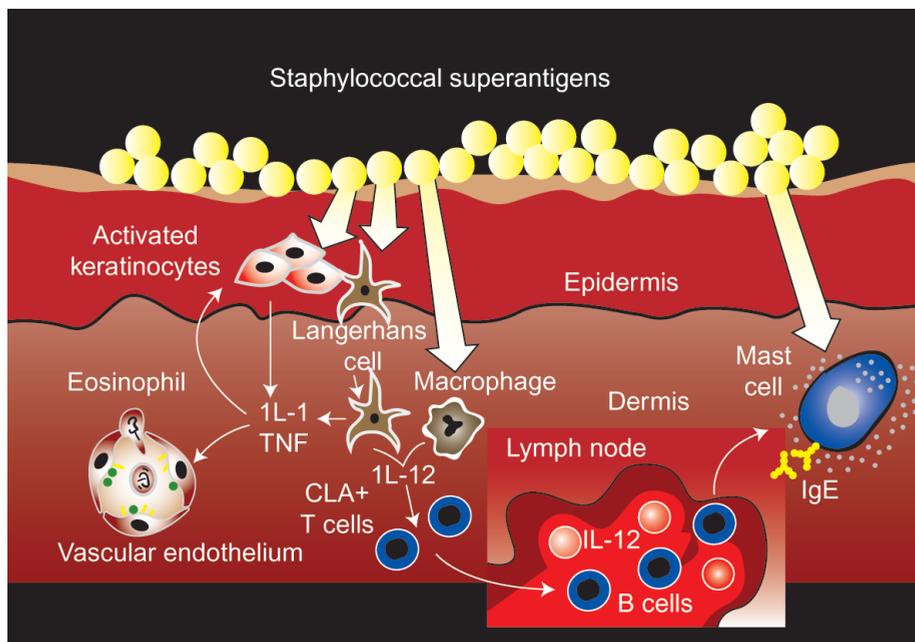

Fig. 2. Immune actions of staphylococcal superantigens. © 2000 Elsevier, reproduced with permission from: Leung DYM. J Allergy Clin Immunol 2000; 105: 860–876 (34).

Table II. *Observations that support the role of staphylococcal superantigens in atopic eczema*

- Severity of atopic eczema correlates with presence of IgE antibodies to superantigens
- Superantigens augment allergen-induced skin inflammation by activating infiltrating mononuclear cells and inducing mast cell degranulation
- Superantigens induce dermatitis when applied to skin in patch testing
- Patients recovering from toxic shock syndrome develop chronic eczema
- Superantigens induce the skin-homing receptor on T cells

the development of skin inflammation in AE. Indeed, a correlation has been found between the presence of IgE to superantigens and severity of AE (38).

Thirdly, epicutaneous application of SEB to normal skin or unaffected AE skin induces skin erythema and induration (39). In one study, half of the AE subjects studied experienced a flare of their skin disease in the elbow flexure ipsilaterally to where the SEB was applied. These observations provide direct in vivo evidence that superantigens can induce skin inflammation in AE. It has also been found that the T cells infiltrating into skin patch test sites stimulated with SEB are selectively expanded with a T-cell repertoire (increased expression of T-cell receptor V-beta 3, 12 and 17) indicative of SEB stimulation (40). Furthermore, in a prospective study, 14 of 68 patients recovering from toxic shock syndrome developed chronic eczematoid eczema, whereas no patients recovering from Gram-negative sepsis developed eczema (41). These investigators concluded that superantigens may induce an atopic eczematoid process in the skin.

A number of factors probably contribute to skin inflammation induced by superantigens. *In vitro*, superantigens can cause marked activation of Th2 cells. Mouse Th2 cells expanded by superantigens induce IL-4 dependent skin inflammation when injected into the skin of mice (42). IL-31 is a novel Th2-cell-derived cytokine that induces severe pruritus and eczema in mice. Human IL-31 is overexpressed in AE skin lesions and their CLA+ skin-homing T cells, compared with psoriasis (43, 44). Moreover, IL-31 is rapidly and selectively upregulated in peripheral blood mononuclear cells treated with staphylococcal superantigens (SEB and TSST-1). This suggests that the pruritus that contributes to the itch cycle of AE may be induced in part by superantigens.

Fig. 2 depicts several additional mechanisms by which staphylococcal superantigens can contribute to AE (34). Superantigens secreted by *S. aureus* at the skin surface can penetrate the skin to stimulate epidermal macrophages or Langerhans' cells to produce IL-1 and TNF-α. Local production of IL-1 and TNF induces the expression of E-selectin on vascular endothelium, allowing an initial influx of CLA+ Th2 memory/effector cells. IL-12 secreted by superantigen-stimulated

Langerhans' cells, which migrate to skin-associated lymph nodes, can upregulate the expression of CLA on T cells. These actions result in the formation of additional skin-homing memory T cells that can migrate to the skin and promote skin inflammation.

In human subjects CD4+CD25+ T regulatory (Treg) cells are thought to suppress the development of Th2 responses (45). Patients with XLAAD/IPEX disease that lack these Treg cells have severe eczema, and increased IgE and eosinophil counts (46). Atopic skin has been reported to have a deficiency of Treg cells (47). We recently also found that superantigens caused a decrease in naturally occurring Treg activity, suggesting a novel mechanism by which superantigens could augment T-cell-activated responses in AE (48, 49).

CLINICAL IMPLICATIONS

Effective treatment of chronic AE requires a multi-pronged approach that involves skin barrier repair, elimination of AE triggers, anti-inflammatory therapy, intervention in the itch–scratch cycle, and treatment of infectious complications of AE (50–55). The concept that infection with *S. aureus* can induce skin inflammation provides a rationale for use of anti-staphylococcal therapy in patients with poorly controlled AE (Table III). Systemic anti-staphylococcal antibiotics are particularly helpful in the treatment of acute exacerbations of AE due to diffuse *S. aureus* infection.

Due to the increased risk of bacterial resistance that may occur with frequent use of antibiotics, it is important to combine antimicrobial therapy with effective skin care, for it is well established that the excoriated inflamed skin of AE predisposes to *S. aureus* colonization and infection. Use of antibiotic therapy must be carried out with good skin hydration, to restore skin barrier function, and effective anti-inflammatory therapy, to reduce overall skin inflammation.

Several studies have demonstrated that the combination of topical corticosteroids with an antibiotic is significantly more effective at reducing skin inflammation due to AE than using the topical corticosteroid or topical antibiotic alone (7, 8). The observation that combined treatment of AE with antibiotics and corticosteroids is more effective than corticosteroids alone suggests that *S. aureus* secretes products that can induce steroid resistance. Recently, we found that when T cells are stimulated with superantigens, compared with other

Table III. *Therapeutic approaches to reduce S. aureus*

- Restore skin barrier function
- Antibiotics for treatment of acute infection
- Topical anti-inflammatory agents to reduce *S. aureus* colonization
- Antiseptics
- Phototherapy

stimuli, they become resistant to the immunosuppressive effects of corticosteroids (56). This is due to superantigen-induced activation of the MEK/ERK (mitogen-activated protein kinase extracellular signal-related kinase) pathway, which leads to phosphorylation of the glucocorticoid receptor. This in turn inhibits the action of steroids by altering the ability of glucocorticoid receptors to translocate from the cytoplasm to the nucleus. Elimination of superantigens from the skin by reducing skin inflammation and judicious use of antimicrobial therapy should therefore enhance the anti-inflammatory effects of corticosteroids. In patients who have repeated relapses of infected AE, the use of treatment with various modalities such as antiseptics (57), phototherapy, or possible systemic treatment should be considered.

CONCLUSION

Colonization and infection with *S. aureus* contributes to the severity of AE, resulting in a vicious cycle of impaired skin barrier and attachment of *S. aureus,* followed by production of staphylococcal virulence factors that induce skin inflammation, leading in turn to sustained *S. aureus* colonization and infection (Fig. 3). Staphylococcal superantigens not only augment allergic skin inflammation to enhance their attachment, but also reduce corticosteroid sensitivity, thereby subverting anti-inflammatory therapy. Reduction in *S. aureus* colonization requires effective skin care, avoidance of triggers, and anti-inflammatory therapy to control skin inflammation. These observations suggest a role for antibiotic/corticosteroid combination creams or ointments in the treatment of AE.
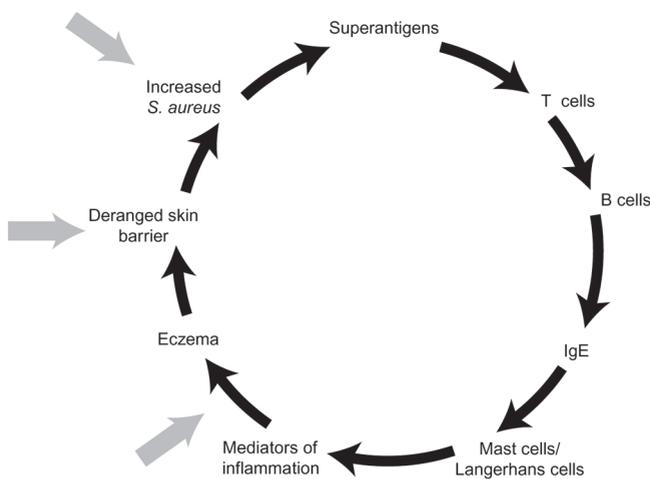

Fig. 3. Vicious cycle of *S. aureus* in atopic eczema. The arrows indicate points where the vicious cycle can be interrupted. © 2005 Society for the Publication of Acta Dermato-Venereologica, reproduced with permission from: Leung DYM. Acta Derm Venereol 2005; Suppl. 215: S11–S15 (58).

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