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

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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. Superantigens 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-

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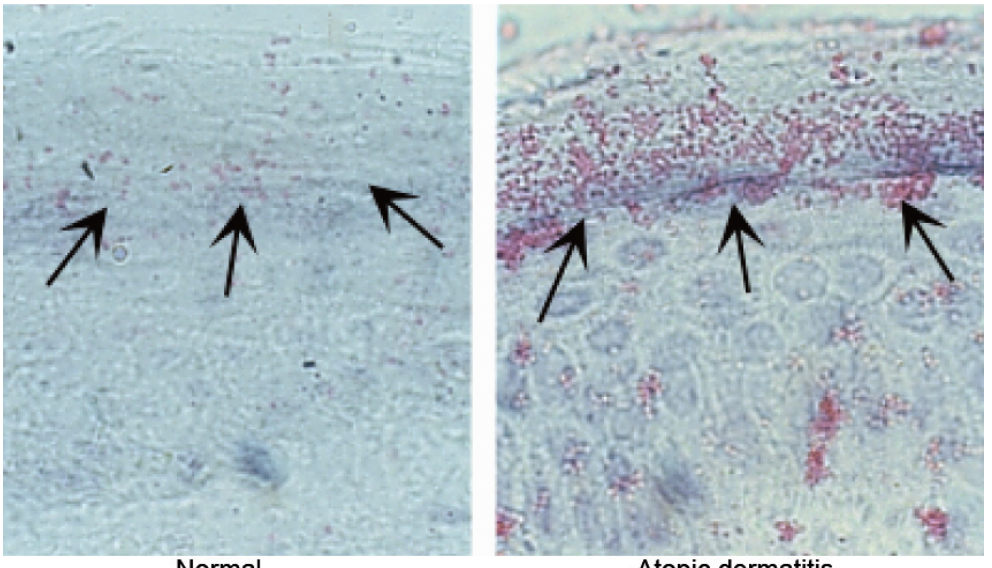

Fig. 1. Atopic skin, compared with normal skin is associated with increased adherence of *S. aureus*. © 2001 Elsevier, reproduced with permission from: Cho S-H, et al. J Allergy Clin Immunol 2001; 108: 269–274 (17).

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

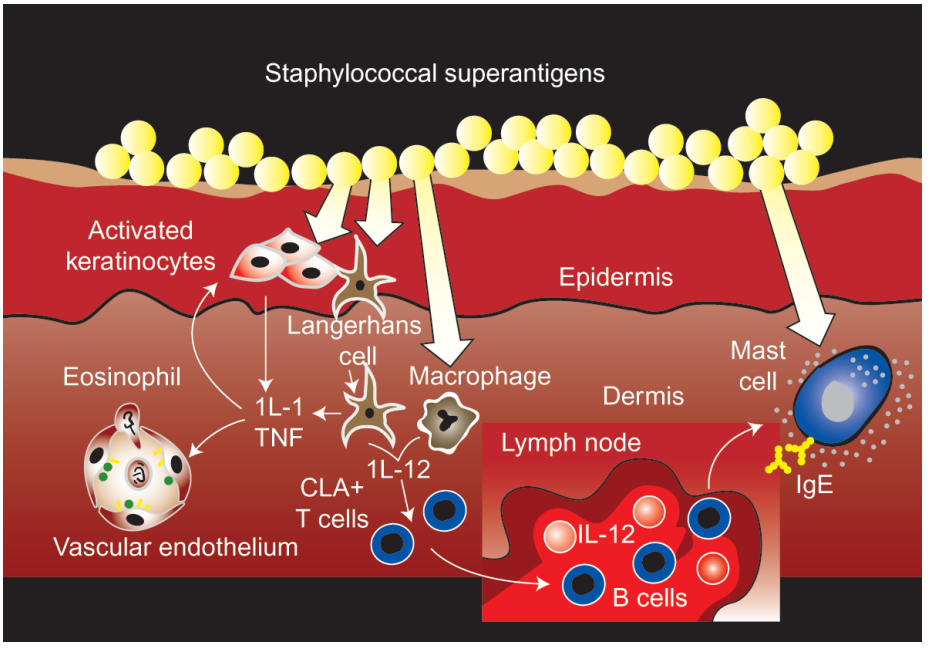

Fig. 2. Immune actions of staphylococcal superantigens. © 2000 Elsevier, reproduced with permission from: Leung DYM. J Allergy Clin Immunol 2000; 105: 860–876 (34).

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 multipronged 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.

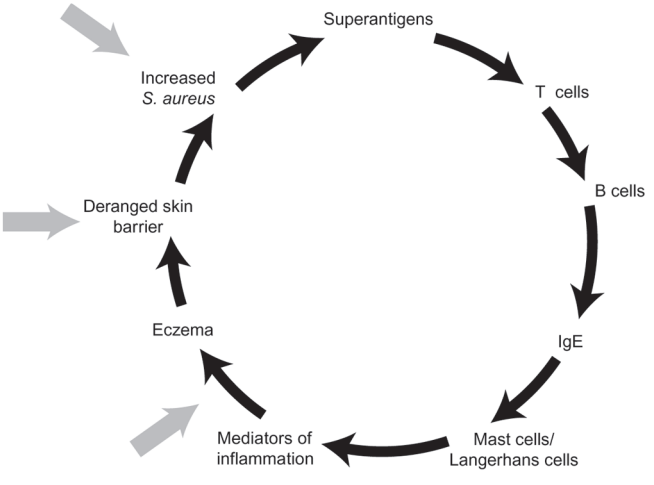

Fig. 3. Vicious cycle of *S. aureus* in atopic eczema. The arrows indicate points where the vicious cycle can be interrupted. © 2005 Society for the Publication of Acta Dermato-Venereologica, reproduced with permission from: Leung DYM. Acta Derm Venereol 2005; Suppl. 215: S11–S15 (58).

REFERENCES

1. Akdis CA, Akdis M, Bieber T, Bindslev-Jensen C, Boguniewicz M, Eigenmann P, et al. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. J Allergy Clin Immunol 2006; 118: 152–169.
2. Homey B, Steinhoff M, Ruzicka T, Leung DY. Cytokines and chemokines orchestrate atopic skin inflammation. J Allergy Clin Immunol 2006; 118: 178–189.
3. McGirt LY, Beck LA. Innate immune defects in atopic dermatitis. J Allergy Clin Immunol 2006; 118: 202–208.
4. Cork MJ, Robinson DA, Vasilopoulos Y, Ferguson A, Moustafa M, MacGowan A, et al. New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene-environment interactions. J Allergy Clin Immunol 2006; 118: 3–21.
5. Morar N, Willis-Owen SA, Moffatt MF, Cookson WO. The genetics of atopic dermatitis. J Allergy Clin Immunol 2006; 118: 24–34.
6. Leyden JJ, Marples RR, Kligman AM. Staphylococcus aureus in the lesions of atopic dermatitis. Br J Dermatol 1974; 90: 525–530.
7. Ramsay CA, Savoie LM, Gilbert M. The treatment of atopic dermatitis with topical fusidic acid and hydrocortisone acetate. J Eur Acad Dermatol Venereol 1996; 7 Suppl 1: S15–S22.
8. Leyden JJ, Kligman AM. The case for steroid-antibiotic combinations. Br J Dermatol 1977; 96: 179–187.
9. Arikawa J, Ishibashi M, Kawashima M, Takagi Y, Ichikawa Y, Imokawa G. Decreased levels of sphingosine, a natural antimicrobial agent, may be associated with vulnerability of the stratum corneum from patients with atopic dermatitis to colonization by Staphylococcus aureus. J Invest Dermatol 2002; 119: 433–439.
10. Nilsson EJ, Henning CG, Magnusson J. Topical corticosteroids and Staphylococcus aureus in atopic dermatitis. J Am Acad Dermatol 1992; 27: 29–34.
11. Stalder JF, Fleury M, Sourisse M, Rostin M, Pheline F, Litoux P. Local steroid therapy and bacterial skin flora in atopic dermatitis. Br J Dermatol 1994; 131: 536–540.
12. Remitz A, Kyllonen H, Granlund H, Reitamo S. Tacrolimus ointment reduces staphylococcal colonization of atopic dermatitis lesions. J Allergy Clin Immunol 2001; 107: 196–197.
13. Cho SH, Strickland I, Tomkinson A, Fehringer AP, Gelfand EW, Leung DY. Preferential binding of Staphylococcus aureus to skin sites of Th2-mediated inflammation in a murine model. J Invest Dermatol 2001; 116: 658–663.
14. Mempel M, Schmidt T, Weidinger S, Schnopp C, Foster T, Ring J, Abeck D. Role of Staphylococcus aureus surface-associated proteins in the attachment to cultured HaCaT keratinocytes in a new adhesion assay. J Invest Dermatol 1998; 111: 452–456.
15. Foster TJ, Hook M. Surface protein adhesins of Staphylococcus aureus. Trends Microbiol 1998; 6: 484–488.
16. Postlethwaite AE, Holness MA, Katai H, Raghow R. Human fibroblasts synthesize elevated levels of extracellular matrix proteins in response to interleukin 4. J Clin Invest 1992; 90: 1479–1485.
17. Cho SH, Strickland I, Boguniewicz M, Leung DY. Fibronectin and fibrinogen contribute to the enhanced binding of Staphylococcus aureus to atopic skin. J Allergy Clin Immunol 2001; 108: 269–274.

18. Morishita Y, Tada J, Sato A, Toi Y, Kanzaki H, Akiyama H, Arata J. Possible influences of Staphylococcus aureus on atopic dermatitis – the colonizing features and the effects of staphylococcal enterotoxins. Clin Exp Allergy 1999; 29: 1110–1117.
19. Christophers E, Henseler T. Contrasting disease patterns in psoriasis and atopic dermatitis. Arch Dermatol Res 1987; 279 (suppl): S48–S51.
20. Grice K, Sattar H, Baker H, Sharratt M. The relationship of transepidermal water loss to skin temperature in psoriasis and eczema. J Invest Dermatol 1975; 64: 313–315.
21. Fulton C, Anderson GM, Zasloff M, Bull R, Quinn AG. Expression of natural peptide antibiotics in human skin. Lancet 1997; 350: 1750–1751.
22. Harder J, Bartels J, Christophers E, Schroder JM. A peptide antibiotic from human skin. Nature 1997; 387: 861.
23. Stolzenberg ED, Anderson GM, Ackermann MR, Whitlock RH, Zasloff M. Epithelial antibiotic induced in states of disease. Proc Natl Acad Sci USA 1997; 94: 8686–8690.
24. Gallo RL, Ono M, Povsic T, Page C, Eriksson E, Klagsbrun M, Bernfield M. Syndecans, cell surface heparan sulfate proteoglycans, are induced by a proline-rich antimicrobial peptide from wounds. Proc Natl Acad Sci USA 1994; 91: 11035–11039.
25. Frohm M, Agerberth B, Ahangari G, Stahle-Backdahl M, Liden S, Wigzell H, Gudmundsson GH. The expression of the gene coding for the antibacterial peptide LL-37 is induced in human keratinocytes during inflammatory disorders. J Biol Chem 1997; 272: 15258–15263.
26. Gropp R, Frye M, Wagner TO, Bargon J. Epithelial defensins impair adenoviral infection: implication for adenovirus-mediated gene therapy. Hum Gene Ther 1999; 10: 957–964.
27. Gallo RL, Murakami M, Ohtake T, Zaiou M. Biology and clinical relevance of naturally occurring antimicrobial peptides. J Allergy Clin Immunol 2002; 110: 823–831.
28. Nizet V, Ohtake T, Lauth X, Trowbridge J, Rudisill J, Dorschner RA, et al. Innate antimicrobial peptide protects the skin from invasive bacterial infection. Nature 2001; 414: 454–457.
29. Ong PY, Ohtake T, Brandt C, Strickland I, Boguniewicz M, Ganz T, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. N Engl J Med 2002; 347: 1151–1160.
30. Nomura I, Goleva E, Howell MD, Hamid QA, Ong PY, Hall CF, et al. Cytokine milieu of atopic dermatitis, as compared to psoriasis, skin prevents induction of innate immune response genes. J Immunol 2003; 171: 3262–3269.
31. Howell MD, Novak N, Bieber T, Pastore S, Girolomoni G, Boguniewicz M, et al. Interleukin-10 downregulates antimicrobial peptide expression in atopic dermatitis. J Invest Dermatol 2005; 125: 738–745.
32. Fiset PO, Leung DY, Hamid Q. Immunopathology of atopic dermatitis. J Allergy Clin Immunol 2006; 118: 287–290.
33. Boguniewicz M, Leung DY. Atopic dermatitis. J Allergy Clin Immunol 2006; 117: S475–S480.
34. Leung DY. Atopic dermatitis: new insights and opportunities for therapeutic intervention. J Allergy Clin Immunol 2000; 105: 860–876.
35. Kotzin BL, Leung DY, Kappler J, Marrack P. Superantigens and their potential role in human disease. Adv Immunol 1993; 54: 99–166.
36. Leung DY, Harbeck R, Bina P, Reiser RF, Yang E, Norris DA, et al. Presence of IgE antibodies to staphylococcal exotoxins on the skin of patients with atopic dermatitis. Evidence for a new group of allergens. J Clin Invest 1993; 92: 1374–1380.
37. Bunikowski R, Mielke M, Skarabis H, Herz U, Bergmann RL, Wahn U, Renz H. Prevalence and role of serum IgE antibodies to the Staphylococcus aureus-derived superantigens SEA and SEB in children with atopic dermatitis. J Allergy Clin Immunol 1999; 103: 119–124.
38. Bunikowski R, Mielke ME, Skarabis H, Worm M, Anagnostopoulos I, Kolde G, et al. Evidence for a disease-promoting effect of Staphylococcus aureus-derived exotoxins in atopic dermatitis. J Allergy Clin Immunol 2000; 105: 814–819.
39. Strange P, Skov L, Lisby S, Nielsen PL, Baadsgaard O. Staphylococcal enterotoxin B applied on intact normal and intact atopic skin induces dermatitis. Arch Dermatol 1996; 132: 27–33.
40. Skov L, Olsen JV, Giorno R, Schlievert PM, Baadsgaard O, Leung DY. Application of Staphylococcal enterotoxin B on normal and atopic skin induces up-regulation of T cells by a superantigen-mediated mechanism. J Allergy Clin Immunol 2000; 105: 820–826.
41. Michie CA, Davis T. Atopic dermatitis and staphylococcal superantigens. Lancet 1996; 347: 324.
42. Müller KM, Jaunin F, Masouye I, Saurat JH, Hauser C. Th2 cells mediate IL-4-dependent local tissue inflammation. J Immunol 1993; 150: 5576–5584.
43. Sonkoly E, Muller A, Lauerma AI, Pivarcsi A, Soto H, Kemeny L, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. J Allergy Clin Immunol 2006; 117: 411–417.
44. Bilsborough J, Leung DY, Maurer M, Howell M, Boguniewicz M, Yao L, et al. IL-31 is associated with cutaneous lymphocyte antigen-positive skin homing T cells in patients with atopic dermatitis. J Allergy Clin Immunol 2006; 117: 418–425.
45. Akdis M, Blaser K, Akdis CA. T regulatory cells in allergy: novel concepts in the pathogenesis, prevention, and treatment of allergic diseases. J Allergy Clin Immunol 2005; 116: 961–968.
46. Chatila TA. Role of regulatory T cells in human diseases. J Allergy Clin Immunol 2005; 116: 949–959.
47. Verhagen J, Akdis M, Traidl-Hoffmann C, Schmid-Grendelmeier P, Hijnen D, Knol EF, et al. Absence of T-regulatory cell expression and function in atopic dermatitis skin. J Allergy Clin Immunol 2006; 117: 176–183.
48. Cardona ID, Goleva E, Ou LS, Leung DY. Staphylococcal enterotoxin B inhibits regulatory T cells by inducing glucocorticoid-induced TNF receptor-related protein ligand on monocytes. J Allergy Clin Immunol 2006; 117: 688–695.
49. Goleva E, Cardona ID, Ou LS, Leung DY. Factors that regulate naturally occurring T regulatory cell-mediated suppression. J Allergy Clin Immunol 2005; 116: 1094–1100.
50. Boguniewicz M, Schmid-Grendelmeier P, Leung DY. Atopic dermatitis. J Allergy Clin Immunol 2006; 118: 40–43.
51. Leung DYM. New insights into the complex gene-environment interactions evolving into atopic dermatitis. J Allergy Clin Immunol 2006; 118: 37–39.
52. Bender BG, Leung DY. Sleep disorders in patients with asthma, atopic dermatitis, and allergic rhinitis. J Allergy Clin Immunol 2005; 116: 1200–1201.
53. Howell MD, Wollenberg A, Gallo RL, Flaig M, Streib JE, Wong C, et al. Cathelicidin deficiency predisposes to eczema herpeticum. J Allergy Clin Immunol 2006; 117: 836–841.
54. Kim HY, Kim HS. Upregulation of MIP-2 (CXCL2) expression by 15-deoxy-Delta (12,14)-prostaglandin J (2) in mouse peritoneal macrophages. Immunol Cell Biol 2007; 85: 60–67.
55. Salt BH, Boguniewicz M, Leung DY. Severe refractory

atopic dermatitis in adults is highly atopic. J Allergy Clin Immunol 2007; 119: 508–509.
56. Li LB, Goleva E, Hall CF, Ou LS, Leung DY. Superantigen-induced corticosteroid resistance of human T cells occurs through activation of the mitogen-activated protein kinase kinase/extracellular signal-regulated kinase (MEK-ERK) pathway. J Allergy Clin Immunol 2004; 114: 1059–1069.
57. Stalder JF, Fleury M, Sourisse M, Allavoine T, Chalamet C, Brosset P, Litoux P. Comparative effects of two topical antiseptics (chlorhexidine vs KMn04) on bacterial skin flora in atopic dermatitis. Acta Derm Venereol 1992; Suppl 176: 132–134.
58. Leung D. Superantigens, steroid insensitivity and innate immunity in atopic eczema. Acta Derm Venereol 2005; Suppl 215: 11–15.