STAPHYLOCOCCUS AUREUS AND ATOPIC DERMATITIS: WHICH CAME FIRST, THE CHICKEN OR THE EGG?

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ABSTRACT

Atopic dermatitis (AD) is a highly pruritic, chronic inflammatory skin disease that affects up to 25% of children and 10% of adults. Approximately 90% of patients with AD are colonised by *Staphylococcus aureus*, compared with only 5–30% of non-atopic individuals. Th2 cytokines have a permissive effect on microbial invasion, the epidermal barrier, and cell-mediated immunity, which lowers the production of antimicrobial proteins. Superantigen-producing *S. aureus* colonisation is correlated with serum interleukin (IL)-4 levels. Up to 50–60% of the *S. aureus* found on patients with AD is toxin-producing.[1] *S. aureus* colonisation, infection, and production of toxins and superantigens is believed to drive, at least in part, the pathogenesis of AD. *S. aureus* mechanically disrupts epidermal integrity through protease activity, and also has the ability to be internalised by keratinocytes in which it activates the inflammasome and induces apoptosis. Some patients with AD produce specific immunoglobulin E (IgE) antibodies directed against staphylococcal superantigens to an extent that correlates with skin disease severity. IL-4 and IL-13 have also been reported to increase staphylococcal α-toxin-induced keratinocyte death via STAT6 signalling. The *S. aureus* superantigens staphylococcal enterotoxin B and toxic shock syndrome toxin 1 promote lymphocyte IL-31 production in patients with AD. IL-31 has, in turn, been shown to reduce filaggrin expression and mediate pro-inflammatory cytokine excretion, as well as induce toxin-specific IgE and basophilic activation. The ability of *S. aureus* to colonise skin affected by AD, and to activate and maintain a Th2 environment allowing, via the destruction of tight junctions, exposure to allergens and thus causing allergic sensitisation, makes it one of the main protagonists of the 'atopic march'.

Keywords: Atopic dermatitis (AD), *Staphylococcus aureus*, atopic march, immunoglobulin E (IgE) sensitisation, skin immunity.

INTRODUCTION

Atopic dermatitis (AD) is a highly pruritic, chronic inflammatory skin disease that affects up to 25% of children and 10% of adults, and which is associated with significant morbidity as well as physical, psychological, and economic impairments to quality of life. The disease often begins in childhood, with approximately 60% of patients developing the disease prior to the age of 1 year, and its prevalence has markedly increased during the past three decades.[1-3] In many patients, the early onset of AD is the first clinical manifestation of allergic disease and often triggers the 'atopic march' (i.e. the subsequent development of food allergies, allergic rhinitis, and asthma), even if recent work suggests that only a small proportion of children (approximately 7%) follow a trajectory profile similar to that of the atopic march.[4] In addition, approximately 20% of patients do not have any evidence of immunoglobin E (IgE) sensitisation,[5] which suggests a degree of heterogeneity within the population. AD is a complex immunological disease based on a variety of genetic traits that cause susceptibility to environmental factors. It is characterised by reduced skin barrier function, intracutaneous and blood T-cell activation, and susceptibility to cutaneous microbial and viral

infections.[6] Mutations in filaggrin (FLG), an epidermal barrier protein, have been identified in approximately 30% of patients with AD.[7] They constitute the strongest known risk factor for AD and are associated with early onset, a more severe course, and higher prevalence of IgE-mediated sensitisation.[8] Levels of FLG are determined by genotype, but expression is also downregulated by Th2 cytokines in patients with AD[9] and FLG proteolysis is accelerated after exposure to either low ambient humidity[10] or skin irritants.[11] Therefore, levels of FLG and its degradation products are influenced not only by the individual's FLG genotype, but also by inflammation and exogenous stressors. A detailed characterisation of AD inflammation has revealed a biphasic cutaneous cytokine milieu with initial recruitment of interleukin (IL)-4-producing Th2 cells, followed by a mixed phenotype in the chronic phase.[12,13] The cutaneous barrier dysfunction also contributes to Th2 cell polarisation and the Th2 cell cytokine IL-4 further reduces the cutaneous barrier, forming a 'vicious circle'. In addition, IL-4 suppresses antimicrobial peptide production and immune function, allowing cutaneous microbes to expand and persist.[14,15] Approximately 90% of patients with AD are colonised by *Staphylococcus aureus*, while only 5–30% of nonatopic individuals are colonised by this bacterium.[16] *S. aureus* is usually recovered in densities of 10^5 colony-forming units (CFU)/cm^2 from lesional atopic eczema sites, but can reach concentrations of up to 10^7 CFU/cm^2, a density which is 1,000-times higher than on nonlesional skin.[17] In addition to higher rates of colonisation, up to 50–60% of the *S. aureus* found on patients with AD is toxin-producing.[18] *S. aureus* colonisation, infection, and production of toxins and superantigens are believed to drive, at least in part, the pathogenesis of AD. The severity of AD has been shown to correlate with the density of colonisation, with superantigen-secreting *S. aureus*[19] and *S. aureus* superantigen augmenting allergen-induced cutaneous inflammation in a murine model of skin inflammation.[20] Patients with AD also produce IgE antibodies directed against the superantigens found on their skin,[21] and the presence of IgE antibodies to the superantigens correlates with skin disease severity. *S. aureus* superantigens drive AD disease pathogenesis by inducing skin inflammation[22] and directly inducing T-cell proliferation.[23]

STAPHYLOCCOCUS AUREUS: THE 'OPPORTUNIST'

S. aureus is an important human pathogen that causes a variety of infections ranging from localised skin and soft-tissue infections (SSTIs) to severe necrotising fasciitis and life-threatening disseminated infections. The ability of *S. aureus* to evoke these diverse clinical manifestations is attributed to its production of numerous exotoxins. One important mechanism promoting colonisation is adherence of *S. aureus* to surface components of the nasal epithelium or epidermal keratinocytes, such as fibrinogen, fibronectin, and cytokeratins. *S. aureus* utilises microbial surface components, such as fibrinogen-binding proteins A and B, iron-regulated surface determinant, and wall teichoic acid, to bind adhesive matrix molecules.[24,25] Interestingly, pH values between 7 and 8, which are usually found in AD after the disruption of the skin barrier (compared with the pH values of 4.2–5.6 found in normal skin), are more likely to support this adhesion process.[26] Furthermore, the expression of fibronectin is regulated by IL-4, the crucial Th2-promoting cytokine that is present in higher concentrations in AD patients.[27]

S. aureus is generally regarded as an extracellular microorganism, but there is ample evidence that it can be internalised by a variety of host cells[28] in a fibronectin-binding protein (FnBP)-dependent manner.[29] Strain-dependent, FnBP-independent invasion mechanisms have also been reported for primary human keratinocytes.[30] Intracellular *S. aureus* has been shown to escape the endosome and induce apoptosis in epithelial cells. Panton–Valentine leukocidin (PVL) is a two-component (LukS-PV and LukF-PV), pore-forming toxin that targets neutrophils and is a useful marker for *S. aureus* strains with the potential to cause severe infections. PVL promotes severe SSTIs by exerting toxic effects on host keratinocytes. PVL also allows bacteria to escape from endosomes and multiply. In fact, PVL-positive, community-acquired, methicillin-resistant *S. aureus* (CA-MRSA) is taken up by human keratinocytes and engulfed within endosomes before the PVL released from CA-MRSA is able to disrupt the endosomal membrane and facilitate the escape of the bacteria into the cytoplasm, where they are then able to replicate.[31] This process stimulates induction of the apoptotic cascade followed by the release of inflammatory cytokines, recruitment of leukocytes, and further cell damage. *S. aureus*

internalised by human keratinocytes can also be recognised by nucleotide-binding oligomerisation domain-like receptors and activate the cascade of the inflammasome. This promotes Th1 or Th17-mediated inflammation and may be important in acute forms of AD.[32] Recent evidence indicates that *S. aureus* secretes extracellular vesicles (EVs) as well as soluble α-toxins.[33] EVs derived from *S. aureus* are 20–200 nm vesicular structures that are membrane-enveloped spherical complexes containing about 90 proteins, DNA, RNA, and toxins. *S. aureus* EVs show potent immunogenicity and are related to AD pathogenesis.[34] α-haemolysin from *S. aureus* is also related to AD disease development and/or progression, with its production being significantly higher in the *S. aureus* present on the cutis of patients with severe AD compared with *S. aureus* from mild and moderate AD.[35] EV-associated α-haemolysin induces necrotic cell death by carrying α-haemolysin into the cytoplasm of keratinocytes, whereas soluble haemolysin induces keratinocyte death via apoptosis. EV-associated α-haemolysin induces IL-1β and IL-6 production in keratinocytes, dermal infiltration of inflammatory cells (particularly eosinophils), skin barrier disruption via keratinocyte cell death,[35] and consequently enhances penetration of high-molecular-weight allergens. In addition, EV-associated α-haemolysin induces epidermal thickening and eosinophilic inflammation in the dermis, whereas the soluble form induces only epidermal thickening.

Staphylococcal toxins are enzymes that injure the skin, resulting in activation and proliferation of epidermal keratinocytes that produce and release IL-18. IL-18 induces super Th1 cells to produce and secrete interferon (IFN)-γ and IL-13. IL-18 is presumed to be involved in the pathogenesis of AD because the serum levels of IL-18 in patients with AD significantly correlate with skin scores of AD lesions.[36] Furthermore, an increase of IL-18 production by epidermal cells was observed in AD mice models induced by subsequent topical application of *S. aureus* products,[37] and production of phenol-soluble modulins by *S. aureus* is necessary and sufficient to stimulate IL-18 release from keratinocytes.[38] The cutaneous application of *S. aureus* EVs induces skin inflammation characterised by infiltration of mast cells (MCs) and eosinophils. This inflammatory response is associated with enhanced production of not only Th1/Th17-type cytokines in the skin,

but also Th2-type cytokines. Fibroblasts, smooth muscle cells, and MCs all have the potential to produce thymic stromal lymphopoietin (TSLP), and *in vitro* stimulation of fibroblasts with *S. aureus* EVs increases the secretion of Th2-type cytokines, such as TSLP, macrophage inflammatory protein 1α, IL-6, and eotaxin, with TSLP activating myeloid dendritic cells to create a Th2-permissive microenvironment. These *in vitro* findings demonstrate that Th2-type inflammation induced by *S. aureus* EVs is mediated by local production of Th2-type cytokines by dermal fibroblasts, and that *S. aureus*-derived EVs are a novel diagnostic and therapeutic target for the control of AD.[39] Finally, the *S. aureus* superantigens staphylococcal enterotoxin B (SEB) and toxic shock syndrome toxin 1 promote lymphocyte IL-31 production in patients with AD. IL-31, in turn, has been shown to reduce FLG expression, mediate pro-inflammatory cytokine excretion, and induce toxin-specific IgE and basophilic activation.[40]

SKIN DEFENCE MECHANISMS AND THE TH2 ENVIRONMENT

Healthy skin is in direct contact with the external environment and is thus continuously exposed to large numbers of microorganisms. On the skin's surface, the presence of commensal microorganisms that occupy niches suitable for bacterial growth combined with a lower temperature and pH creates an environment that resists pathogen growth. To cope with substantial microbial exposure, the epithelial surface produces a diverse arsenal of antimicrobial proteins (AMPs) that directly kill or inhibit the growth of microorganisms. The most abundant AMPs produced by human keratinocytes are human β-defensin (HBD)-1, HBD-2, HBD-3, the cathelicidin IL-37, and the AMP ribonuclease 7. The aqueous and lipid components of the skin surface combine with AMPs produced by keratinocytes to enhance the barrier/protective function. The aqueous/lipid layer may serve a function that is similar to that of the intestinal mucus by trapping AMPs at the epithelial surface.[41] Resident bone marrow-derived cells in the dermis, such as MCs and Langerhans cells, provide essential additional AMPs after skin injury or in the early stages of infection. Many AMPs are involved in this defence, such as HBD-1, HBD-2, HBD-3, HBD-4, cathelicidin, dermicidin, ribonuclease 7, psoriasin, lactoferrin, lysozyme, secretory leukocyte protease inhibitor, elafin, α-melanocyte-stimulating hormone,

catestatin, and calprotectin. Inhibition of AMP expression in AD seems to be partially due to the excess production of the Th2 cell cytokines IL-4 and IL-13, which in turn induce the expression of SOCS1 and SOCS3 via STAT6.[42] Furthermore, the Th2 cytokines inhibit lamellar body production, which are organelles critical for epidermal barrier formation that normally occurs during keratinocyte differentiation. Lamellar bodies are also involved in the transport of acid sphingomyelinase, an enzyme that cleaves the α-toxin receptor sphingomyelin. The reduction in lamellar bodies may result in reduced surface acid sphingomyelinase, as well as reduced levels of ceramides. Staphylococcal α-toxin is one of the most prominent and destructive cytolytic toxins. This pore-forming toxin requires that the host expresses sphingomyelin on its cell surface; α-toxin specifically recognises the phosphocholine head group of sphingomyelin and, following binding, α-toxin heptamerises and becomes irreversibly inserted into the cell membrane. A Th2 cytokine milieu renders cells more sensitive to α-toxin-induced cell death. Therefore, the increased cell death in AD skin correlates with increased exposure to Th2 cytokines.[43] The ability of exogenous sphingomyelinase or phosphocholine to reverse α-toxin toxicity not only confirms the mechanism, but also provides a rationale for possible future therapeutics. Epidermal barrier protein FLG also plays an important role in protecting cells by mediating the secretion of sphingomyelinase. Sphingomyelinase is the primary enzyme responsible for producing ceramide, and levels of this enzyme are reported to be decreased in atopic skin. In addition, sphingomyelinase is an enzyme that reduces the number of α-toxin binding sites on the keratinocyte surface, and deficiency in FLG implies decreased sphingomyelinase enzyme activity and increased keratinocyte α-toxin-mediated cytotoxicity.[44]

IL-4 and IL-13 have also been shown to inhibit FLG expression,[9] and therefore a positive feedback pathway can be envisaged in which Th2 cytokines not only provide a permissive environment for *S. aureus*, but also enhance the effects of staphylococcal products. Among these, δ-toxin is a potent inducer of MC degranulation and promotes local inflammation by release of pro-inflammatory mediators by activating MCs. In addition, IgE enhanced δ-toxin-induced MC degranulation in the absence of antigens, and *S. aureus* isolates recovered from AD patients produced high levels of δ-toxin.[22] Staphylococcal superantigens may exacerbate AD by acting as a new group of allergens, since specific IgE to staphylococcal enterotoxin A and B could be detected in the sera of 57% of AD patients, most of whom were identified as carriers of toxigenic *S. aureus* strains.[17] The presence of IgE antibodies to SEB is associated with severe skin lesions quantified by the SCORAD score in adults. Therefore, staphylococcal exotoxins, especially SEB, may exacerbate skin lesions in AD not only in their function as superantigens, but also as a new group of allergens.[45] In patients with asthma and allergic rhinitis, significantly higher levels of blood eosinophils and specific IgE to indoor allergens have been observed, as have higher levels of total IgE in patients with high serum levels of IgE specific to staphylococcal superantigens. Eosinophilic inflammation and IgE production in response to indoor allergens are greater in patients with an IgE response to more than two staphylococcal superantigens. These findings suggest that IgE specific for staphylococcal superantigens may be a risk factor for eosinophilic inflammation and the development of an IgE response to indoor allergens.[46] The *S. aureus* strains from patients with steroid-resistant AD have shown the ability to produce large numbers of different superantigen types per organism. Each superantigen is known to activate only a subset of T cells expressing particular Vβ T cell receptor regions. The net effect of *S. aureus* strains producing a larger number of superantigen types would be to recruit larger numbers of T cells to produce pro-inflammatory cytokines and to induce a wider spectrum of T cells that fail to respond to the immunosuppressive effects of corticosteroids. This process could thus contribute to steroid-resistant AD in some patients.[47] *S. aureus* produces various molecules that can stimulate cells independently of IgE, such as peptidoglycan and lipoproteins.[48] The human innate immune system recognises bacterial lipoproteins through Toll-like receptor (TLR) 2, which forms a heterodimer with either TLR6 or TLR1 for the specific recognition of diacylated or triacylated lipoproteins/lipopeptides, respectively. The *S. aureus*-derived ligands for the TLR2–TLR6 heterodimer could induce expression of TSLP, the master switch for Th2 responses, in keratinocytes, leading to Th2 skewing in the sensitisation to environmental allergens and *S. aureus*-derived allergens through the skin, the exacerbation of AD, or both. Furthermore, TSLP induces invariant natural killer T cells to secrete

IL-4, IL-13, and additional IFN-γ when cocultured with dendritic cells. Therefore, TSLP represents a critical factor linking responses at the interfaces between the body and the environment with allergic Type 2 immune responses.[49]

CONCLUSIONS

From the above observations it can be inferred that *S. aureus* is not only a coloniser of altered skin, which allows its survival due to genetic and local immunological factors, but is also capable of inducing the maintenance of an environment favourable to its survival via interactions with the cutaneous immune system,[50] e.g. maintaining a low level of AMPs and creating an ecosystem that is almost free from bacteria that could interfere with its growth, such as *S. epidermidis*.[51] Furthermore, the ability to form a biofilm, especially in terms of eccrine ducts due to the local presence of water and salts,[52] makes the eradication of *S. aureus* from the skin difficult. However, this is a necessary condition for breaking the vicious circle of *S. aureus* infection–inflammation–maintenance, and ameliorating the allergic environment leading to Th2 sensitisation. Considering the poor action of systemic antibiotic therapy due to the presence of MRSA, new therapeutic strategies to maintain a reduced cutaneous bacterial load as far as possible could also include, in addition to the constant application of skin barrier repair creams[53] alone or in combination with topical antibiotics,[54] the regular use of bleach baths[55] that reversibly inhibit the expression of CCL2 and superoxide dismutase 2, two NF-κB-dependent genes, in primary human keratinocytes.[56] The difficulty is that the skin is rapidly recolonised by *S. aureus*, the 'opportunist'.

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