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Invited review article

Role of the microbiota in skin immunity and atopic dermatitis

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ABSTRACT

Atopic dermatitis (AD) is a chronic inflammatory skin disease that affects 15–20% of children and 2–5% of adults in industrialized countries. The pathogen *Staphylococcus aureus* selectively colonizes the lesional skin of AD patients while this bacterium is absent in the skin of the majority of healthy individuals. However, the role of *S. aureus* in the pathogenesis of AD remains poorly understood. In addition to *S. aureus*, recent studies show a contribution of the skin microbiota to the regulation of immune responses in the skin as well as to the development of inflammatory skin disease. This review summarizes current knowledge about the role of the microbiota in skin immune responses and the role of *S. aureus* virulent factors in the pathogenesis of AD.

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Introduction

The skin, one of our body's largest organs, is exposed to a wide variety of external stimuli including microorganisms. One of the most important functions of the skin is to protect the host from harmful environmental stimuli including invasion by pathogenic microorganisms.^{1,2} The protective function of the skin is implemented by the stratified squamous epithelium of the epidermis as a barrier, and pro-inflammatory and anti-microbial molecules produced by keratinocytes and immune cells. Although the majority of microorganisms that live in the human skin are harmless and even beneficial, some resident microorganisms are potentially pathogenic under certain conditions and are referred to as "pathobionts". For example, *S. epidermidis* normally colonizes the human skin, but it can cause serious diseases in some individuals.³ Likewise, the pathogen *Staphylococcus aureus*, a common cause of skin and systemic infections, can reside in the skin of 10–20% of healthy individuals as a harmless commensal.⁴ However, *S. aureus* colonizes the lesional skin of ~90% of atopic dermatitis (AD), and its increased colonization is associated with disease flare.⁵ Another feature of the skin of patients with AD is the presence of a dysbiotic microbiota.⁵ However, the mechanism by which the normal skin microbiota transitions from a neutral state to dysbiosis and the contribution of the abnormal microbiota to the pathogenesis of AD remains

unclear. Recent advances in the analysis of the skin microbiota by high-throughput microbial gene sequencing has enabled an unbiased identification and quantification of bacterial species, viruses and fungi.^{6–8} Moreover, AD mouse models and gnotobiotic mice have allowed mechanistic studies to understand the contribution of specific microorganisms and virulence factors to the development of dermatitis *in vivo*. In this review, we provide an overview of the role of microorganisms in the regulation of immune responses in the healthy skin, summarize the current knowledge about the contribution of the skin microbiota to the pathogenesis of AD, and finally discuss recent findings about the role of specific *S. aureus* virulence factors in the pathogenesis of AD.

Role of microorganisms in the healthy human skin

Microbial colonization in the human skin

The human skin is the home of a rich community of microorganisms. There is a wide variation in the composition of the skin microbiota depending on the individual, age, site, and time of analysis.^{8,9} Unlike the intestinal microbiota, the population of bacteria in the skin is dominated by few taxa including *Staphylococcus* spp., and the genera *Corynebacterium* and *Propionibacterium* which represent greater than 60% of the bacterial load in the human skin.⁴ Notably, physiologically comparable skin sites contain similar bacterial communities. For instance, sebaceous skin such as that of the glabella (between the eyebrows), external auditory canal (inside the ear), manubrium (upper chest) and back predominantly harbor *Propionibacteria* spp. and *Staphylococci*.⁹ Likewise, moist

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skin sites, including the armpit, inner elbow and inguinal crease, are dominated by *Corynebacteria* spp., whereas dry skin sites such as the volar forearm, hypothenar palm and buttock accommodates a mixed population of bacteria, with greater prevalence of β -*Proteobacteria* and *Flavobacteriales*.⁹ In addition, analysis of the skin microbiota from monozygotic and dizygotic twins and their mothers has revealed that the microbial diversity of the skin is significantly influenced by age and skin pigmentation.^{10,11}

The initial microbial colonization of the skin in infants is influenced by the route of delivery. Babies delivered vaginally acquire a microbiota that is similar to that of the mother's vagina whereas the microbiota of babies delivered by caesarean section resembles that of the skin.¹² Early occupation of the skin by specific microbes can trigger local activation of the host immune system. For example, colonization of the skin by *S. epidermidis* in neonates is associated with induction of *S. epidermidis*-specific FOXP3⁺ T_{reg} cells, although this immune response is not observed in the adult skin.¹³ As humans mature from infancy to adulthood, physiologic changes occur in the skin leading to significant shifts in the microbiota. During adolescence, the microbiota is dominated by lipophilic bacteria which reflects sexual maturation and the associated increase in activity of hormone-stimulated sebaceous glands.¹⁴

The resident microorganisms regulate skin immune function

The skin is the largest organ at the interface between the external environment and host tissues. The epidermis located on the skin surface is important in maintaining the physical and immunological barrier of the skin. This barrier function is critical for protection against continuous assaults by foreign and potentially pathogenic organisms.¹⁵ Epidermal keratinocytes produce antimicrobial proteins (AMPs) that exhibit direct bacteriostatic or bactericidal activities against microbes. In the human skin, AMPs are dominated by several peptides including β -defensin 2 and cathelicidin.¹⁶ Although some AMPs are constitutively expressed, production of several AMPs can be controlled by specific members of the skin microbiota including *S. epidermidis* and *Propionibacterium* spp. which in turn promote neutrophil recruitment and killing of pathogens such as *S. aureus*.^{15–18} In addition, complement C5a receptor (C5aR) regulates the expression of cutaneous AMPs, pattern recognition receptors and proinflammatory mediators.¹⁹ Mice deficient in C5aR develop an abnormal skin microbial community with reduced bacterial diversity and altered composition.¹⁹ Conversely, comparison of gene expression profiles in the skin of germ-free mice and conventionally raised mice revealed that the commensal microbiota regulates expression of complement genes in the skin.¹⁹ Although these studies suggest that the complement system regulates the skin microbiota, further studies are needed to understand the underlying mechanism.

CD4⁺ T-helper type 2 cells that are characterized by the expression of interleukin (IL)-4, IL-5, IL-9 and IL-13 promote pathological inflammation associated with asthma and allergic diseases.²⁰ Another cytokine that regulates type II allergic reactions is thymic stromal lymphopoietin (TSLP). TSLP promotes type II allergic reactions through the regulation of IL-3-independent basophil hematopoiesis.^{21,22} Dysregulated production of TSLP is associated with asthma, atopic dermatitis and food allergies in humans.²² In the skin, the commensal microbiota can control adaptive immune responses by regulating the expression of TSLP in keratinocytes.²³ Although the microbiota can limit the expression of TSLP in keratinocytes, commensal microbes do not appear to influence allergic skin inflammation and airway hypersensitivity in an atopic mouse model of inflammation.²⁴ In addition, studies in mice have shown that the skin microbiota is not affected by the absence of B cells and T cells, Langerhans cells, Toll-like receptor or

IL-1 receptor signaling, arguing against a role for adaptive and innate immunity in shaping the skin microbiota.²⁵ Further studies are needed to understand the role, if any, of the microbiota in allergic skin disease.

Staphylococcus epidermidis promotes immune responses against pathogens through IL-1 dependent signaling

Resident skin bacteria provide the first line of defense against potentially dangerous pathogens. In mice, the skin microbiota plays a local role in controlling the inflammatory milieu and fine-tuning the function of resident T lymphocytes via IL-1 receptor signaling.²⁶ *S. epidermidis*, a common colonizer of the human skin, induces the expression of IL-1 α and inhibits the expression of IL-1 receptor antagonist at the same time, thereby promoting production of IL-17A and IFN γ by skin-resident $\gamma\delta$ T cells.²⁶ The production of IL-17A and IFN γ by T cells, in turn, promotes protective immunity against invading pathogens such as the parasite *Leishmania major*.²⁷ IL-17 also regulates protective immunity against *S. aureus* and fungal infections in the skin. For example, humans with chronic mucocutaneous candidiasis who develop autoantibodies specific for IL-17A, IL-17F, and IL-22, or patients with mutations in the genes encoding IL-17F and IL-17RA, suffer from *Candida* infections at mucosal and cutaneous sites as well as *S. aureus* skin infections.^{28,29} IL-17A and IL-17F protect the host against fungal and bacterial infection by inducing the production of chemokines that recruit neutrophils and via local production of AMPs.^{30–32} These observations indicate that specific members of the microbiota promote protective immunity by recruiting and activation of immune cells in the skin.

Dysbiotic microbiota in the skin of AD patients and AD mouse models

Skin colonization by S. aureus is associated with disease severity and flares in AD patients

AD (also known as atopic eczema) is a chronic inflammatory skin disease characterized by intense itching and recurrent eczematous lesions affecting 10–20% of children in western countries.³³ Although AD often begins during the first two years of life, it is also highly prevalent in adults. AD inflicts a substantial psychosocial burden on patients, and increases the risk of food allergy, asthma, allergic rhinitis and other immune-mediated inflammatory diseases.^{34–36} AD is classically regarded as a childhood disorder mediated by an imbalance towards a T-helper-2 (Th2) immune response, leading to enhanced IgE responses to allergens. However, it is now recognized that the pathophysiology of AD is more complex than previously thought. For example, AD is associated with defects in the epidermal barrier that can be explained, at least in part, by inherited mutations in keratinocyte proteins such as filaggrin that increase the susceptibility to AD.³⁷ Another prominent feature of AD is the link between AD lesions and *S. aureus* colonization. Notably, ~90% of AD patients are colonized with *S. aureus* in the lesional skin whereas the great majority of healthy individuals do not harbor the bacterium in the skin.^{5,38} Furthermore, increased *S. aureus* loads in the affected skin correlate with disease flares.^{5,39} 16S rRNA bacterial gene sequencing of sequential skin samples from children with AD has revealed that the bacterial community structure, particularly the proportion of *S. aureus* dramatically changed during AD flares.⁵ The abundance of the skin commensal *S. epidermidis* also significantly increases during AD flares. Additionally, an increase in *Streptococcus*, *Propionibacterium*, and *Corynebacterium* species is also observed after therapy.⁵ These findings indicate that increased colonization by *S. aureus* is characteristic of lesional skin in AD and associated with disease flares.

However, whether the role of *S. aureus* is causative in AD remains to be determined.

Immune reactivity to *S. aureus* in AD patients

Initial studies more than 40 years ago showed that specific IgE against *S. aureus* proteins could be detected in the serum of AD patients.^{40,41} These studies revealed that the presence of specific IgE antibodies against several *S. aureus* antigens was associated with severe skin manifestations in AD patients.⁴² Consistent with these observations, positive immediate and late skin reactivity could be induced in sensitized AD patients with *S. aureus* extracts.⁴² The anti-*S. aureus* IgE reactivity against a variety of bacterial antigens was detected in patients with AD, but not in those suffering from other skin disorders including allergic asthma and rhinoconjunctivitis.⁴² These studies indicate that AD patients exhibit immune response to *S. aureus*. However, the significance of immune reactivity against the bacterium remains unclear, and further studies are required to understand why and how immune reactivity against *S. aureus* is selectively triggered in AD patients but not in other individuals whose skin also harbors this bacterium.

S. aureus colonization in atopic dermatitis mouse models

Several AD mouse models have been developed to understand the pathogenesis of AD. Filaggrin-deficient flaky tail mice (*Flgft/ft*), carry a loss-of-function mutation in the *filaggrin* gene, display altered skin barrier function and develop spontaneous dermatitis that resembles AD.⁴³ The loss-of-function mutations in the *Filaggrin* gene are strong predisposing factors for the development of human AD.⁴⁴ Bacterial entry into the epidermis is increased in the skin of ovalbumin-sensitized *Flgft/ft* mice and that the abundance of *S. aureus* directly correlates with increased expression of IL-4, IL-13, IL-22, TSLP and other cytokines associated with AD.⁴⁵ Taken together, these studies provide a plausible mechanism linking skin barrier defects and *S. aureus* colonization leading to increased production of inflammatory cytokines and exacerbation of AD.

Nc/Nga mice, an inbred mouse strain, is another mouse model of spontaneous AD.⁴⁶ Skin changes closely mimicking those of human AD develop only when Nc/Nga mice are kept under conventional conditions, particularly when the mouse skin is colonized by mites.⁴⁷ DS-Ng mice, another inbred strain, also develop spontaneous dermatitis when maintained under conventional conditions⁴⁸ and the severity of dermatitis correlates with the serum levels of total IgE.⁴⁹ Notably, the lesional skin of DS-Ng mice is markedly colonized with *S. aureus*.⁴⁹

Several genetically engineered mouse models of AD have been developed to study AD pathogenesis. These mutant mice include transgenic mice overexpressing IL-4, IL-31, TSLP and IL-18.^{50–53} Keratinocyte specific IL-4 transgenic mice are spontaneously colonized by *S. aureus* in the skin.⁵⁰ Genetic deficiency of ADAM17, a transmembrane metalloproteinase that cleaves cell surface proteins, is associated with eczematous dermatitis in humans (INFLAMMATORY SKIN AND BOWEL DISEASE, MIM: 614328).⁵⁴ Notably, ADAM17-deficient mice exhibit skin barrier dysfunction and develop dysbiosis characterized by decreased bacterial diversity and increased skin colonization by bacteria including *Corynebacterium mastitidis*, *C. bovis* and *S. aureus* during the onset of eczematous dermatitis.⁵⁵ Treatment with antibiotics that deplete these bacterial species greatly reduces dysbiosis and skin inflammation. Collectively, these studies indicate that some animal models of AD are also characterized by skin colonization by *S. aureus*, showing similarity to human AD. However, the origin and the role of *S. aureus*, a human bacterium, in mouse models of allergic skin disease need to be further investigated.

Eczema in primary immune deficiency disorders

Cutaneous manifestations are common in primary immune deficiency diseases, affecting between 40% and 70% of patients with diagnosed primary immune deficiency. Not only skin infections, but also noninfectious cutaneous manifestations including eczematous lesions are observed in patients with primary immune deficiencies.⁵⁶ In addition to the above mentioned ADAM17-deficiency, hyper IgE syndrome (HIES, MIM: 147060) is a primary immunodeficiency often caused by mutations in STAT3, which is a signal transducer and activator of transcription in immune signaling pathways.^{57,58} The main clinical characteristics of HIES include increased serum IgE levels, eczematous dermatitis, recurrent skin and pulmonary infections by *S. aureus*, and mucocutaneous candidiasis due to impaired Th1 and Th17 responses.⁵⁹ Analysis of the skin microbiota of HIES patients revealed increased abundance of Gram-negative bacteria, particularly *Acinetobacter* spp., and reduced presence of *Corynebacterium* spp., when compared to healthy controls.⁶⁰ Exposure of healthy human primary leukocytes to *Acinetobacter* suppresses the release of tumor necrosis factor α (TNF α), IFN γ and IL-22 in response to *Candida albicans* and *S. aureus*, whereas *Corynebacteria*, a normal skin colonizer, does not.⁶⁰ Thus, STAT3 signaling not only regulates immune responses, but also appears to influence the skin microbiota that in turn can amplify defective immune response against fungal and microbial pathogens.⁶⁰

Specific virulence factors from *S. aureus* associate with AD pathogenesis

PSMs: a family of virulence peptides produced by *S. aureus*

The virulence of *S. aureus* is defined by a large repertoire of factors.⁶¹ These include phenol-soluble modulins (PSMs), a family of peptides regulated by the accessory gene regulatory (Agr) virulence system of *S. aureus*.⁶² PSM peptides form amphipathic α -helical structures capable of forming pores in artificial membranes and are highly cytotoxic to a wide variety of cells including keratinocytes.^{63,64} PSMs also contribute to biofilm development, an activity that may be important for staphylococcal colonization.⁶⁵

S. aureus PSMs are regulated by quorum sensing system

Quorum sensing (QS) in bacteria including *S. aureus* regulates gene expression in response to variation in cell-population density.⁶⁶ Cell to cell communication through auto inducer molecules occurs within and between bacterial species as a strategy for the bacteria to sense neighboring cell density and coordinate gene expression, thereby promoting harmony in the entire bacterial community.⁶⁶ In *Staphylococci*, PSMs are encoded at three different locations in the genome and regulated tightly by QS via the Agr system.⁶⁷ The *agr* loci produce *RNAII* and *RNAIII* transcripts. *RNAII* is produced via an operon of four genes, *agrBDCA*, that encode factors required for the synthesis of auto inducing peptide (AIP) and the Agr-regulatory cascade. AIP, a peptide pheromone, is translated from *agrD* while *AgrB* transports AIP into the extracellular space allowing its binding to the extracellular domain of *AgrC* (Fig. 1). *AgrA* and *AgrC* form a two-component signal transduction system that regulates downstream signaling events including production of *RNAIII*, which regulates virulence factors and also contains embedded *hld* gene sequence that produces δ -toxin.⁶⁸ This regulation is important for the timing of virulence factor expression during infection and the development of acute disease, while low activity of Agr is associated with chronic Staphylococcal infections such as those involving biofilm formation.^{69,70} Although additional

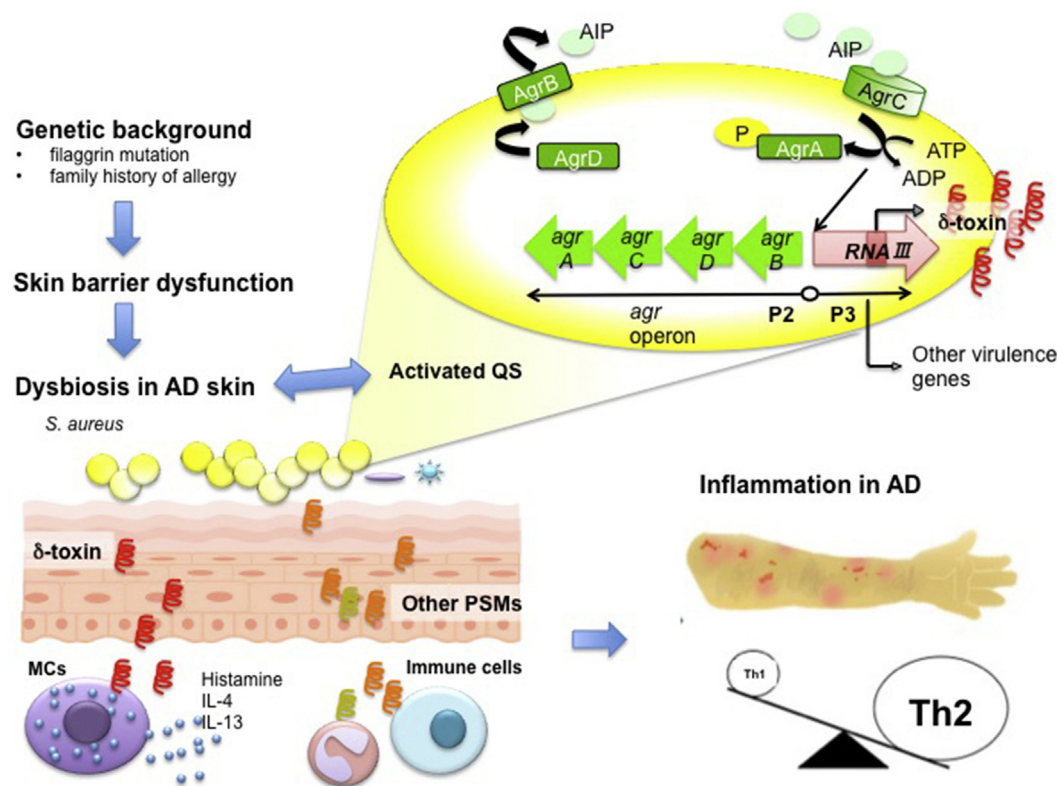


Fig. 1. A model for the role of *S. aureus* QS-regulated Agr virulence in AD pathogenesis. Skin barrier dysfunction due to genetic mutations such as filaggrin mutations and a family history of allergy are associated with increased *S. aureus* colonization in the skin and development of AD. Dysbiotic microbiota in AD skin promotes the production of virulence factors via Agr virulence through QS of *S. aureus*. Agr-dependent δ -toxin induces MC-degranulation and Th2-type skin inflammation. Additional Agr-regulated PSMs may contribute to AD pathogenesis by acting on keratinocytes and dermal immune cells. RNA III, a regulatory RNA induced via Agr, also controls the expression of several downstream virulence factors in *S. aureus*. AD, atopic dermatitis; QS, quorum sensing; AIP, auto inducing peptide.

clinical and basic studies are necessary to determine the role of *S. aureus* in AD, strategies to inhibit QS of *S. aureus* might be beneficial for the treatment of AD.

δ -toxin produced by S. aureus induces mast cell degranulation and promotes allergic skin inflammation

All cutaneous mouse models of skin infection by *S. aureus* have relied on subepidermal inoculation or epicutaneous colonization after physical disruption of the epidermis. Recently, however, we have reported a model of epicutaneous *S. aureus* colonization without physical disruption of the epidermis that triggers robust inflammation in the absence of epidermal disruption has been developed.⁶³ Using this newly developed model of *S. aureus*-driven skin inflammation that induces Agr virulence, it was discovered that δ -toxin, a PSM peptide also known as PSM γ , induces mast cell (MC) degranulation of membrane-bound cytosolic granules, including histamine, IL-4 and IL-13, leading to the release of a plethora of molecules that are important in triggering Th2 type skin inflammation including IgE production.⁶³ Furthermore, *S. aureus* isolates recovered from the lesional skin of AD patients produced high levels of δ -toxin.⁶³ This discovery not only provides a plausible link between skin *S. aureus* colonization and the pathogenesis of AD, but also identifies a potential mechanism for colonized *S. aureus* to trigger Th2 type skin inflammation, a hallmark of AD.

Concluding remarks

The human skin harbors a diverse community of microorganisms. Selective members of the microbiota regulate local induction

of immune cells and promote protective immunity against pathogens. *S. aureus* selectively colonizes the lesional skin of the AD and increased *S. aureus* colonization correlates with disease severity and disease flares of AD. However, the role of *S. aureus* in AD pathogenesis remains unclear. The QS system of *S. aureus* that regulates virulence factors could play a role in AD pathogenesis. Indeed, δ -toxin, one of the PSM peptides regulated by QS, promotes allergic skin disease by inducing mast cell degranulation and triggering Th2 type skin inflammation including IgE production. Further studies are needed to understand the role of *S. aureus* PSMs including δ -toxin and other QS-regulated virulence factors in the pathogenesis of AD. Additionally, unraveling factors in the skin that promote induction of *S. aureus* virulence factors through QS, and developing strategies to inhibit QS of *S. aureus*, will likely advance the treatment for AD.

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Conflict of interest

The authors have no conflict of interest to declare.

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