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Host-pathogen interactions between the skin and *Staphylococcus aureus*

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Abstract

Staphylococcus aureus is responsible for the vast majority of bacterial skin infections in humans. The propensity for *S. aureus* to infect skin involves a balance between cutaneous immune defense mechanisms and virulence factors of the pathogen. The tissue architecture of the skin is different than other epithelia especially since it possesses a corneal layer, which is an important barrier that protects against the pathogenic microorganisms in the environment. The skin surface, epidermis and dermis each contribute to host defense against *S. aureus*. Conversely, *S. aureus* utilizes various mechanisms to evade these host defenses to promote colonization and infection of the skin. This review will focus on host-pathogen interactions at the skin interface during the pathogenesis of *S. aureus* colonization and infection.

Introduction

Staphylococcus aureus skin infections

S. aureus is a gram positive extracellular bacterium that is responsible for the vast majority of skin infections, including superficial infections such as impetigo and infected abrasions as well as more invasive infections such as cellulitis, folliculitis, subcutaneous abscesses and infected ulcers and wounds [1;2]. A large epidemiological study conducted in the United States found that *S. aureus* skin infections result in 11.6 million outpatient and emergency room visits and nearly 500,000 hospital admissions per year [1]. These *S. aureus* skin infections represent a major threat to public health given the massive numbers of infections as well as the widespread emergence of antibiotic resistant strains such as methicillin-resistant *S. aureus* (MRSA), including hospital- and community-acquired MRSA (CA-MRSA) infections [3-5]. Furthermore, the USA300 isolate, which is the most common community-acquired MRSA strain in the United States, is highly virulent and frequently associated with skin infections [3-5]. In this review, we will describe key interactions between the host and pathogen during *S. aureus* colonization of the skin (and mucosa), which is a risk factor for subsequent infection, and during different types of *S. aureus* skin

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infections that are categorized according to the anatomic site in the skin that is involved. Colonization by *S. aureus* occurs when *S. aureus* exists as a commensal organism on the surface of the skin (or mucosa) without any signs or symptoms of an infection (e.g. warmth, erythema, edema, pain/tenderness and drainage of pus) [6;7]. Impetigo is characterized by honey-colored crusted sores and erosions (and sometimes vesicles) on the surface of the skin and is caused by *S. aureus* infection of the epidermis. Cellulitis appears as a warm and erythematous enlarging plaque that results from a *S. aureus* infection that involves the dermis and subcutaneous layers of the skin [3-5]. Folliculitis clinically presents as follicularly-based erythematous papules and pustules and occurs when one or more hair follicles are infected with *S. aureus* [3-5]. Subcutaneous abscesses (which are also called boils) present as erythematous and edematous nodules that result from a deep *S. aureus* infection of a hair follicle and surrounding skin tissue [3-5]. Ulcers and wounds appear as open sores or craters in the skin. If they become infected, they are often drain purulent material and are surrounded by warmth and erythema as a result of a *S. aureus* infection that involves the deep dermis and subcutaneous tissues in an around the ulcer or wound [3-5].

Architecture of the skin

The skin is an important barrier that protects the body from pathogenic microorganisms encountered in the environment (Fig. 1A). The outermost layer of the skin, the corneal layer, is a unique layer that is not present in other epithelia that are also exposed to the environment such as the gut and lung [8;9]. The corneal layer is comprised of terminally differentiated keratinocytes that are devoid of organelles and contain highly crosslinked keratin fibrils [8;9]. The corneal layer functions as the major physical barrier of the skin. Beneath the corneal layer are the granular, spinous and basal layers of the epidermis. The epidermis is continuously being reformed as keratinocytes migrate from the basal layer to the corneal layer, where they are eventually shed [8;9]. Below the epidermis is the dermis, which is essentially a fibrous stroma consisting of collagen and elastin fibers [8;9]. The dermis can be subdivided into the papillary dermis, which is the uppermost layer between the rete ridges of the epidermis, and the deeper reticular dermis. There are also skin appendages such as sweat glands (eccrine and apocrine), sebaceous glands and hair follicles that span these layers and open onto the skin surface. Finally, the vasculature of the skin includes a superficial and deep plexus, with additional networks around skin appendages. The superficial plexus is comprised of arterioles and venules that are interconnected by capillary loops within the papillary dermis.

In addition to a physical barrier, the skin is also an immunologic barrier. The keratinocytes in the epidermis express pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors that recognize pathogen-associated molecular patterns (PAMPs) of microorganisms [8;9]. After recognition of PAMPs, PRRs trigger production of proinflammatory mediators such as cytokines, chemokines and antimicrobial peptides to initiate early innate cutaneous immune responses [8;9]. These early cutaneous immune responses include activation of the endothelial cells that line the skin vasculature to promote recruitment of immune cells from the circulation to the skin [8;9]. In addition, there are numerous resident immune cells in the skin. In the epidermis there are dendritic cells called Langerhans cells [8;9]. In the dermis, there are dermal dendritic cells, macrophages, mast cells, T and B cells, plasma cells and NK cells [8;9]. Each of these cell types can participate in cutaneous immune responses, including host defense against pathogens and in various immune-based skin diseases such as allergic contact dermatitis, atopic dermatitis and psoriasis [8;9]. In this review, we will focus on the interaction between *S. aureus* and the skin in the pathogenesis of colonization and skin infections.

Host-pathogen interactions during skin colonization

S. aureus frequently colonizes the skin and mucosa of humans. In the United States, it is estimated that approximately 30% of healthy individuals are colonized in the skin or mucosa with *S. aureus* [6]. Colonization by *S. aureus* is determined by host factors and commensal organisms that resist colonization versus *S. aureus* virulence factors that facilitate colonization. It is critical to understand these mechanisms as colonization is an important risk factor for subsequent *S. aureus* infection [7].

Host factors that inhibit colonization

The surface of the skin has constitutive properties that prevent colonization and infection by *S. aureus* (Fig. 1A). First, the surface of the skin has a low temperature and pH that resist microbial growth [10;11]. With particular relevance to *S. aureus*, the epidermal structural component filaggrin has been shown to be broken down during epidermal differentiation into urocanic acid and pyrrolidone carboxylic acid [12]. These breakdown products not only contribute to the low pH of the skin surface but also have been shown to reduce the growth of *S. aureus* and decrease expression of bacterial factors involved in colonization such as clumping factor B (ClfB) and fibronectin binding protein A (FnbpA) (see below) [12]. Second, normal commensal organisms on the skin surface such as *S. epidermidis*, *P. acnes* and *Malassezia* spp. occupy microbial niches, which prevent colonization and invasion by *S. aureus* and other pathogens [10;11]. Skin commensals have also been shown to directly inhibit *S. aureus* colonization of skin and nasal mucosa. For example, *S. epidermidis* secretes a serine protease called Esp, which inhibits colonization by *S. aureus* by destroying *S. aureus* biofilms [13]. *S. epidermidis* also produces phenol-soluble modulins (PSM γ and PSM δ) that have direct antimicrobial activity against *S. aureus* [14]. Finally, *S. epidermidis* activates TLR2 on keratinocytes, leading to production of antimicrobial peptides (e.g. human β -defensin 2 [hBD2], hBD3 and RNase 7), which amplify the immune response and promote killing of *S. aureus* [15;16]. Finally, there are antimicrobial peptides produced by keratinocytes that are present in the corneal layer and on the skin surface that have bacteriostatic or bactericidal activity against *S. aureus*, including hBD2, hBD3, LL-37 (cathelicidin) and RNase 7 [17-20]. The importance of antimicrobial peptides in host defense against *S. aureus* colonization is demonstrated by the increased *S. aureus* colonization of skin lesions of atopic dermatitis, which have been shown to have decreased levels of β -defensins and cathelicidin [21].

S. aureus virulence factors that promote colonization

One important mechanism to promote colonization is *S. aureus* adherence to surface components such as fibrinogen, fibronectin and cytokeratins of nasal epithelium or epidermal keratinocytes. *S. aureus* utilizes microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) to bind to these components, including fibronectin-binding protein A (Fnbp A) and Fnbp B, fibrinogen-binding proteins (ClfA and ClfB), iron regulated surface determinant A (IsdA) and wall teichoic acid (WTA) (Fig. 1B) [22-25]. With particular relevance to *S. aureus* binding to human skin, skin lesions from atopic dermatitis patients, which are highly susceptible to *S. aureus* colonization, have increased Th2 cytokines (such as IL-4) that enhance *S. aureus*-mediated fibronectin and fibrinogen binding [25;26]. In addition, *S. aureus* produces superantigens such as staphylococcal enterotoxins A and B (SEA and SEB) and toxic shock syndrome toxin-1 (TSST-1) that have been shown to skew the cutaneous immune response towards the Th2 cytokine profile, which might contribute to the increased colonization of *S. aureus* in atopic dermatitis [27]. *S. aureus* also has mechanisms to evade host antimicrobial peptide responses. For example, IsdA enhances bacterial cellular hydrophobicity, which renders *S. aureus* resistant to bactericidal human skin fatty acids (which are present in sebum) as well as to β -defensins and cathelicidin [28]. Furthermore, *S. aureus* secretes a protein called

aureolysin, which is an extracellular metalloproteinase that inhibits cathelicidin antimicrobial activity [29]. Taken together, there are a variety of *S. aureus*-derived factors that facilitate binding and survival of *S. aureus* to promote colonization of human nasal mucosa and skin.

Host-pathogen interactions during infection

Cutaneous host defense mechanisms against infection

There are several cutaneous immune responses that have been shown to protect against *S. aureus* skin infections. Keratinocytes and other resident cells in the skin express PRRs that recognize components of *S. aureus* (Fig. 2) [30]. In particular, keratinocytes express TLR2 on the cell membrane, which can heterodimerize with TLR1 or TLR6 to recognize tri-acyl and diacyl lipopeptides (including *S. aureus* lipoteichoic acid), respectively [30]. In addition to TLRs, keratinocytes also express a cytoplasmic PRR, NOD2, which recognizes muramyl-dipeptide, a breakdown product of *S. aureus* peptidoglycan [31]. Triggering of these PRRs results in activation of signaling cascades that leads to production of pro-inflammatory cytokines, chemokines and antimicrobial peptides [32].

Neutrophil recruitment to the site of *S. aureus* infection in the skin is a hallmark of *S. aureus* infections and is required for bacterial clearance (Fig. 3) [33;34]. In a mouse model of *S. aureus* cutaneous infection, mice deficient in IL-1R had impaired neutrophil recruitment to the site of infection in the skin [35]. IL-1R is activated by its ligands IL-1 α and IL-1 β [8;9]. By investigating mice deficient in IL-1 α or IL-1 β , it was found that both IL-1 α and IL-1 β contributed to host defense against a superficial *S. aureus* skin infection whereas IL-1 β largely mediated host defense during a deeper intradermal *S. aureus* infection [36]. These data suggest that both IL-1 α and IL-1 β contribute to host defense against a superficial *S. aureus* skin infections such as impetigo or an infected abrasions whereas IL-1 β plays a predominant host defense role against deeper *S. aureus* skin infection such as cellulitis, folliculitis, subcutaneous abscesses and infected ulcers/wounds. This compartmentalization of IL-1 α and IL-1 β in the cutaneous immune response against *S. aureus* is likely the result of differential expression of these cytokines. Pre-made stores of IL-1 α are released from keratinocytes in response to an infection and induces keratinocytes to produce neutrophil chemokines, such as CXCL1, CXCL2 and IL-8 [37]. In contrast, IL-1 β is induced by many different cell types during an infection in the skin [8;9]. Furthermore, IL-1 β release during a *S. aureus* skin infection requires activation of the inflammasome, an intracellular complex of proteins that triggers caspase-1-dependent cleavage of pro-IL-1 β into its active form [38]. In this context, inflammasome activation has been shown to be mediated by *S. aureus* toxins such as α , β , and γ hemolysins and lysozyme digestion of *S. aureus* peptidoglycan [39;40]. Finally, human patients with defects in signaling molecules downstream of IL-1R and TLR family members (MyD88 and IRAK-4) were found to be highly susceptible to *S. aureus* cutaneous infections [41;42], suggesting an important role for the IL-1R signaling pathway in host defense against *S. aureus* skin infections in humans.

In addition to IL-1, recent studies have uncovered a critical role for IL-17 in neutrophil recruitment and host defense against cutaneous *S. aureus* infections (Fig. 3). IL-17, which is predominantly produced by T cell subsets (such as Th17 cells, NKT cells and $\gamma\delta$ T cells) and NK cells, has been known to induce neutrophil recruitment via induction of neutrophil chemokines (CXCL1, CXCL2 and IL-8) and granulopoiesis factors (G-CSF and GM-CSF) [43;44]. Mice deficient in the two major forms of IL-17, IL-17A and IL-17F, were found to develop spontaneous *S. aureus* cutaneous abscesses [45]. Furthermore, mice deficient in the IL-17 receptor (IL-17RA) or mice treated with an anti-IL-17 neutralizing antibody had impaired clearance of a *S. aureus* cutaneous infection [46]. In this mouse model, $\gamma\delta$ T cells in mouse skin were responsible for IL-17 production [46]. In humans, patients with hyper-

IgE syndrome, who suffer from recurrent and severe *S. aureus* skin infections, possess STAT3 mutations that render them deficient in Th17 cells [47]. These findings in mice and humans provide evidence of an important role for IL-17 in host defense against cutaneous *S. aureus* infections.

S. aureus virulence factors that promote infection

During an infection, *S. aureus* has several mechanisms to kill host immune cells and inhibit neutrophil recruitment and antimicrobial function (Fig. 4) [48;49]. There are pore-forming toxins of *S. aureus* that have the capacity to lyse host cells, including (1) the single-component α -hemolysin (or α -toxin) and (2) biocomponent leukotoxins, including γ -hemolysin, Panton-Valentine leukocidin (PVL), leukocidin E/D, and leukocidin M/F-PV-like [48]. Although PVL had initially been epidemiologically linked with CA-MRSA cutaneous infections, α -toxin and phenol-soluble modulins (PSMs) are key *S. aureus* factors that contribute to the enhanced virulence of CA-MRSA skin infections [49;50]. In addition to inducing lysis of host cells, *S. aureus* inhibits neutrophil recruitment by the secretion of chemotaxis inhibitory protein of staphylococci (CHIPS), which interacts with the CD5aR and the formyl peptide receptor (FPR) [48] and extracellular adherence protein (Eap), which reduces endothelial expression of ICAM-1 [51]. *S. aureus* also produces factors that inhibit reactive oxygen species (ROS)-mediated killing by neutrophils, such as the golden carotenoid pigment of *S. aureus* and superoxide dismutase enzymes [52;53]. Taken together, *S. aureus* is well-equipped with several evasion mechanisms to block essential immune-mediated functions during an infection.

Conclusion

In summary, the architecture of the skin provides unique interactions between the host and *S. aureus*. The cutaneous host defense mechanisms that protect against colonization include the epidermal barrier, commensal microorganisms and antimicrobial peptides. During an infection, cells in the epidermis and dermis recognize the pathogen and elicit early innate immune responses, including the recruitment of neutrophils from the circulation. On the other hand, *S. aureus* possesses numerous factors that promote adherence to the skin, evade neutrophil recruitment and function and inhibit immune responses. It is important to understand these host-pathogen interactions for the development of future vaccines and other immune-based therapeutic strategies.

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Highlights

- *S. aureus* is a major cause of skin and soft tissue infections.
- Commensal organisms and antimicrobial peptides protect against *S. aureus* skin colonization.
- Neutrophil recruitment to the skin promotes bacterial clearance.
- *S. aureus* possesses virulence factors that contribute to skin colonization and infection.

Figure 1. Host and pathogen interactions during *S. aureus* colonization

A. The surface of the skin has constitutive properties such as a low temperature and pH, skin commensals and antimicrobial peptides that resist *S. aureus* colonization. The epidermis is composed of layers of keratinocytes, including the corneal, granular, spinous, and basal layers. There are sweat glands, sebaceous glands, and hair follicles that span these layers. In addition, there are many resident immune cells in skin that participate in immune responses, including Langerhans cells in the epidermis and dermal dendritic cells, macrophages, mast cells, T and B cells, plasma cells and NK cells in the dermis. B. *S. aureus* colonization requires adherence to the surface of the skin (and nasal mucosa), which is mediated by *S. aureus* surface components such as fibronectin-binding protein A (Fnbp A) and Fnbp B, fibrinogen-binding proteins (ClfA and ClfB), iron regulated surface determinant A (IsdA) and wall teichoic acid (WTA). Immune evasion is also mediated by IsdA, which evades host antimicrobial responses.

Figure 2. Pattern recognition receptors in host defense against *S. aureus* skin infections

A. Keratinocytes express pattern recognition receptors such as Toll-like receptor 2 (TLR2), which recognizes *S. aureus* lipopeptides and lipoteichoic acid, and nucleotide-binding oligomerization domain containing 2 (NOD2), which recognizes the *S. aureus* peptidoglycan breakdown product muramyl peptide. Both TLR2 and NOD2 signaling leads to activation of NF-κB and other transcription factors that induce transcription of proinflammatory mediators (cytokines, chemokines, adhesion molecules and antimicrobial peptides) involved in cutaneous host defense against *S. aureus*.

Figure 3. IL-1-mediated and IL17-mediated cutaneous immune response against *S. aureus*
S. aureus infection of skin results in production of IL-1 α , IL-1 β and IL-17. These proinflammatory cytokines induce keratinocyte production of antimicrobial peptides (e.g. β -defensins 2 and 3, cathelicidin, RNase 7) and cytokines, chemokines, adhesion molecules and granulopoiesis factors that promote neutrophil recruitment. Recruited neutrophils from the circulation form an abscess that helps control and limit the spread of infection, which is ultimately required for bacterial clearance.

Figure 4. *S. aureus* virulence factors during cutaneous infection

S. aureus secretes several virulence factors that evade host immune defenses. α -hemolysin (or α -toxin), phenol-soluble modulins (PSMs) and Panton-Valentine leukocidin (PVL) have the capacity to lyse host cells, which is a mechanism to evade immune responses. In addition, *S. aureus* secretes factors that inhibit neutrophil function such as chemotaxis inhibitory protein of staphylococci (CHIPS) extracellular adherence protein (Eap). Finally, *S. aureus* possesses factors that inhibit reactive oxygen species (ROS)-mediated killing by neutrophils such as the golden carotenoid pigment of *S. aureus* and superoxide dismutase enzymes.