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Immune and Inflammatory Responses to *Staphylococcus aureus* Skin Infections

Qi Liu¹, Momina Mazhar¹, and Lloyd S. Miller^{1,2,3,4}

¹Department of Dermatology, Johns Hopkins University School of Medicine, Baltimore, MD 21231, USA

²Department of Medicine, Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA

³Department of Orthopaedic Surgery, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA

⁴Department of Materials Science and Engineering, Johns Hopkins University, Baltimore, MD, 21218, USA

Abstract

Purpose of Review—There have been recent advances in our understanding of cutaneous immune responses to the important human skin pathogen, *Staphylococcus aureus* (*S. aureus*). This review will highlight these insights into innate and adaptive immune mechanisms in host defense and cutaneous inflammation in response to *S. aureus* skin infections.

Recent Findings—Antimicrobial peptides, pattern recognition receptors and inflammasome activation function in innate immunity as well as T cells and their effector cytokines play a key role in adaptive immunity against *S. aureus* skin infections. In addition, certain mechanisms by which *S. aureus* contributes to aberrant cutaneous inflammation, such as in flares of the inflammatory skin disease atopic dermatitis have also been identified.

Summary—These cutaneous immune mechanisms could provide new targets for future vaccines and immune-based therapies to combat skin infections and cutaneous inflammation caused by *S. aureus*.

Keywords

Staphylococcus aureus; antimicrobial peptides; Toll-like receptors; inflammasome; T cells; neutrophils

*Corresponding author: Lloyd S. Miller, M.D., Ph.D., Johns Hopkins Department of Dermatology, Cancer Research Building II, Suite 205, 1550 Orleans Street, Baltimore, MD 21231, Phone: (410) 955-8662, Fax: (410) 955-8645, lloydmliller@jhmi.edu.

Conflict of Interest

L.S.M. has received grant support from MedImmune, Pfizer, Regeneron Pharmaceuticals, Moderna Therapeutics, and Boehringer Ingelheim, is a shareholder of Noveome Biotherapeutics, and is on the scientific advisory board for Integrated Biotherapeutics, which are all developing vaccines and therapeutics against *S. aureus* infections and inflammatory skin diseases.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

S. aureus is the most common cause of bacterial skin infections in humans, including infections such as impetigo (superficial infection of the epidermis), cellulitis (infection spreading through dermal and subcutaneous tissue planes), ecthyma (deep ulcerative skin infections), folliculitis (infection of hair follicles), furunculosis (deep hair follicle infections also known as boils), and carbuncles (deep communicating furuncles) as well as abscesses, wounds, and ulcers (1-3). Such infections cause between 11 and 14 million outpatient and emergency room visits and nearly 500,000 hospital admissions per year in the U.S. (4, 5). In addition, the inpatient costs for *S. aureus* skin infections alone range from \$3.2-\$4.2 billion each year in the U.S. (6). Moreover, community-acquired methicillin-resistant *S. aureus* (CA-MRSA) strains are causing severe skin infections in healthy people outside of hospitals and becoming increasingly resistant to antibiotics, which is creating a serious public health threat (7, 8).

An important risk factor for *S. aureus* skin infections is the colonization of mucosa or skin surfaces by *S. aureus*. By microbiologic culture techniques, *S. aureus* colonization is found in the anterior nares in ~30% of the population (and transiently in up to 60-80% of the population), but other sites of colonization (such as the pharynx, rectal mucosa, or the skin in the inguinal region, axillae and peri-rectum) are also common (9, 10). Increased *S. aureus* skin colonization is also associated with the marked skin inflammation in disease flares of atopic dermatitis (AD) (11, 12), which is a chronic and relapsing inflammatory skin disease affecting 15-30% of children and 5% of adults, resulting in annual healthcare costs of \$5.2 billion in the U.S. (13-15). However, the skin inflammation induced by *S. aureus* in AD was previously thought to be primarily caused by many bacterial-derived factors, such as *S. aureus* cytolytic toxins that damage cells and superantigens that activate T cells, which result in the production of proinflammatory cytokines and other inflammatory mediators (16-18).

Neutrophil responses are involved in host defense against *S. aureus* infections, including *S. aureus* skin infections. Indeed, the formation of a neutrophil abscess is a hallmark of *S. aureus* infections, and *S. aureus* is considered a classic pyogenic (pus-forming) infection. The important role of neutrophils is best exemplified by the finding that patients with congenital or acquired defects in neutrophil number or function are highly susceptible to *S. aureus* skin infections and other invasive infections (3). For neutrophils to function they must be recruited from the bloodstream to the site of the *S. aureus* infection where they promote their antimicrobial function via phagocytosis of the bacteria in phagosomes. Bacterial killing within the phagosomes is mediated by reactive oxygen species (ROS), antimicrobial peptides, enzymatic digestion and proteins that sequester essential nutrients, as well as via the formation of neutrophil extracellular traps (NETs) (3). Recently, there has been a focus on T cells and how they engage neutrophilic responses for enhanced clearance of *S. aureus* skin infections.

In an era of declining antibiotic development and rising drug resistance, a greater understanding of the immune responses that protect against *S. aureus* skin infections is needed to guide future host-directed therapies. This is especially relevant as all conventional antibody-based *S. aureus* vaccines have failed in clinical trials, including the recent clinical

trial against bacteremia/deep sternal wound infections after cardiothoracic surgery in which the vaccinated patients who became infected were 5 times more likely to die (19-24). In addition, since *S. aureus* skin colonization is highly associated with flares of skin inflammation as in AD, a better understanding of how *S. aureus* promotes skin inflammation could reveal immune targets to reduce skin inflammation. Recently, there have been significant advances in the cutaneous innate and adaptive immune responses involved in host defense against *S. aureus* as well as advances in mechanisms by which *S. aureus* contributes to aberrant skin inflammation, which will be discussed in the review.

Antimicrobial peptides

Antimicrobial peptides (AMPs) are typically less than 50 amino acids in length and have amphipathic structures that bind selectively to negatively charged bacterial membranes to promote osmotic lysis and bacterial cell death. Several types of AMPs that possess antimicrobial activity against *S. aureus* are produced by different cell types and play an important role in the innate immune response against *S. aureus* infections in the skin (Table I). These include β -defensins such as human β -defensin 1 (hBD1) as well as hBD2 and hBD3 (and their mouse orthologs mouse β -defensin 3 [mBD3] and mBD14), which are produced by keratinocytes and myeloid cells and have bacteriostatic and bactericidal activity against *S. aureus* (25-29). Notably, polymorphisms in hBD1 have been linked with increased *S. aureus* nasal colonization (30). β -defensins are induced by inflammatory signals such as Toll-like receptors (TLRs, see section below) (31-33), inflammatory cytokines such as IL-1 β , IL-17 and IL-22 (34-36), and the activation of growth factor receptors on keratinocytes, as occurs during wound healing (37, 38). Cathelicidin (also called LL-37) is an AMP produced by keratinocytes and myeloid cells (including neutrophils) that has potent antimicrobial activity against *S. aureus* (27, 39, 40). In humans, cathelicidin production by keratinocytes and monocytes/macrophages is greatly induced by exposure to vitamin D as well as various inflammatory mediators (40-42), and vitamin D deficiency has been linked to an increase in *S. aureus* skin infections in children (43). Interestingly, a recent report revealed that if a *S. aureus* skin infection involved the deep dermis, adipocytes were activated to produce cathelicidin, which effectively mediated bacterial clearance (44, 45). Human keratinocytes also produce RNase7 (46, 47) and REG3A (the mouse ortholog Reg3 γ), which are also important in providing antimicrobial activity against *S. aureus* (48, 49). In human sweat, the major AMP produced by eccrine glands is dermcidin, which also has potent activity against *S. aureus* (50, 51). Many of these AMPs, including hBD2, hBD3 and dermcidin, are decreased in the skin of AD patients, which provides an explanation for the increased *S. aureus* skin colonization and *S. aureus* skin infections (especially impetiginization) observed in this disease (27, 50, 52).

In addition to cells that reside in the skin, human neutrophils are rapidly recruited to the site of *S. aureus* skin infection, and they produce α -defensins (also known as human neutrophil peptides [HNPs]) that are secreted into the neutrophil phagosome to promote antimicrobial activity (53). If *S. aureus* bacteria enter the cytoplasm of neutrophils, about 50% of the protein fraction of human neutrophils contain calprotectin (S100A8/S100A9) which sequesters iron, manganese and zinc to inhibit bacterial growth (54, 55).

Many of these AMPs not only have antimicrobial activity but also promote chemotaxis of other immune cells. For example, HBDs have chemotactic activity for dendritic cells and T cells via interactions with chemokine receptors CCR2 and CCR6 (56-58); cathelicidin has chemotactic activity for neutrophils, monocytes and T cells via interaction with formyl peptide receptors (59-61); and HNP3 has chemotactic activity for macrophages, dendritic cells and T cells (62). Therefore, multiple different AMPs are produced by keratinocytes and stromal and resident immune cells in the skin as well as recruited neutrophils and other immune cells, which all contribute to host defense against *S. aureus* skin infections.

Pattern recognition receptors

Pattern recognition receptors (PRRs) are host cell receptors that recognize pathogen associated molecular patterns (PAMPs) found on microorganisms, which enable PRRs to recognize foreign microbial components and initiate host defense responses. These PRRs activate different signaling pathways that ultimately result in the production of cytokines, chemokines, adhesion molecules and AMPs involved in host defense. Several PRRs have been implicated in the recognition *S. aureus* components, especially certain TLRs and nucleotide-binding oligomerization domain-containing protein 2 (NOD2) (Fig. 1). Of the 10 known human TLRs, TLR2 is found on the cell membrane. TLR2 heterodimerizes with TLR1 to recognize triacyl lipopeptides or with TLR6 to recognize diacyl lipopeptides, including *S. aureus* lipoteichoic acid (which is diacylated), and interacts with co-receptors CD14 and CD36 which impact ligand specificity (63-65). Gene polymorphisms in TLRs 1, 2 and 6 are associated with increased susceptibility to *S. aureus* skin infections (66), and TLR2-deficient mice have an increased susceptibility to *S. aureus* skin infections (65, 67, 68). TLRs 1, 2 and 6 are found in the cell membrane of a variety of cell types in the skin, including keratinocytes, Langerhans cells, monocytes/macrophages, dendritic cells, mast cells, endothelial cells, fibroblasts, and adipocytes. Thus, many cell types in the skin can recognize *S. aureus* lipopeptides and lipoteichoic acid and contribute to cutaneous host defense (69).

In addition to TLR2, TLR9 is found in endosomal membranes, recognizes double-stranded DNA, primarily induces a type I interferon response and has also been implicated in host defense against *S. aureus* infections. Human TLR9 recognizes CpG motifs of *S. aureus* double-stranded DNA (70). In addition, women with a particular polymorphism in the promoter region of TLR9 resulting in decreased TLR9 expression and persistent *S. aureus* nasal colonization (71). Recently, it was reported that stimulator of interferon genes (STING), a cytosolic DNA sensor (*i.e.*, cyclic guanosine-adenosine synthase [cGAS]), suppressed TLR-induced genes in macrophages *in vitro*, and mice deficient in STING had enhanced clearance of an *S. aureus* skin infection compared with wt mice (72). These findings indicate that STING responds to *S. aureus* DNA in the cytoplasm and has an opposing role in host defense by downregulating TLR-mediated host defense mechanisms against *S. aureus* skin infections.

Another important PRR for *S. aureus* is NOD2 that recognizes the Gram-positive peptidoglycan breakdown product muramyl dipeptide (MDP), including MDP derived from *S. aureus* peptidoglycan (73). In cultured keratinocytes exposed to *S. aureus*, inhibition or

overexpression of NOD2 resulted in more or less *S. aureus* survival respectively that correlated with IL-17C expression (74). Furthermore, mice deficient in NOD2 had an increased susceptibility to an *S. aureus* skin infection, which was mediated in part by reduced expression of IL-6 and IL-1 β that impacted the neutrophilic response (67, 75). Taken together, several PRRs, including TLRs 1, 2, 6 in the cell membrane, TLR9 in endosomal membranes, and STING and NOD2 in the cytoplasm, promote and regulate cutaneous host defense against *S. aureus* skin infections. Importantly, the cellular compartment in which these different PRRs are located and the signaling pathways these PRRs initiate are crucial in how they ultimately contribute to host defense against *S. aureus* skin infections.

Inflammasomes

Our laboratory and others have found a key role for IL-1 β in promoting neutrophil recruitment and host defense against *S. aureus* skin infections (67, 68, 76-78). Although transcription and translation of pro-IL-1 β is induced by PRRs (such as TLR2 and NOD2, as described above), inflammatory cytokines, and other mediators (such as TNF), a second signal typically mediated by inflammasome complexes is required to process pro-IL-1 β into active IL-1 β (as well as pro-IL-18 to active IL-18) (79-81). These inflammasomes form complexes of proteins in the cytoplasm that undergo massive oligomerization, which ultimately results in release of mature and active IL-1 β from the cell and subsequent triggering of IL-1R/MyD88-signaling (79-81). Several reports have found that the NLRP3 (nucleotide binding domain [NOD]-, leucine-rich repeat (LRR)- and pyrin domain-containing 3) inflammasome can be triggered by the creation pores in the cell membrane that lead to potassium (K⁺) efflux in response to the activity of *S. aureus* pore-forming toxins (α -, β -, and γ -toxins, and Panton-Valentin leukocidin [PVL]) and purinergic receptors that recognize ATP produced by damaged cells during an infection (such as P2X7) as well as lysosomal rupture in macrophage cultures *in vitro* and in mouse models of *S. aureus* skin infections *in vivo* (Fig. 2) (77, 78, 82-86). The NLRP3 inflammasome has been shown to be critical for promoting IL-1 β activity at the site of a *S. aureus* skin infection in mice by mediating neutrophil recruitment to the site of infection in the skin (67, 77). Interestingly, NLRP3 inflammasome activity is reduced in lesional AD skin and in keratinocytes in response to Th2 cytokines (*i.e.*, IL-4, IL-5 and IL-13, which are increased in AD affected skin (87)), providing another mechanism for increased *S. aureus* colonization and *S. aureus* skin infections in AD.

T cells in host defense against *S. aureus* skin infections

Although enhancing opsonophagocytosis (*i.e.*, antibody-mediated phagocytosis) by inducing high titers of antibodies against bacterial surface components has been a successful vaccination approach for other bacterial pathogens, this has not been the case for *S. aureus*. Several vaccines targeting opsonophagocytosis by producing antibodies against *S. aureus* cell surface molecules, including capsular polysaccharides 5 and 8, clumping factor A (ClfA) and iron surface determinant B (IsdB), have all failed in human clinical trials (19-21). Although the reason for these failures is not entirely clear, *S. aureus* produces many virulence factors to evade antibody-mediated immune responses (88, 89). More recent

vaccination attempts have alternatively targeted the production of antibodies that neutralize *S. aureus* toxins and virulence factors, and such attempts are currently in various stages of preclinical and clinical development and are reviewed elsewhere (90-93).

However, there has been a major focus on T cell responses, as they might provide an alternative strategy to targeting antibody responses for an effective adaptive immune response to protect against *S. aureus* skin infections and other invasive infections. Several findings in humans have suggested a role for T cells in immunity to *S. aureus* skin infections. These findings include the following: (i) patients with autosomal dominant hyper-IgE syndrome, who are highly susceptible to recurrent *Candida albicans* and *S. aureus* skin infections, were found to have a deficiency in IL-17A- and IL-17F-producing CD4⁺ T helper cells (*i.e.*, Th17 cells) (94); (ii) rare humans identified with IL-17Ra-deficiency or IL-17F-deficiency who have an increased susceptibility to *Candida albicans* infections and a lesser susceptibility to *S. aureus* skin infections (95, 96); (iii) patients with atopic dermatitis who have increased *S. aureus* skin colonization and *S. aureus* impetiginization and skin infections have increased Th2 cells and cytokines in their affected skin (16-18); and (iv) patients with HIV disease who are highly susceptible to *S. aureus* skin infection that is associated with decreased CD4⁺ T helper cells in their blood (97, 98). Similarly, in mouse models of *S. aureus* skin infections, IL-17A and IL-17F (primarily produced by $\gamma\delta$ T cells) promote neutrophil recruitment, AMP production and increased *S. aureus* bacterial clearance from the skin (99-103), including a specific role for IL-17A in host defense against repeated *S. aureus* skin infection exposures (104). Mice deficient in both IL-17A and IL-17F also develop spontaneous mucocutaneous *S. aureus* infections (105) and are more susceptible to *S. aureus* nasal colonization (106, 107). However, the findings in humans with primary deficiency disorders such as the aforementioned hyper-IgE syndrome, IL-17Ra-deficiency, IL-17F-deficiency and other disorders with defective IL-17 responses primarily suffer from mucocutaneous candidiasis rather than *S. aureus* skin infections (108), suggesting that mechanisms other than IL-17 responses are crucial for durable protection against *S. aureus* skin infections. Notably, protection against *S. aureus* skin infections in patients with HIV disease was recently found to be more dependent upon IFN γ rather than IL-17 (109). Similarly, mice deficient in both IL-17RA and IFN γ R had more severe spontaneous mucocutaneous *S. aureus* infections than mice deficient in IL-17RA alone (110). Finally, we recently reported that following an initial *S. aureus* skin infection in mice, clonally expanded $\gamma\delta$ T cells in skin draining lymph nodes were capable of mediating long-term memory protection lasting at least 140 days by trafficking from lymph nodes to the infected skin where they produced IFN γ and TNF to enhance the neutrophil response against a subsequent *S. aureus* skin challenge (111). Therefore, the role of T cells in immunity to *S. aureus* skin infections likely involves multiple T cell effector cytokines, including IL-17, IFN γ and TNF (Fig. 3), and these T cell responses could serve as more effective immune mechanisms to target in future vaccine efforts.

A novel mechanism by which *S. aureus* promotes skin inflammation

S. aureus colonization and superficial infection (impetiginization) of the skin is associated with skin inflammation during disease flares of AD, which was previously thought to be caused by the action of *S. aureus* toxins and superantigens (16-18). In particular,

superantigens of *S. aureus* have been shown to skew T cell responses towards Th2 cells that produce IL-4 (112). However, our laboratory and another group simultaneously reported that IL-36R (an IL-1R family member activated by IL-36 α , IL-36 β and IL-36 γ that signals via the IL-1R/TLR signaling adapter molecule MyD88) was required to induce skin inflammation following *S. aureus* exposure to the surface of mouse skin (*i.e.*, epicutaneous exposure) (Fig. 4) (113, 114). The mechanism by which IL-36R promoted skin inflammation involved increased expression of IL-36 α in keratinocytes (in part by the activity of the *S. aureus*-derived toxin phenol-soluble modulin α [PSM α]) that subsequently induced IL-17-producing $\gamma\delta$ and CD4⁺ T cells that were essential for mediating the skin inflammation. These results likely relate to human AD because *IL-36 α* and *IL-36 γ* transcripts were found to be increased in the affected human skin of AD patients (115). In addition, increased IL-17 cytokines and increased numbers of Th17 cells were reported in the skin and peripheral blood from humans with acute AD (116, 117). These findings extend the role of IL-36 cytokines in the skin as a prior study found that humans with loss-of-function mutations in *IL-36RN*, which encodes the IL-36 receptor antagonist (IL-36Ra) develop generalized pustular psoriasis (118), and IL-36 cytokines were subsequently found to be elevated in other forms of psoriasis (119). It should be mentioned that the anatomical site of *S. aureus* exposure of the skin was an important determinant in eliciting differential immune responses. As mentioned above, *S. aureus* epicutaneous exposure in mice resulted in IL-36-mediated skin inflammation (Fig 4) (113, 114). By contrast, exposure of *S. aureus* in an intradermal infection model in mice resulted in IL-1 β -mediated neutrophil recruitment and abscess formation (67, 68, 76-78). Taken together, this newly reported role for IL-36 provides a potentially important mechanism by which *S. aureus* exposure to the skin surface induces skin inflammation by triggering T cell IL-17 responses (120). Future work will determine whether IL-36 could serve as a target for future biologic therapies to reduce skin inflammation in AD, psoriasis and perhaps other inflammatory skin diseases.

Conclusions

S. aureus is an important human skin bacterial pathogen, and CA-MRSA strains are spreading through the normal human population, becoming more resistant to antibiotics and creating a serious public health concern. Recent insights have revealed key roles for antimicrobial peptides, TLRs, NOD2, STING, the NLRP3 inflammasome and T cells (and their effector cytokines IL-17, IFN γ and TNF) in cutaneous host defense against *S. aureus* skin infections. In addition, *S. aureus* epicutaneous exposure to the skin resulted in IL-36-mediated, T cell-dependent IL-17 production that induced skin inflammation, providing a newly identified mechanism by which *S. aureus* induces skin inflammation in AD and potentially in other inflammatory skin diseases. These immune mechanisms might serve as more effective immune targets for the future development of vaccines and immunotherapies against *S. aureus* skin infections and *S. aureus*-associated inflammatory skin diseases.

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Orchestrate IL-17-Dependent Skin Inflammation. *Cell Host Microbe*. 2017;22(5):667–77 e5. <https://doi.org/10.1016/j.chom.2017.10.008>. [PubMed: 29120744] References 113 and 114 were the first to demonstrate that *S. aureus* epicutaneous exposure induced IL-36 α production by keratinocytes that stimulated T cells to produce IL-17 to promote skin inflammation. This represents a previously unrecognized mechanism by which *S. aureus* promotes cutaneous inflammation that likely relates to disease flares of atopic dermatitis and potentially other inflammatory skin diseases.

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Figure 1. Pattern recognition receptors that recognize components of *S. aureus*.

Different components of *S. aureus* are recognized by specific pattern recognition receptors (PRRs) that include the following: TLR1/2 heterodimer that recognizes triacyl lipopeptides and is found on the cell membrane; TLR2/6 heterodimer that recognizes diacyl lipopeptides as well as lipoteichoic acid (LTA) and is found on the cell membrane; NOD2 that recognizes the *S. aureus* peptidoglycan (PGN) breakdown product muramyl dipeptide (MDP) and is found in the cytoplasm; TLR9 that recognizes CpG motifs of *S. aureus* DNA and is found in endosomal membranes; and STING that recognizes DNA (cyclic guanosine-adenosine synthase [cGAS]) and is found in the cytoplasm. TLRs and NOD2 lead to inflammatory signaling pathways such as the activation of NF- κ B (nuclear factor- κ B) that leads to production of proinflammatory cytokines, chemokines, adhesion molecules and antimicrobial peptides involved in cutaneous host defense against *S. aureus* skin infections. STING has been shown to suppress protective TLR responses against *S. aureus* skin infections and thus serves as PRR that regulates cutaneous host defense mechanisms.

Figure 2. Mechanisms of inflammasome-mediated production of IL- β production during *S. aureus* skin infections.

The production and secretion of IL-1 β during *S. aureus* skin infections requires two signals. Signal 1 involves the transcription of pro-IL-1 β in response to PRRs (such as TLRs and NOD2) and proinflammatory cytokines (such as TNF). Signal 2 involves NLRP3 (nucleotide binding domain [NOD]-, leucine-rich repeat (LRR)-, and pyrin domain-containing 3) inflammasome activation, which results formation of these cytoplasmic complexes of proteins, including the inflammasome adaptor protein ASC (apoptosis-associated speck-like protein containing CARD [caspase activation and recruitment domain]) that undergo massive oligomerization ultimately leading to the processing of pro-caspase-1 to activate caspase-1 that cleaves pro-IL-1 β into active and mature IL-1 β , which then can be secreted from the cell to elicit IL-1R-dependent immune responses. It has been shown that NLRP3 inflammasome activation in response to *S. aureus* can be triggered by potassium (K⁺) efflux, which can be initiated by pore-forming toxins (such as α -, β - or γ -hemolysins and Pantone-Valentine Leukocidin [PVL]), purinergic receptors (such as P2X7 activated by ATP released by damaged cells during infection) and lysosomal rupture during the intracellular digestion of *S. aureus* bacteria in phagocytes such as macrophages.

Figure 3. The role of T cells and effector cytokines in cutaneous host defense against *S. aureus* skin infections.

Following the invasion of *S. aureus* into the skin, components of *S. aureus* are recognized by pattern recognition receptors (PRRs) expressed by keratinocytes and resident immune cells such as dendritic cells and macrophages as well as rapidly recruited immune cells such as neutrophils. These cells produce IL-1 β and other proinflammatory mediators that promote T and B cell immune responses. IL-1 β , in particular, has been shown to activate T cells (Th17 cells and $\gamma\delta$ T cells) to produce IL-17 (*i.e.*, IL-17A and IL-17F). The T cell effector cytokines IL-17A/F, IFN γ and TNF promote antimicrobial peptide production by keratinocytes as well as the production of chemokines, cytokines, adhesion molecules and granulopoiesis factors that promote neutrophil recruitment from the bloodstream to form an abscess to facilitate bacterial clearance. The B cell responses following a *S. aureus* skin infection include antibody production that promotes opsonophagocytosis (*i.e.*, antibody-mediated phagocytosis) by monocytes/macrophages and neutrophils to help facilitate *S. aureus* skin infection clearance.

Figure 4. *S. aureus* induces skin inflammation versus abscess formation depending on the anatomical location of the bacterial exposure in the skin.

Following *S. aureus* exposure to the skin surface (*i.e.*, epicutaneous exposure), keratinocytes produce IL-36 α (in a mechanism dependent upon *S. aureus*-derived phenol-soluble modulin α [PSMa]), which triggers $\gamma\delta$ T cells and CD4⁺ T cells (*i.e.*, Th17 cells) to produce IL-17 that subsequently induces skin inflammation. In contrast, following an *S. aureus* intradermal inoculation, IL-1 β is produced by immune cells (especially neutrophils and monocytes/macrophages), which trigger $\gamma\delta$ T cells and CD4⁺ T cells (*i.e.*, Th17 cells) to produce IL-17 that subsequently induce neutrophil and monocyte recruitment to form an abscess to promote bacterial clearance.

Table I.Antimicrobial peptides with activity against *Staphylococcus aureus*.

Antimicrobial peptides (AMPs)	Cell source	Antimicrobial activity	Other properties	Regulation	References
β -defensins (human β defensins [hBDs])	Keratinocytes Macrophages DCs	hBDs 1 and 2 have weak bacteriostatic activity hBD3 has strong <i>in vitro</i> antimicrobial activity	Chemotaxis of dendritic cells and T cells via CCR2 and CCR6	TLRs and proinflammatory cytokines hBD3: growth factor receptor activation	(25–29, 56–58)
Cathelicidin (LL-37)	Keratinocytes Macrophages Neutrophils Eccrine glands Mast cells Adipocytes	Antimicrobial activity	Chemotaxis of neutrophils, monocytes and T cells via formyl peptide receptors Angiogenesis Wound healing	TLRs, inflammatory cytokines, Vitamin D	(27, 39, 40, 59–61)
RNase7	Keratinocytes	Antimicrobial activity		TLRs and proinflammatory cytokines	(46, 47)
REG3A	Keratinocytes	Antimicrobial activity			(48, 49)
Dermcidin	Eccrine glands	Antimicrobial activity		Constitutive	(50, 51)
α -defensin (human neutrophil peptides [HNPs])	Neutrophils	Antimicrobial activity	Chemotaxis of macrophages, dendritic cells and T cells	Constitutive	(53, 62)
Calprotectin (S100A8/S100A9)	Keratinocytes Neutrophils	Sequesters iron, manganese and zinc		Constitutive and inducible	(54, 55)