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Staphylococcus Aureus and Barrier Immunity: Molecular Crosstalk at Skin and Mucosal Surfaces

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ABSTRACT

Staphylococcus aureus is a common human commensal and opportunistic pathogen that colonizes epithelial surfaces such as the skin, anterior nares, and other mucosal tissues. Although often harmless during asymptomatic carriage, it can cause invasive infection when host defense mechanisms are compromised. Barrier immunity against S. aureus involves more than physical protection and includes coordinated interactions between epithelial cells, innate immune responses, and adaptive immunity. Keratinocytes and epithelial cells recognize microbial signals and respond by producing antimicrobial peptides and inflammatory mediators that promote neutrophil recruitment and activation. Cytokine networks, particularly IL 17–mediated responses, further amplify antimicrobial defense and support barrier integrity. S. aureus has evolved multiple immune evasion mechanisms that facilitate persistence within host tissues. These include toxin-mediated epithelial damage, inhibition of complement activation and opsonization, impairment of neutrophil function, and biofilm formation that protects bacteria from immune clearance. As a result, the outcome of colonization or infection depends on a delicate balance between host barrier defenses, microbial competition within the microbiome, and inflammatory responses. Disruption of this balance can lead to recurrent infections, chronic inflammation, and immune mediated pathology. This review summarizes recent advances in the molecular mechanisms underlying barrier immunity to S. aureus, with particular emphasis on epithelial sensing, neutrophil biology, antimicrobial peptides, and IL 17–centered immune responses. We also discuss emerging translational strategies, including host directed immunotherapies, vaccine development, and microbiome based approaches aimed at preventing colonization and reducing recurrent S. aureus infections.

Keywords

Staphylococcus aureus, Barrier immunity, Neutrophils, IL-17, Antimicrobial peptides, Biofilm, Colonization.

Introduction

Staphylococcus aureus is one of the most successful human-adapted bacteria, capable of existing as a commensal colonizer of epithelial surfaces while also causing diseases ranging from superficial skin and soft tissue infections to pneumonia, bacteremia, osteomyelitis, and sepsis [1,2]. A defining feature of *S. aureus* biology is its dual lifestyle: in many individuals it persists asymptomatically in the anterior nares or on the skin, yet under permissive conditions it can transition into an aggressive pathogen [3,4]. This behavior reflects the complex interplay between bacterial virulence regulation and host barrier immunity.

Barrier tissues are not simply passive surfaces; they are immune-active organs that detect microbial signals through pattern recognition receptors, produce cytokines and chemokines, synthesize antimicrobial peptides (AMPs), and orchestrate recruitment and activation of innate and adaptive immune cells [5]. In the skin, keratinocytes, resident immune cells, fibroblasts, and the microbiota together create a niche that determines whether *S. aureus* is eliminated, tolerated, or allowed to expand [5,6]. In the nasal mucosa, epithelial cells and local immune circuits regulate colonization resistance, AMPs, neutrophil responses, and IL-17-dependent clearance [7].

At the same time, *S. aureus* is a master of immune evasion. It can subvert complement, impair opsonophagocytosis, interfere with neutrophil function, and exploit biofilm growth to persist in hostile environments [8]. Recent studies have also connected *S. aureus* colonization to broader immunological consequences, including IL-23/IL-17 axis activation and autoimmune-like inflammation, underscoring that epithelial colonization is not immunologically neutral [9]. These findings have elevated barrier immunity to a central concept in *S. aureus* pathogenesis and therapeutic design.

This review focuses on the molecular crosstalk between *S. aureus* and host barrier immunity at skin and mucosal surfaces. We emphasize how epithelial sensing, IL-17 pathways, antimicrobial peptides, neutrophil biology, and biofilm-associated immune evasion together shape colonization outcomes and disease progression.

Skin and mucosal surfaces as immune-active barriers

The skin and mucosal epithelium constitute the first line of defense against *S. aureus*. Their protective role depends on multiple layers of defense, including structural integrity, tight junctions, desquamation, secreted antimicrobial factors, and immune surveillance [10]. Unlike sterile internal tissues, barrier surfaces are colonized by diverse microbial communities that influence immune tone and competitive exclusion of pathogens.

Skin barrier immunity

The epidermis provides a physical and biochemical barrier through keratinized layers, tight junctions, and lipid-rich structures. Keratinocytes are highly responsive to microbial cues and can produce IL-1 family cytokines, TNF-related factors, chemokines, and AMPs in response to staphylococcal products [11]. When this barrier is compromised, *S. aureus* gains access to deeper tissues and can trigger local neutrophilic inflammation or chronic skin disease.

Mucosal barrier immunity

At mucosal sites, especially the anterior nares, epithelial cells integrate microbial sensing and immune signaling to prevent stable colonization. IL-17-associated pathways are especially important because they drive epithelial AMP production and enhance neutrophil-mediated clearance [12]. The nasal niche is clinically relevant because persistent carriage is a major reservoir for recurrent endogenous infection and transmission [10].

Barrier dysfunction and disease susceptibility

Barrier defects, including eczema, altered lipid composition, reduced AMP expression, and dysregulated inflammation, increase susceptibility to *S. aureus* colonization and infection [13,14]. The host response can be double-edged: insufficient immunity permits persistence, but excessive inflammation can damage the barrier and further promote colonization and invasion [15].

Molecular sensing of *S. aureus* at epithelial surfaces

Barrier immunity begins with microbial sensing. Epithelial cells detect *S. aureus* through conserved microbial and danger-associated molecular patterns, activating inflammatory and antimicrobial programs [16].

Pattern recognition receptors

Keratinocytes and mucosal epithelial cells express toll-like receptors and other sensing systems that respond to staphylococcal lipoproteins, peptidoglycan fragments, and secreted virulence factors [17]. These pathways induce NF-κB-dependent cytokines and chemokines that recruit immune cells to the infected site.

Inflammasome and IL-1 signaling

IL-1 family cytokines are central to epithelial immunity against *S. aureus*. They promote myeloid recruitment, amplify local inflammation, and support IL-17-associated responses [18]. In some settings, IL-1-driven inflammation is necessary for control, but unregulated IL-1 signaling can contribute to tissue injury.

Epithelial cytokine networks

Epithelial cells exposed to *S. aureus* can produce IL-6, CXCL8/IL-8, CXCL1, CXCL2, and thymic stromal lymphopoietin-like signals that shape neutrophil trafficking and adaptive immune polarization [19]. These mediators determine whether the response remains localized and protective or becomes damaging and chronic.

Neutrophils as central effectors of anti-staphylococcal barrier immunity

Neutrophils are among the most important innate immune cells in protection against *S. aureus* [20]. Their rapid recruitment to sites of colonization or infection is essential for bacterial containment.

Table 1: Key host-defense layers in barrier immunity against *S. aureus.*

Barrier layer	Main host components	Major functions	Representative relevance
Physical barrier	Stratum corneum, tight junctions, mucus, desquamation	Prevent bacterial entry	Skin and nasal mucosa
Epithelial sensing	Keratinocytes, nasal epithelial cells, PRRs	Detect bacterial products and activate signaling	NF-κB, IL-1, chemokines
Antimicrobial layer	Defensins, cathelicidins, other AMPs	Direct bacterial killing and growth restriction	IL-17-induced AMP responses
Innate cellular immunity	Neutrophils, macrophages, resident myeloid cells	Phagocytosis, ROS, NETs, degranulation	Rapid bacterial clearance
Adaptive immunity	Th17 cells, IL-17/IL-22 axis, tissue-resident memory	Sustained mucosal and cutaneous protection	Colonization control
Ecological defense	Commensal microbiota	Colonization resistance	Competition and immune modulation

Recruitment and activation

Keratinocyte-derived chemokines and IL-17-associated signals drive neutrophil mobilization from blood into infected tissue [17]. Once recruited, neutrophils phagocytose bacteria, release reactive oxygen species, degranulate, and form neutrophil extracellular traps (NETs) [21].

Protective and pathological roles

Although neutrophils are essential for defense, they can also cause tissue damage if excessively activated [22]. In the skin, persistent neutrophilic inflammation may contribute to chronic lesions, impaired healing, and autoimmune-like manifestations.

Neutrophil failure in *S. aureus* infection

S. aureus can resist neutrophil killing through multiple mechanisms, including resistance to oxidative stress, toxin-mediated lysis, and biofilm-associated protection [23]. Delayed neutrophil recruitment has been directly shown to facilitate nascent biofilm formation and immune evasion [24].

The IL-17 axis in barrier defense against *S. aureus*

The IL-17 pathway is one of the strongest and most reproducible immune circuits linked to protection against *S. aureus* colonization and skin infection [25].

IL-17-producing cells

Th17 cells, γδ T cells, and other innate-like lymphocytes contribute to IL-17 production at barrier sites [16]. These cells amplify epithelial defense by inducing AMPs and neutrophil-attracting chemokines.

IL-17 and antimicrobial peptides

A key function of IL-17 is to stimulate epithelial AMP production, including molecules that directly kill bacteria or limit colonization [26]. In the nasal mucosa, IL-17A and IL-17F are critical for AMP production and clearance of *S. aureus* colonization [27].

IL-17 in skin colonization and inflammation

A major recent finding showed that *S. aureus* skin colonization can promote SLE-like autoimmune inflammation through neutrophil activation and the IL-23/IL-17 axis [9]. This study highlights the fact that colonization itself can shape immune pathology, especially in genetically or immunologically susceptible hosts.

Antimicrobial peptides: Molecular weapons at epithelial surfaces

AMPs are a key effector mechanism of barrier immunity [16]. These small cationic molecules are produced by epithelial cells and immune cells and can directly damage bacterial membranes or modulate inflammation.

Major AMP families

Important AMP families in barrier defense include defensins, cathelicidins such as LL-37, and related epithelial antimicrobial molecules [16]. Their expression is often enhanced by IL-17 and IL-22 signaling.

Functional role in *S. aureus* control

AMPs can reduce colonization, limit bacterial growth, and prevent transition to invasive disease [28]. Reduced AMP expression, whether due to host genetics, inflammation, or bacterial suppression, is associated with increased susceptibility.

AMP evasion by *S. aureus*

S. aureus can modify its surface charge, secrete proteases, and alter membrane composition to resist AMPs [29]. This is one reason why AMP biology is central to pathogenesis and a valuable therapeutic target.

Immune evasion strategies used by *S. aureus*

A major reason *S. aureus* is such a formidable pathogen is its large repertoire of immune evasion mechanisms [8].

Avoiding opsonophagocytosis

S. aureus expresses surface factors that interfere with antibody and complement-mediated recognition. Protein A is a classic example because it can bind immunoglobulins in a nonproductive orientation [30].

Neutralizing neutrophils

The bacterium produces toxins, leukocidins, and enzymes that impair neutrophil recruitment, survival, and function [31]. These mechanisms are especially relevant at skin and mucosal sites where neutrophils are dominant effectors.

Biofilm formation

Biofilms provide a protected bacterial lifestyle characterized by extracellular matrix production, slow growth, and altered immune recognition [32]. Biofilms reduce antibiotic susceptibility and blunt innate immune access, making them highly relevant for chronic and device-associated infections.

Modulation of inflammatory signaling

By altering host signaling pathways, *S. aureus* can both provoke damaging inflammation and evade effective clearance [8]. This inflammatory manipulation supports persistence and transmission.

Biofilm-associated immune evasion at barrier surfaces

Biofilm formation is a central theme in *S. aureus* persistence, particularly at epithelial surfaces and on damaged tissue [3].

Biofilm as a survival strategy

Biofilms protect bacteria from immune cells, antimicrobials, and environmental stressors. They are especially relevant when host immunity is delayed or ineffective [33].

Neutrophil delay and biofilm initiation

A recent study demonstrated that delayed neutrophil recruitment permits nascent *S. aureus* biofilm formation and immune evasion [24]. This finding directly links a host kinetic defect with bacterial persistence.

Clinical implications

Biofilm-associated infections often recur and are difficult to eradicate. At barrier sites, biofilms may promote long-term colonization and provide a reservoir for invasive disease [34].

Skin colonization, inflammation, and systemic immune consequences

The relationship between colonization and disease is more complex than simple carriage. Colonization can actively reshape host immunity [35].

Recent work showed that *S. aureus* skin colonization promotes SLE-like autoimmune inflammation via neutrophil activation and the IL-23/IL-17 axis [9]. This suggests that persistent epithelial colonization can generate immune outputs beyond local infection, potentially influencing systemic inflammatory phenotypes in susceptible individuals. Such findings broaden the conceptual framework of *S. aureus* pathogenesis from a localized infectious process to a host-microbe immune interaction with systemic consequences.

Microbiome competition and colonization resistance

Barrier immunity operates in the context of the microbiome. Commensal bacteria can suppress *S. aureus* through nutrient competition, bacteriocins, and immune modulation [36]. Conversely, dysbiosis can create ecological space for *S. aureus* overgrowth. The barrier is therefore an immunological and ecological system, not merely a tissue structure.

Potential translational strategies include:

- Microbiome restoration
- Targeted probiotics or commensal replacement
- AMP-enhancing approaches
- Colonization-blocking vaccines
- Host-directed therapies that preserve barrier integrity

Translational opportunities

The molecular understanding of *S. aureus* barrier immunity opens several therapeutic directions.

Host-directed immunotherapy

Modulating IL-17, IL-1, or neutrophil pathways may improve clearance in selected settings, but such strategies require careful balancing to avoid excessive inflammation [37].

Vaccination

A major challenge in *S. aureus* vaccine development is the need to elicit protective immunity without exacerbating inflammation

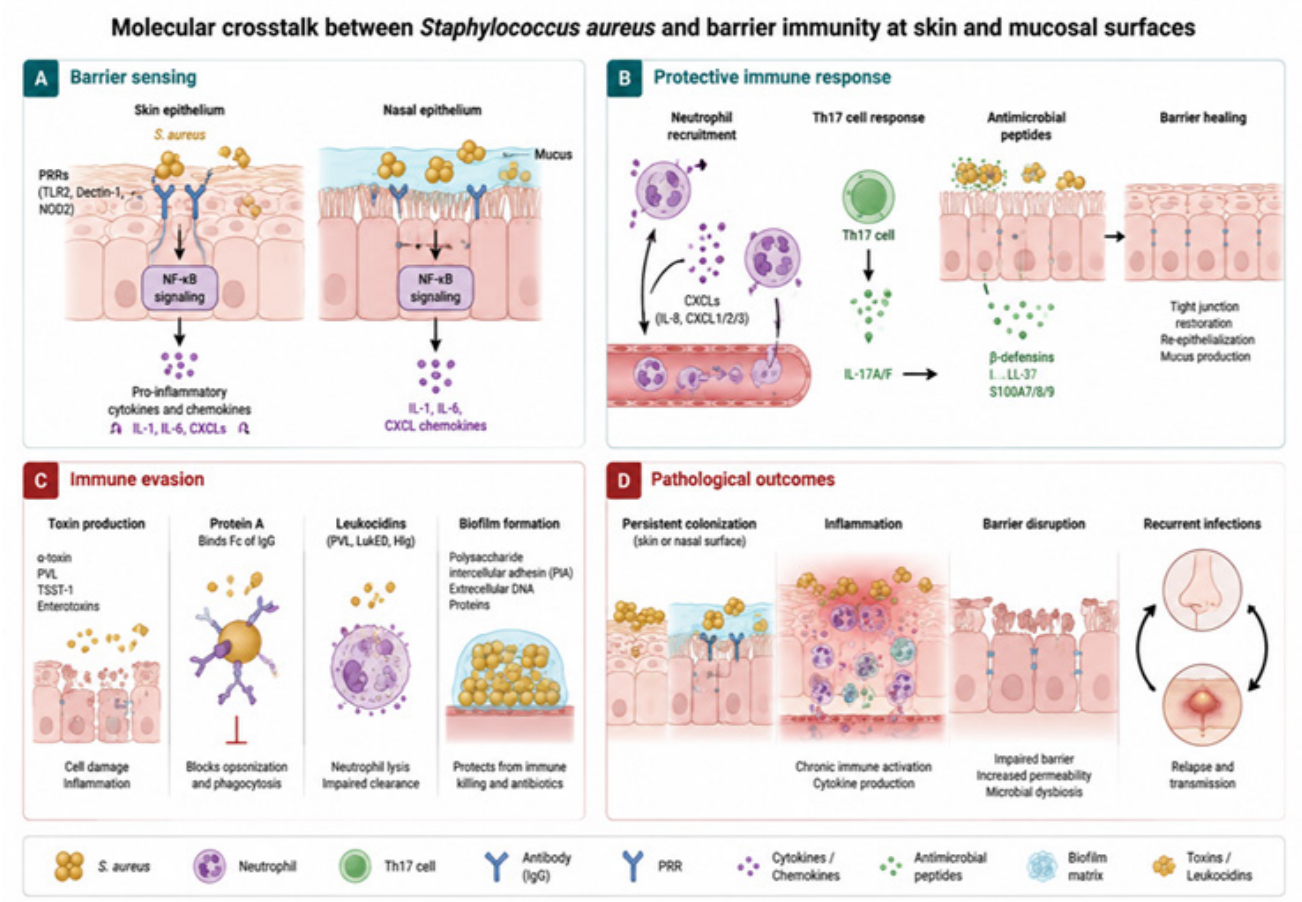

Figure 1: A conceptual model of the molecular interplay between *Staphylococcus aureus* and barrier immunity at skin and mucosal surfaces. Epithelial sensing initiates cytokine and chemokine production, leading to neutrophil recruitment and IL-17-driven antimicrobial peptide induction. *S. aureus* counteracts these responses through immune evasion strategies, including toxin production, opsonization interference, and biofilm formation. The balance between host defense and bacterial persistence determines colonization, infection, and inflammatory outcomes.

Table 2: Major immune evasion strategies of *S. aureus.*

Bacterial strategy	Mechanism	Immune consequence	Review relevance
Opsonization interference	Surface proteins inhibit effective antibody/complement recognition	Reduced phagocytosis	Immune escape
Leukocidins/toxins	Damage or kill neutrophils and other host cells	Impaired innate clearance	Acute infection
Proteases and enzymes	Degrade host antimicrobial factors	Reduced AMP activity	Barrier failure
Biofilm formation	Matrix-mediated protection and altered growth	Immune shielding and persistence	Chronic colonization
Immune signaling modulation	Alters cytokine/inflammatory responses	Dysregulated immunity	Chronic disease

or failing to cover strain diversity [38]. Barrier-immunity-based vaccine design may improve the odds of success.

Anti-biofilm strategies

Compounds that disrupt biofilm formation, restore neutrophil access, or enhance local AMP activity are attractive adjuncts [39].

Personalized risk stratification

Host factors such as barrier defects, immune dysregulation, and microbiome composition may help identify individuals at high risk for recurrent *S. aureus* disease [8].

Conclusion

S. aureus barrier immunity is shaped by a complex molecular dialogue between bacterial virulence programs and host epithelial defense systems. At skin and mucosal surfaces, the outcome of this interaction depends on epithelial sensing, IL-17-driven AMP induction, neutrophil recruitment, and the preservation of tissue integrity [40]. At the same time, *S. aureus* subverts host defenses through immune evasion, toxin production, and biofilm formation [8]. Recent studies have further shown that colonization itself can trigger autoimmune-like inflammation, highlighting the broader immunological impact of this pathogen. Future research should integrate epithelial biology, immunometabolism, microbiome ecology, and single-cell/spatial technologies to define precise mechanisms of colonization resistance and to develop effective host-directed interventions. Because of its strong clinical relevance and rich mechanistic depth, this topic is highly suitable for a high-citation review article in molecular immunology and infectious disease.

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