

Skin Dysbiosis and *Staphylococcus Aureus* Colonization in Psoriasis

Review Article

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ABSTRACT

Background: Psoriasis is a chronic inflammatory skin disease that affects 2-3 % of population and results from a complex interaction of genetic and environmental factors. It significantly impacts patients' quality of life. Recent studies highlighted a strong association between dysbiosis of the skin microbiome, specifically colonization by *Staphylococcus aureus* (*S. aureus*), and the severity of psoriasis. *S. aureus*, particularly toxigenic strains that produce superantigens such as staphylococcal enterotoxins (SEs) and toxic shock syndrome toxin-1 (TSST-1), contributes to the exacerbation of skin inflammation by activating the immune system in an abnormal manner. This review highlights the correlation between dysbiosis and *S. aureus* skin colonization to pathogenesis of psoriasis.

Conclusion: This review explores a significant association between dysbiosis and *S. aureus* colonization, particularly by superantigen-producing strains, and increased psoriasis severity. Accordingly, targeting microbial colonization might offer new therapeutic opportunities for patients with psoriasis.

Key Words: Colonization, dysbiosis, psoriasis, *staphylococcus aureus*, superantigen.

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INTRODUCTION

Psoriasis is a multifaceted, immune-mediated systemic disease influenced by both genetic and environmental factors. It affects 2 to 3% of the global population with significant impact on patients' quality of life. Psoriasis is linked to an inflammatory reaction driven by compromised epidermal integrity, a loss of immune tolerance to the skin microbiome, and an inflammatory response in the skin^[1].

The normal flora of human skin is essential for maintaining immune system homeostasis. This flora varies greatly among individuals due to differences in host-microbe interactions and genetic variations in the stratum corneum. Disruptions in the composition of the skin normal flora can lead to various skin disorders. Consequently, the microbial flora composition of diseased skin in psoriasis patients differs from that of healthy skin^[2].

Dysbiosis of the skin flora increases heavy staphylococcal colonization, providing more opportunities for their toxins to exert harmful effects. Staphylococcal toxins contribute to skin disorders by activating both CD4 and CD8 T-cells and can trigger polyclonal B-cell activation. Unlike typical peptide antigens, staphylococcal

enterotoxins (ETs) and toxic shock syndrome toxin-1 (TSST-1) function as superantigens^[3]. They bind to the T-cell receptor (TCR) outside the peptide-binding groove on the V β region of the TCR, in conjunction with the major histocompatibility complex (MHC) class II molecule of the antigen-presenting cell (APC)^[5]. *Staphylococcus aureus* (*S. aureus*) is one of the most common bacteria colonizing the skin in chronic dermatological conditions such as atopic dermatitis and psoriasis. *S. aureus* exerts its pathological effects on the skin by producing toxins, including superantigens such as Staphylococcal enterotoxins (SEs) [types A to V] and toxic shock syndrome toxin-1 (TSST-1)^[11].

Enterotoxins trigger the Signal transducer and activator of transcription (STAT3), $\gamma\delta$ T cells need STAT3 signals to proliferate and produce IL-17 and IL-22, which are accountable for the skin pathology in psoriasis^[4]. IL-22 plays a vital role in cutaneous immunity against *S. aureus* by enhancing the expression of antimicrobial peptide genes. Consequently, heavy colonization by *S. aureus* results in chronic overexpression of IL-22, leading to pathological effects. Targeting IL-22 and restoring the normal skin microbiome could serve as new strategies for treating psoriasis.

SKIN MICROBIOME

The composition of the microbiome is unique to everyone, and typically, the interaction between microbes and their host occurs in a state of harmony. However, in individuals with genetic predispositions, certain microbes can trigger autoimmune responses. The cutaneous microbiota has been implicated in the induction of psoriatic lesions, exemplified by the association of streptococcal β -hemolytic group A throat infections with guttate psoriasis. T cells isolated from psoriatic lesions exhibit antigen-specific reactivity to streptococcal and staphylococcal peptidoglycan^[6]. Interestingly, the exacerbation of skin inflammation does not correlate with an increase in IL-17-producing CD4+ or CD8+ T cells. Instead, the severity of skin inflammation is primarily attributed to a significant rise in IL-22 produced by skin T cells, particularly CD4+ T cells expressing IL-22. This suggests that IL-22-producing T cells, especially CD4+ T cells, play a crucial role in the worsening of skin inflammation. Additionally, other microorganisms, including *Staphylococcus aureus*, *Malassezia*, and *Candida*, are also implicated in the pathogenesis of psoriasis^[12].

INTESTINAL MICROBIOME

Disordered microbiota in the intestinal tract may play a role in the onset of psoriasis by disrupting immune tolerance. For instance, *Bacteroides fragilis* can promote the differentiation of regulatory T cells (Tregs) through the production of polysaccharide A, thereby regulating the balance between Th1 and Th2 responses. In contrast, segmented filamentous bacteria are known to direct Th17 cell differentiation, while *Clostridium* species support Treg development. Furthermore, multiple studies have demonstrated the presence of intestinal inflammation in psoriatic arthritis, highlighting a clear correlation between psoriasis and inflammatory bowel disease (IBD)^[10].

MICROBIOME COMPOSITION IN PSORIASIS

Interactions between commensal organisms and the host occur through the recognition of microbial-associated molecular patterns (MAMPs) by specific pattern recognition receptors (PRRs), which play a pivotal role in modulating the postnatal immune system. Notably, keratinocytes produce cathelicidins like LL-37 in response to commensal microorganisms. LL-37 binds to the nucleic acids of epithelial cells affected by apoptosis due to various external stressors, such as infections or trauma, particularly in susceptible individuals^[7].

The binding of self-DNA to LL-37 prompts plasmacytoid dendritic cells (pDC) to produce type I interferons, while interactions with self-RNA lead myeloid dendritic cells (mDC) to produce (TNF α) and iNOS^[3]. These cytokines facilitate the differentiation of naive T cells into (Th17) cells, which subsequently generate interleukin-17 (IL-17) and IL-22^[9].

The skin microbiome significance in psoriasis is highlighted by findings showing a correlation between beta-defensin levels and IL-17 concentrations in patients. IL-17 is a key inflammatory cytokine in psoriasis, and treatment with eculizumab, an anti-IL-17 antibody, reduces beta-defensin levels in proportion to Psoriasis Area and Severity Index (PASI) scores. Moreover, IL-17 is shown to downregulate filaggrin and cellular adhesion-related genes, disrupting the skin barrier and fostering a hypoxic environment that increases vascular endothelial growth factor (VEGF) expression, contributing to psoriasis pathology. Elevated levels of the IL-9 receptor (IL-9R) and IL-9 have been found in psoriatic lesions, with IL-9 playing a role in micro angiogenesis and Th17 cell-associated inflammation by inducing angiogenic markers and promoting cytokine secretion. Innate immune defenses, such as TLRs, PRRs, and antimicrobial peptides (AMPs), are implicated in psoriasis pathogenesis, particularly regarding Th1 and Th17 cell responses to skin microbiota^[5]. AMPs, like LL-37 and human β - defensins, contribute not just to pathogen defense but also to chemotaxis, angiogenesis, and keratinocyte proliferation. IL-23 has been demonstrated to upregulate Human Beta-Defensin 2 (HBD-2) expression, promoting keratinocyte activities, cytokine production, and Th17 expansion, thus influencing psoriasis development^[8].

Clinical studies show that psoriatic patients present increased abundance of Firmicutes, decreased Actinobacteria, lower alpha diversity, greater heterogeneity, and diminished microbial stability in their skin microbiomes. The genus *Streptococcus* is the most prevalent in psoriatic skin, with infections from beta hemolytic *Streptococcus pyogenes* linked to both guttate and chronic plaque psoriasis following throat and nasal infections. Tonsillectomy has proven effective for psoriasis associated with *Streptococcus* infections, targeting cutaneous lymphocyte antigen positive (CLA+) tonsillar T cells that express IL-23 receptors, suggesting a mechanism related to Th17, Th22, or Th1 polarization. Streptococcal superantigens, particularly streptococcal peptidoglycan, stimulate T lymphocytes by binding to class II MHC molecules and specific T-cell receptor V β segments, inducing inflammatory cytokine release^[9].

WHEN *S. AUREUS* PREDOMINATES

Epithelial antimicrobial defense mechanisms involve host-defense lipids, peptides, and proteins produced by epithelial and immune cells, which exhibit broad-spectrum antimicrobial activity against pathogens while modulating the innate immune response. Current knowledge of how antimicrobial peptides (AMPs) interact with *Staphylococcus aureus* and their effects on nasal colonization is limited. Nasal secretions from *S. aureus* carriers show elevated levels of α -defensins and human β - defensin 2, potentially creating a favorable environment for colonization. Among AMPs, human β -defensin-3 (hBD-3) demonstrates potent antibacterial effects against *S. aureus*, with its production

stimulated by the organism and skin barrier disruption^[1]. Persistent carriers have significantly lower levels of hBD-3, potentially linked to polymorphisms in the DEFB1 gene promoter. The multifunctional cathelicidin LL-37 also shows efficacy against *S. aureus*, with higher concentrations found in the nasal secretions of carriers, although the general implications remain unclear^[6].

***S. AUREUS* COLONIZATION AND PSORIASIS**

Numerous studies reported elevated *Staphylococcus* levels on the skin of psoriasis patients. A meta-analysis of 21 studies found that colonization of *Staphylococcus aureus* in psoriatic individuals is approximately 4.5 times higher than in healthy controls. *S. aureus* was detected in 64% of lesional skin samples, compared to 30% in non-lesional or healthy skin. Additionally, 60% of psoriatic patients harbored *Staphylococcal* enterotoxins and toxic shock syndrome toxin-1 (TSST-1). Genes encoding these toxins and the regulatory locus *agr* (accessory gene regulator), which promotes *S. aureus* aggregation, may act as superantigens, contributing to psoriasis pathogenesis through HLA-DR expression in keratinocytes and TNF secretion, which trigger inflammatory responses^[4].

In murine experiments, significant Th17 polarization was observed in mice colonized with *S. aureus*, whereas such polarization was absent in those colonized with *Staphylococcus epidermidis* or in uncolonized control mice^[10]. Moreover, high Psoriasis Area and Severity Index (PASI) scores showed a significant correlation with toxin-positive *S. aureus* colonization. *Staphylococcal* peptidoglycan (PG) could also be recognized by psoriatic T-cell lines through interferon-gamma (IFN- γ) activation. Paradoxically, another study reported that *S. aureus* colonization was significantly lower in lesional psoriatic skin compared to controls (3% vs. 27.3%), suggesting that *Staphylococcus* may not be an essential factor in the development of psoriasis.

THERAPEUTIC IMPLICATIONS

Restoring normal flora is increasingly recognized as a potential strategy in the treatment of psoriasis. The skin microbiome plays a crucial role in maintaining skin health and modulating immune responses. Emerging evidence suggests that restoring normal flora may support the skin inherent ability to manage inflammatory processes and could lead to better clinical outcomes in psoriasis patients^[8]. Continued research into the skin microbiome holds promise for the development of novel adjunct therapies that complement existing psoriasis treatments.

Decolonization

Decolonization refers to the process of reducing or eliminating pathogenic organisms, such as *Staphylococcus aureus*, from the skin microbiome. In the context of psoriasis treatment, decolonization strategies aim to restore a healthy balance of skin flora, which can be disrupted

by an overgrowth of harmful bacteria^[7]. By employing decolonization methods, such as topical antiseptics, antibiotics, and skin care regimens designed to reinstate beneficial bacteria, clinicians aim to enhance the skin's overall health and improve treatment outcomes. These approaches may help reduce the severity of psoriatic symptoms and protect against secondary infections.

Research into decolonization techniques has shown promise, suggesting that restoring normal flora can play a supportive role in managing psoriasis by promoting skin barrier function and modulating immune responses. Further investigation is required to optimize these methods and fully understand their impact on psoriasis treatment^[3].

Probiotics

Probiotics, which are live microorganisms that confer health benefits when consumed in adequate amounts, have gained attention as a potential adjunctive treatment in psoriasis management. Research suggests that probiotics can influence the immune system and promote an anti-inflammatory environment, which may help reduce the severity of psoriasis^[5]. Probiotic supplementation, whether orally or topically, aims to enhance the population of beneficial bacteria on the skin, thereby competing with and inhibiting pathogenic organisms such as *Staphylococcus aureus*. Overall, there is a need for large-scale, long-term, blinded, and randomized clinical trials to fully elucidate the therapeutic potential of bacteriotherapy with beneficial commensal strains. Preclinical studies utilizing various murine models have demonstrated that the topical application of *Staphylococcus epidermidis* offers a range of beneficial effects, including anti-inflammatory properties, enhanced wound healing, and suppression of UV-B-induced skin damage^[11].

CONCLUSION

This review explores a significant association between dysbiosis and *S. aureus* colonization, particularly by superantigen-producing strains, and increased psoriasis severity. Accordingly, targeting microbial colonization might offer new therapeutic opportunities for patients with psoriasis.

AUTHORS' CONTRIBUTION

All authors contributed equally to this review. The first draft of the manuscript was written by A.I.D. R.A. and F.Y.F., edited by M.A.K. All authors reviewed and approved the final manuscript.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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