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Mechanisms of microbial pathogenesis and the role of the skin microbiome in psoriasis: A review

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Abstract The pathogenesis of psoriasis may involve a breakdown of immune tolerance to cutaneous microorganisms. Psoriasis is associated with a higher incidence of Crohn disease and periodontitis, two diseases involving impaired tolerance and abnormal immune activation in response to intestinal and oral microbiota, respectively. In addition, guttate and chronic plaque psoriasis are associated with *Streptococcus pyogenes* colonization. The aim of this review is to characterize the microorganisms implicated in psoriasis by examining results of major association studies and possible mechanisms of pathogenesis. Although studies show relative increases in *Streptococcus* and *Staphylococcus* and decreases in *Malassezia* and *Cutibacterium,* they differ in methods of sampling and methods of microbial analysis. As such, no definitive associations between microbes and psoriasis have been found to date. It also remains unclear if changes in the microbiomal composition have a causal association with psoriasis or are simply a consequence of the inflammatory microenvironment. Techniques enabling strain-level analysis rather than species-level analysis of the skin microbiome are likely necessary to determine microbiomal signatures of psoriasis. Future investigations may lead to new diagnostic tests and novel treatments, such as probiotics or bacterial transplantation.

Introduction

The skin microbiome is comprised of a diverse community of microorganisms, most of which are benign commensals that protect against pathogenic organisms and educate the innate

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and adaptive immune responses.[1,2] Psoriasis is a chronic inflammatory disorder characterized by keratinocyte hyperproliferation and thickening of the stratum corneum.[3] A breakdown of immune tolerance to cutaneous microorganisms is implicated in the pathogenesis of psoriasis.[3]

The high incidence of Crohn disease (CD) and periodontitis in patients with psoriasis supports the presence of an abnormal immune response to microbial components in psoriatic skin. After all, CD and periodontitis are due to impaired tolerance and abnormal immune activation in response to intestinal and oral microbiota, respectively.[4] CD also increases the risk of psoriasis fivefold, and their shared immunopathogenic pathways, genetic mutations, and responses to similar therapies imply a common pathogenesis.[4,5]

Investigations into the relationship between the skin microbiome and dermatologic disease in the past have yielded a number of single organism-disease associations—*Staphylococcus aureus* and atopic dermatitis (AD),[6,7] *Cutibacterium acnes* (formerly *Propionibactrium acnes*) and acne,[8,9] and *Malassezia furfur* and seborrheic dermatitis.[10,11] Guttate psoriasis (GP) and chronic plaque psoriasis (CPP) are linked to colonization with *Streptococcus pyogenes,* but other organisms belonging to the psoriasis-associated microbiome remain unknown.

This review reveals the current state of research on the microorganisms implicated in psoriasis. By interpreting results of the major association studies and examining the mechanisms by which microbes might be involved in pathogenesis, we aim to present the findings of recent investigations and facilitate future studies on the microbiome in psoriasis.

Methods

Searches of both Medline and Scopus were conducted using the following search terms: psoriasis, pathogenesis, microbiome, microbiota, flora, bacteria, fungus, virus, colonization, infection, and superantigen. No limits were placed on publication date. In gathering the results of association studies, exclusion criteria consisted of contributions on studies using culture-dependent techniques as well as nonEnglish-language contributions and those not specific to psoriasis. All studies were evaluated by two authors.

Results

Studies show relative increases in *Streptococcus* and *Staphylococcus* and decreases in *Malassezia* and *Cutibacterium.* Methods of sampling psoriatic skin included swabs (three studies), biopsies (one study), scale collection (one study), and curettage (one study). Changes in microbiomal composition were analyzed using 16S and 26S ribosomal marker gene sequencing (five studies) and whole-exome shotgun metagenomics (one study).

Streptococcus

Association studies

Str pyogenes has a strong association with psoriasis.[12–16] Fahlen et al[17] and Gao et al[18] found higher rates of *Streptococcus* in psoriatic lesions compared with normal skin. One study identified *Streptococcus* as the most common genus in both psoriatic and control skin at 33% and 27%, respectively.[17] Another study detected streptococci in 14.3% and 7.1%, respectively.[18] Further studies confirmed these results in a study of three first cousins: one with psoriasis, one with AD, and one healthy control. Comparisons showed higher levels of streptococci in psoriatic skin than in AD or control skin.[19]

Mechanism of action

Str pyogenes is implicated in both GP and CPP and is thought to elicit disease via superantigen-induced T-cell activation and local superantigen effects. *Str pyogenes* throat infections frequently precede GP.[15,16] Streptococcal isolates from throat cultures of patients with GP secrete the superantigen streptococcal pyrogenic exotoxin C.[20] There is also selective accumulation of V-beta 2 T cells in GP lesions.[20,21] Due to the fact that streptococcal pyrogenic exotoxin C is an activator of V-beta 2 T-cell expansion,[20] streptococcal superantigens may induce GP lesions via T-cell activation and polyclonal expansion in lymph nodes that drain the pharynx. Superantigens may also increase T-cell expression of the skin-homing receptor cutaneous lymphocyte antigen, suggesting a mechanism by which activated T cells in the pharynx migrate to the skin.[20,22] Activated T cells in the skin direct their cytotoxic effects against both bacterial and skin-specific antigens. Elevated levels of interferon gamma-producing T-helper 1 (Th1) cells that recognize group A streptococcal cell wall antigens have been detected in both GP and CPP lesions.[23–25] The majority of these Th1 cells specifically target streptococcal peptidoglycan.[26] Whether these Th1 cells originate from the tonsils remains unknown.

Sequence homology between a recombinant streptococcal M protein and the 50-kDa type I keratin[13,20] suggests that streptococcal superantigen-induced T cells target skin-specific antigens via molecular mimicry, inciting chronic inflammatory processes from acute disease. The persistence of superantigen-activated T cells explains the high incidence (70%) of patients with GP who develop CPP.[27] Superantigen-activated T cells may also be primarily autoreactive, directing proinflammatory cytokines and cytotoxicity toward skin cells expressing autoantigens without homology or molecular mimicry between bacterial and skin-specific antigens.

Lastly, streptococcal superantigens present in the dermal layers bind directly to constitutively expressed human leukocyte antigen, DR isotype (HLA-DR) molecules on macrophages, dendritic cells, and keratinocytes that enhance inflammation.[28] The combined migration of activated T cells into the skin and local actions of streptococcal superantigens lead to interleukin-1 and tumor necrosis factor-alpha release, which may elicit or exacerbate psoriatic inflammation.

Staphylococcus

Association studies

Staphylococcus appears to be increased in psoriatic skin compared with healthy skin. In a 16S ribosomal RNA (rRNA) profiling study of 51 matched control, nonlesional, and lesional samples, a combined increased abundance of *Staphylococcus, Streptococcus, Corynebacterium,* and *Cutibacterium* was a potentially useful predictor of psoriasis.[29,30] More recently, whole-genome shotgun metagenomics was performed for the first time in psoriasis using lesional and nonlesional samples from 28 individuals. The results showed increased *Staphylococcus* in psoriatic lesions compared with nonlesional skin. They also identified four *Sta epidermidis* strains present in diseased skin and absent in unaffected skin harboring either staphylococcal secretory antigen A, an extracellular protein implicated in psoriasis, or esxA, a virulence factor of *Sta aureus.* These results suggest the importance of using strain-resolving techniques to capture the strain-level heterogeneity within the psoriasis-associated microbiome.

Although most studies demonstrate increased levels of *Staphylococcus* in psoriasis, some show decreased levels. One study found that staphylococci were less common in psoriasis (5%) than in controls (16%) in both limb and trunk samples, suggesting that the differences were related to disease itself rather than body site. Another study described the psoriasis-induced upregulation of antimicrobial peptides—specifically, cathelicidin antimicrobial peptide, 18 kDa and human beta-defensin 2—against *Sta aureus,* a possible explanation for the low levels of *Sta aureus* in these studies.[31,32]

Mechanism of action

Staphylococcal superantigens may play a role in the formation of psoriatic lesions. *Sta aureus* colonizes psoriatic lesions in 60% of patients, and 60% of isolates secrete staphylococcal enterotoxins and toxic shock syndrome toxin-1 (TSST-1).[33] Patients with toxin-positive *Sta aureus* in the skin have been shown to have a higher Psoriasis Area and Severity Index score than those who have toxin-negative *Sta aureus* or who lack *Sta aureus* colonization.[33,34]

Application of staphylococcal superantigens by patch testing induces significantly more inflammation in unaffected skin of psoriasis patients than in healthy control skin[35]; however, T cells in these patients did not exhibit the V-beta expansions expected from superantigen T-cell interaction.[35] Instead, increased keratinocyte production of tumor necrosis factor-alpha[35] and expression of HLA-DR,[36] a molecule that binds superantigens and activates T cells,[28] were observed in psoriasis patients, but not in normal controls. Application of a mutant TSST-1 protein that did not bind HLA-DR failed to elicit an inflammatory reaction, suggesting indirect T-cell activation via HLA-DR rather than direct T-cell activation by superantigens.[35]

Another study found that many patients do not bear superantigen-producing *Sta aureus* at all.[37] Out of 100 psoriasis patients, *Sta aureus* producing TSST-1 or staphylococcal enterotoxin B were isolated from lesional skin in only five patients and nonlesional skin in four patients. Because all patients had CPP as opposed to GP, bacterial superantigens may not be required to sustain prolonged disease activity.

Malassezia

Association studies

Malassezia is the most abundant fungal genus in the skin and is implicated in psoriasis.[38] As part of normal human skin flora, it inhabits the superficial layers of the stratum corneum, particularly in areas rich in sebaceous glands—the scalp, chest, and back. Patients with scalp psoriasis who received oral ketoconazole showed clinical improvement and decreased *Malassezia* cell counts[39]; moreover, patch testing with heat-killed *Malassezia* on the unaffected skin of 10 patients induced skin lesions clinically and histologically resembling psoriasis.[40]

Despite these findings, data do not support differing levels of *Malassezia* in psoriatic lesions versus normal skin. An rRNA clone library method identified *M restricta* and *M globosa* as the most abundant *Malassezia* species in both psoriasis patients and control subjects; *M furfur* was rare.[41] A similar study in Japanese patients characterized *M restricta* as the most abundant fungal species in the skin.[42] Neither study showed a correlation between Psoriasis Area and Severity Index score and *Malassezia* colonization. Only one study showed a difference in *Malassezia* colonization rates, with psoriatic skin exhibiting lower abundance.[38]

Mechanism of action

The mechanisms by which *Malassezia* may provoke or exacerbate psoriasis have yet to be determined; however, multiple cellular responses to *Malassezia* in psoriasis patients have been observed. *Malassezia*-derived components act as chemoattractants for polymorphonuclear leukocytes in psoriasis. Antibodies to N-acetyl glucosamine moieties of *Malassezia* glycoproteins and T cells specific to *Malassezia* have been isolated from psoriatic lesions.[43–45]

Other studies report the presence of serum antibodies to *Malassezia* proteins and *M furfur*-induced cytokine release from Th1 and peripheral blood mononuclear cells in patients with psoriasis but not in unaffected patients.[46,47] *Malassezia* has also been shown to invade keratinocytes and upregulate expression of transforming growth factor-beta, heat shock protein 70, and integrin chains, all of which are associated with cell cycle acceleration and hyperproliferation of keratinocytes.[48,49]

Higher expression of these molecules in *Malassezia*-colonized psoriatic skin supports a possible association.[48]

Cutibacterium

Association studies

Cutibacteria are common in normal skin and have been found at lower levels in most studies comparing psoriatic lesions to normal skin.[17–19] An increased ratio of *Streptococcus* to *Cutibacterium* has also been observed.[17,18] One

Table 1 Summary of microbiome association studies in psoriasis

Study	Study design			Organism			
	Size	Sampling	Analysis	*Streptococcus*	*Staphylococcus*	*Malassezia*	*Cutibacterium*
Gao et al[18]	013 (P) 6 (C)	Swab	16S rRNA	14.3% (P) vs 7.1% (C)	18.8% (P) vs 15.7% (C)		2.8% (P) vs 19.1% (C)
Fahlen et al[17]	10 (P) 12 (C)	Biopsy	16S rRNA	33% (P) vs 27% (C)	5% (P) vs 16% (C)		0.0001669% (P) vs 0.0254% (C)
Alekseyenko et al[29]	51 (P) 51 (U) 51 (C)	Swab	16S rRNA	Higher * (P)	Higher * (P)		Higher * (P)
Takemoto et al[38]	12 (P) 12 (C)	Scale collection	26S rRNA			47% (P) vs 76% (C)	
Drago et al[19]	1 (P) 1 (AD) 1 (C)	Curettage	16S rRNA	Higher (P)	Lower (P)		Lower (P)
Tett et al[56]	28 (P) 28 (C)	Swab	Shotgun metagenomics		Higher (P)		

AD, atopic dermatitis; C, control; N/A, not available P, psoriasis; P-L, psoriatic lesion; P-NL, nonlesional skin; rRNA, ribosomal RNA; U, unaffected.
* Combined abundance.

study[29] reported a combined increased abundance of *Corynebacterium, Cutibacterium, Staphylococcus,* and *Streptococcus* in psoriatic plaques—the only report suggesting increased *Cutibacterium* in psoriasis.[30]

Mechanism of action

The major species of Cutibacteria, *C acnes,* is a dominant microorganism in normal healthy skin and is thought to serve a protective role via immunomodulatory actions in signaling cells,[19,50] inhibiting colonization by pathogenic microorganisms.[18] A decrease in *C acnes* may impair this skin protective barrier function and thus aggravate disease.[18]

Other microorganisms

Candida albicans is associated with persistence and worsening of skin lesions, particularly in inverse psoriasis.[4,51] The mechanism remains unknown[22]; however, one proposed mechanism is the release of superantigens similar to that seen in *Streptococcus* and *Staphylococcus*.[22]

Rhodobacter produces lycogen, which reduces inflammation and inhibits melanogenesis.[19] Decreased rhodobacteria is associated with impairment of skin protective barrier function and worsening of psoriasis.[19] *Paracoccus* may be increased in psoriatic lesions and is linked to formation of psoriatic pustules.[52]

HIV and human papilloma virus-5 (HPV-5) are also implicated in psoriasis. Psoriasis is more severe in individuals infected with HIV.[53] HIV-infected cells are thought to release substance P, a proinflammatory neuropeptide that stimulates keratinocyte proliferation.[22,54] HPV-5 was detected in 92% of 48 psoriatic skin samples. HPV-5-specific antibodies were isolated from 25% of patients with psoriasis versus 2% to 5% in controls[55]; however, epidermal hyperproliferation promotes HPV-5 keratinocyte infection, and so HPV-5 infection may not play a causative role—psoriasis more likely facilitates HPV-5 infection.[22]

Discussion

Although skin microbiome studies may offer insights into the pathogenesis of psoriasis, conflicting findings preclude meaningful conclusions on the roles of specific microbes (Table 1; Figure 1). Differences in sampling methods contribute to these discrepancies. Three studies used swabs,[18,29,56] whereas only one study[17] used biopsies. Biopsies account for organisms in the epidermis, dermis, and superficial adipose tissue.[57] Microbes may be internalized in epidermal or dermal cells or reside in the pilosebaceous unit, areas likely missed by swabs.[17,57]

Methods of analysis also differed among studies. Until recently, data on the psoriasis-associated microbiome had been derived solely from pregenomic culture-dependent studies,[56] which limit the number and diversity of detectable microbes to those that are cultivable. Culture-independent approaches using ribosomal marker genes, such as 16S and 26S rRNA sequencing, eliminate the bias toward cultivable microbes, yielding a more diverse profile of the microbial community.[58] Most studies in our report used this method of analysis.[17–19,29,38]

Even rRNA sequencing-based methods are limited in their taxonomic resolution.[59] The newest method of analysis, whole-genome shotgun metagenomics—employed by the Human Microbiome Project Consortium,[60] one study[61] in normal skin, and another study[56] for psoriasis—permits analysis at strain-level resolutions.[56,59] Strain-level rather than species-

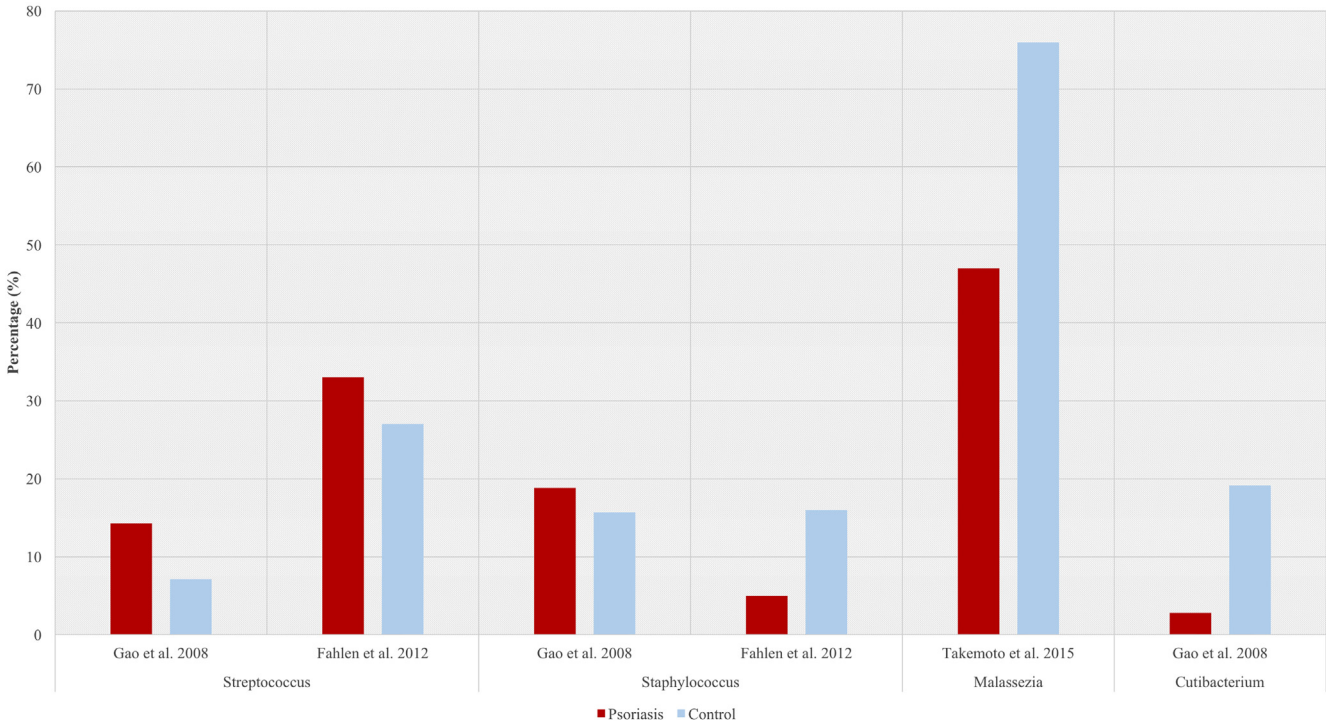

Fig. 1 Summary of microbiome association studies in psoriasis using culture-independent sampling methods. The results of Fahlen et al[17] for *Cutibacterium* are not included due to disproportionately small numbers (0.0001669% in psoriasis vs 0.0254% in controls). Studies that did not report explicit quantitative changes (Drago et al[19]) and those that did not compare psoriatic skin to control skin (Tett et al[56]) are also not included.

level differences may be a key determinant in the pathogenesis of psoriasis.[56]

It remains unclear whether changes in the microbiomal composition play a causative role in psoriasis or merely represent a consequence of the inflammatory microenvironment. For this reason, longitudinal studies examining the dynamics of microbial populations during disease onset and progression are required. Further investigations studying changes at the strain level using shotgun metagenomics are likely necessary to construct microbiomic signatures of psoriasis. These investigations may lead to new diagnostic tests involving microbiome-derived metabolites as well as novel treatments, such as probiotics or bacterial transplantation.[62,63]

Conclusions

1. The pathogenesis of psoriasis may involve a breakdown of immune tolerance to cutaneous microorganisms.
2. Studies show relative increases in *Streptococcus* and *Staphylococcus* and decreases in *Malassezia* and *Cutibacterium*.
3. No definitive associations have been found to date, and it remains unclear if microbiomal changes have a causal association with psoriasis.

Acknowledgments

Conflicts of interest

Dr. Lewis, Mr. Chan, Dr. Hinojosa, Dr. Hsu, and Dr. Feldman declare that they have no conflict of interest.

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