



Interplay Between Skin Microbiota Dysbiosis and the Host Immune System in Psoriasis: Potential Pathogenesis

Xiaoqian Liang[†], Caixin Ou[†], Jiayi Zhuang, Jinsheng Li, Fangfei Zhang, Yuanqiu Zhong and Yongfeng Chen*

Department of Dermatology, Dermatology Hospital of Southern Medical University, Guangzhou, China

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*Correspondence:

Yongfeng Chen
gdcyf@163.com

[†]These authors have contributed
equally to this work and share
first authorship

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Psoriasis is a multifactorial immune-mediated disease. The highly effective and eligible treatment for psoriasis is limited, for its specific pathogenesis is incompletely elucidated. Skin microbiota is a research hotspot in the pathogenesis of immune-mediated inflammatory skin diseases nowadays, and it may have significant involvement in the provocation or exacerbation of psoriasis with broadly applicable prospects. It is postulated that skin microbiota alternation may interplay with innate immunity such as antimicrobial peptides and Toll-like receptors to stimulate T-cell populations, resulting in immune cascade responses and ultimately psoriasis. Achieving a thorough understanding of its underlying pathogenesis is crucial. Herein, we discuss the potential immunopathogenesis of psoriasis from the aspect of skin microbiota in an attempt to yield insights for novel therapeutic and preventive modalities for psoriasis.

Keywords: psoriasis, skin microbiota, immunology, pathogenesis, Th17, inflammation

1 INTRODUCTION

Psoriasis is a chronic systemic inflammatory disease contributed by genetic, immunological, and environmental factors, with a prevalence rate of 2%–4% of the worldwide population (1). Thus far, psoriasis has no known cure, and innovative biological therapies are of great prospects. Emerging evidence supports the vital role of gut microbiota in psoriasis, and the relevant products such as probiotics have facilitated its treatment improvement, with an encouraging reduction in Psoriasis Area and Severity Index (PASI) and lower risk of relapse during follow-up (2, 3). In view of psoriasis being a skin disease, skin microbiota alternation may act more significantly to trigger or exacerbate psoriasis. Current research has put emphasis on the role of skin microbiome in immune-mediated inflammatory skin diseases, including atopic dermatitis, acne vulgaris, vitiligo, and systemic lupus erythematosus (4–8), yet there are certain blank regions in psoriasis. Even though the causal link between skin microbiome and psoriasis remains elusive, evolving knowledge supports its potential role interplaying on T helper cell 17 (Th17) in psoriatic patients, acting on inflammatory cells and cytokine pathways to induce immunity disorder on skin, confirmed by detection of plasma metabolism and bacterial metabolites (9). Furthermore, patients with psoriasis have higher risks of associated comorbidities, such as psoriasis arthritis (PSA), inflammatory bowel disease, periodontitis, cardiometabolic dysfunction, depression, and metabolic syndrome, which may be

due to concurrent susceptible locus and aberrant impaired tolerance in response to microbiota (10–14). With the update of whole-genome shotgun (WGS) metagenomic sequencing (15), the assessment accuracy of bacterial species, community diversity, and gene prediction has been greatly optimized in trials. In the forthcoming period, specific skin microbiome signature might be a promising concept for the diagnostic, therapeutic, and preventive strategies for psoriasis. Novel therapeutic modalities that target or restore the altered skin microbiota are valuable adjuncts for the management of psoriasis and its comorbidities. This article describes the potential pathogenesis of psoriasis concerning how skin microbiota interplay with the host immune system, aiming at providing new insights regarding the immunopathogenesis of psoriasis. A good knowledge about their intrinsic and comprehensive interplay is certainly beneficial to form the basis of innovative treatment selection and may help revolutionize an unprecedented era of biologic therapies for psoriatic patients.

1.1 The Widely Accepted Immunopathogenesis of Psoriasis

The predominant pathogenesis of psoriasis involves a cross-talk between innate and adaptive immunity through interleukin (IL)-23/Th17 axis and immune responses on resident skin cells (16). It is well recognized that overactive responses of IL-17-producing dermal T cells, namely, Th17 cells, play a significant role in triggering psoriasis (17). Stimulated by antimicrobial peptides (AMPs) such as LL-37 produced by epidermis, dendritic cells (DCs) release IL-12, IL-23, etc., to expand the differentiated Th17 cell populations, in which IL-23 acts significantly (18, 19). Alongside Th1 cells, and Th22 cells, Th17 subsets produce pro-inflammatory mediators such as IL-17A, 17F, tumor necrosis factor (TNF)- α , interferon (IFN)- α , and IL-22, leading to hyperproliferation of keratinocytes and immune cell infiltration on skin to amplify psoriatic inflammation (20, 21). Of note, there is a positive feedback loop that the activated and proliferative keratinocytes subsequently release richer AMPs and cytokines such as IL-1, IL-24, CCL20, and CXCL1–3, serving as chemoattractants to facilitate leukocyte recruitment, angiogenesis, and further keratinocyte proliferation in psoriatic skin (22).

Growing experience has revealed that IL-17 could downregulate filaggrin and genes associated with cellular adhesion to induce skin barrier disruption (23), thereby eliciting a hypoxia environment and the upregulated expression of vascular endothelial growth factor (VEGF) as part of the pathological basis of psoriasis (24), which is in agreement with the theory that psoriasis could be triggered in the context of reactive oxygen species (ROS) production and a decrease in antioxidant activity (25). On the other hand, markedly higher IL-9 and IL-9 expression was detected in psoriatic skin lesions. IL-9 would incur micrangium angiogenesis and Th17-associated inflammation by stimulating angiogenic markers (VEGF and CD31) and promote secretion of IL-17, IL-13, IFN- γ , and TNF- α (26). By and large, a psoriasis lesion is provoked by either exogenous skin disruption or endogenous

infiltration of activated immunocytes (22). On the basis of preliminary studies indicating the key regulatory function of nuclear factor- κ B (NF- κ B) in TNF production, cell death, immune infiltration, and hyperkeratosis, NF- κ B and mitogen-activated protein kinase (MAPK) signaling pathways have been identified to organize psoriatic skin in a Th17-associated manner (27, 28).

1.2 Normal Skin Microbial Community

As the powerful protective barrier, skin is home to diverse immune functions and trillions of microorganisms. Generally, skin microbiota consists of resident and transient flora, along with dynamic characteristics across space and time (29), shouldering their responsibility for host homeostasis on skin principally through effector T cells and DCs (30).

Since microbiota composition is altered in accordance with genetics, site, sampling techniques, etc., there is no uniform standard of healthy skin microbiome. Notwithstanding, 90% of individuals have a “core” commensal microbiome encoding unique products, with remarkable ability to calibrate both innate and adaptive immunity, further completed by Human Microbiome Project (31, 32). On healthy skin, the predominant four phyla are as follows: Actinobacteria (51.8%), Firmicutes (24.4%), Proteobacteria (16.5%), and Bacteroidetes (6.3%); and the three most prevalent genera are *Corynebacterium* (22.8%; Actinobacteria), *Propionibacterium* (23.0%; Actinobacteria), and *Staphylococcus* (16.8%; Firmicutes) (33). With regard to fungi, *Malassezia* is the predominant flora (34).

1.3 Psoriasis-Associated Microbial Community

Epithelial immune microenvironment regulates the pathogenic inflammatory loop in psoriasis, in which keratinocytes serve as amplifiers and microorganisms as the primary trigger (35). Cutaneous innate immune defenses, including Toll-like receptors (TLRs), pattern recognition receptors, proteoglycan recognition proteins (PGRPs), and antimicrobial peptides (AMPs) have been implicated as potential contributors to psoriasis *via* Th1/Th17 cell populations in response to cutaneous microbiota (36). TLRs and PGRPs, also called pathogen-recognition receptors (PRRs), are capable of recognizing microbiota and thus altering innate and adaptive immune responses (37). While AMPs, such as LL37, Human β -defensins (HBD), and human S100A7, can not only resist pathogens but also elicit chemotaxis, angiogenesis, and keratinocyte proliferation (22). It has been demonstrated that IL-23 upregulated Human β -defensins (HBD)-2 expression to stimulate keratinocyte proliferation and cytokine production along with Th17 cell expansion, probably involved in the pathogenesis of psoriasis (38).

Ongoing efforts are further completely establishing the pathogenesis of psoriasis and yielding insights for more effective treatment paradigms. Herein, we summarize multiple clinical trials regarding the altered skin microbiota in psoriasis (Tables 1–3), shedding light on how skin microbiota influence host innate and adaptive immunity under the inflammatory

TABLE 1 | Summary of published clinical trials involving skin bacterial microbiota in psoriasis.

Study	Psoriasis Patients			Healthy Controls			Psoriasis type	Psoriasis severity	Sampling	Method
	Number	Mean or Median Age	Sex ratio (M:F)	Number	Mean or Median Age	Sex ratio (M:F)				
(9)	32	38.16 (17–74)	–	29	35.53 (23–54)	–	Severe psoriasis (PASI score ≥ 12)	PASI: 38.96 \pm 2.64 BSA: 24.85 \pm 2.82 PGA: 4.41 \pm 0.13	Swab	16S rRNA (V3–V4)
(39)	28	42.3 \pm 14.1	11:7	26	43.6 \pm 15.1	10:16	Plaque psoriasis	PASI: 11.1 \pm 8.9	Swab	16S rRNA (V1–V3)
(40)	8	–	–	8	–	–	–	–	Swab	16S rRNA
(41)	1	50 \pm 3 (all subjects)	1:0	1	50 \pm 3 (all subjects)	1:0	–	PASI: 20.0	Curettage	16S rRNA (V2–4–8, V3–6,7–9)
(42)	51	49.1 \pm 16.4	39:12	37	–	–	Chronic plaque psoriasis	PASI: 8.7 \pm 10.1 BSA: 9.4 \pm 13.9 PGA: 6.6 \pm 6.9	Swab	16S rRNA (V1–V3)
(43)	10	24–60	5:5	12	34–62	7:5	Chronic plaque psoriasis	–	Biopsy	16S rRNA (V3–V4)
(44)	6	–	3:3	–	–	–	–	BSA: 12 \pm 5.7	Swab	16S rDNA

PASI, Psoriasis Area and Severity Index; BSA, Body Surface Area score; PGA, Psoriasis Global Assessment score.

condition in an effort to unveil the underlying causative association between psoriasis and skin microbiota dysbiosis (**Figure 1**). As a whole, psoriatic lesions trend to decreased taxonomic and species level diversity in terms of both richness and evenness, whereas with greater intragroup variability. Studies proposed that the altered skin microbiota may promote their translocation into the bloodstream or shed some cell components as inflammagens, thereby driving the systemic inflammation in the host. The commensal skin microbes are reported with weak relevance with disease-related transcripts (50).

1.3.1 Bacteria

Cutaneotype 2, which is enriched for Firmicutes and Actinobacteria, is most prevalent in psoriatic subjects (43, 51). While in the trial of Yerushalmi et al. (37), it displayed a higher relative abundance of Firmicutes and lower relative abundance of Actinobacteria, with decreased alpha diversity, more heterogeneity, and reduced stability (**Tables 1, 2**).

1.3.1.1 *Streptococcus*

At the genus level, *Streptococcus* is the most common flora identified in psoriatic skin. Some people developed psoriasis outbreaks following *Streptococcus* infection. Evidence indicates that throat and nasal streptococcal infection, especially beta-hemolytic *Streptococcus pyogenes*, is responsible for guttate psoriasis (GP) and chronic plaque psoriasis (CPP). Tonsillectomy is proven to be a feasible strategy for *Streptococcus*-associated psoriasis, owing to a high frequency of cutaneous lymphocyte-associated antigen (CLA) + tonsil T cells that preferentially express IL-23 receptors, and these cells are postulated to be correlated with Th17, Th22, or Th1 polarization.

Superantigens are powerful T lymphocyte-stimulating agents. Streptococcal peptidoglycan (PG) has been implicated to function as superantigens, binding to class II major histocompatibility complex (MHC) molecules and V β segments of the T-cell receptor to initiate pathological responses and cytokine release in an antigen-specific manner (52). Similarly, streptococcal M proteins and pyrogenic exotoxin A, B, C also act as superantigens, binding directly to HLA-DR molecules on DCs, macrophages, and keratinocytes and activating T-lymphocyte subpopulations that express specific inflammation-associated V β families. It has been testified that selective aggregation of V β 2+ T cells ($p < 0.05$) can be found in skin biopsies from all patients with GP lesions (53).

After recognizing IL-12 and superantigens that resemble M protein and keratin homologous peptides, CLA+ T cells could migrate to skin and subsequently react with streptococcal epitopes or skin-specific epitopes *via* molecular mimicry, resulting in psoriatic inflammation. In addition, CLA+ T cells are detected with decreased levels as psoriasis is ameliorated (54).

A preliminary study has demonstrated that dermal Th1 cell populations in GP and CPP lesions can selectively recognize lower MWt proteins (approximately 20–100 kDa) extracted from group A streptococci (GAS) cell wall, thereby increasingly producing IFN- γ in a self-HLA-DR allele-restricted manner. However, the contents of MWt proteins warrant further research to identify, implying that large proportions of Th1 cells specifically target streptococcal PG to initiate or exacerbate psoriatic inflammation (55). To sum up, psoriatic dermal streptococcal-specific CD4+ T-cell lines proliferate and release IFN- γ , IL-1, etc., in response to streptococcal PG (56). The theory of superantigen-activating T cells provides an explanation for 70% of GP patients who develop CPP (51).

TABLE 2 | Summary of bacterial diversity and taxonomic characteristics on psoriatic skin in clinical trials.

Study	Diversity	Relative Abundance			
		Phyla level	Family level	Genus level	Species level
(9)	α : Not significant	–	–	<i>Lactobacillus</i> : L > H ($p < 0.001$) <i>Luteimonas</i> : L > H ($p = 0.05$) <i>Thermomonas</i> : L > H ($p = 0.02$) <i>Vibrio</i> : L > H ($p < 0.05$)	–
(39)	α : L > U > H ($p = 0.005$) β : Not significant	<i>Actinobacteria</i> : H > U > L <i>Proteobacteria</i> : L > U > H	–	<i>Propionibacterium</i> : H > U > L	<i>Propionibacterium acnes</i> : H > U > L ($p = 0.0002$) <i>Propionibacterium granulosum</i> : H > U > L ($p = 0.014$) <i>Staphylococcus sciuri</i> : U > L > H ($p = 0.032$) <i>Staphylococcus aureus</i> : L > U > H ($p = 0.007$) <i>Staphylococcus pettenkoferi</i> : L > U > H ($p = 0.012$) <i>Staphylococcus epidermidis</i> : H > U > L (not significant)
(40)	α : H > L ($p = 0.04$)	<i>Actinobacteria</i> : H > L ($p = 0.0001$) <i>Firmicutes</i> : L > H ($p = 0.009$)	–	<i>Alloicoccus</i> : L > H ($p = 0.01$), U > H ($p = 0.003$) <i>Aerococcus</i> : L > H ($p = 0.01$) <i>Propionibacterium</i> : H > L ($p = 0.08$) <i>Gallicola</i> : L > H ($p = 0.09$), L > U ($p = 0.04$)	<i>Acinetobacter</i> spp.: L \approx U > H <i>Staphylococcus pettenkoferi</i> : L \approx U > H <i>Streptococcus</i> spp.: L \approx U > H
(41)	–	<i>Firmicutes</i> : H > L <i>Proteobacteria</i> : L > H	<i>Streptococcaceae</i> : L > H <i>Rhodobacteraceae</i> : L > H <i>Campylobacteraceae</i> : L > H <i>Staphylococcaceae</i> : H > L <i>Propionibacteriaceae</i> : H > L	<i>Paracoccus</i> : L > H	<i>Propionibacterium acnes</i> : H > L <i>Staphylococcus aureus</i> : H > L ($p < 0.05$)
(42)	α : H > U > L ($p < 0.05$) β : L > U > H ($p < 0.05$)	<i>Proteobacteria</i> : H > U > L	–	<i>Streptococcus</i> : L > U > H <i>Staphylococcus</i> : L > U > H	–
(43)	α : H > L (not significant) β : H > L	<i>Firmicutes</i> : H > L <i>Proteobacteria</i> : L > H (trunk $p = 0.0113$) <i>Actinobacteria</i> : H > L ($p = 0.034$)	–	<i>Streptococcus</i> : L > H <i>Staphylococcus</i> : H > L <i>Propionibacteria</i> : H > L ($p = 0.061$)	–
(44)	α : L > U > H ($p < 0.001$)	<i>Firmicutes</i> : L > U > H ($p < 0.001$) <i>Actinobacteria</i> : H > U > L ($p < 0.01$) <i>Proteobacteria</i> : H > L \approx U ($p < 0.001$)	–	<i>Streptococcus</i> : L > U > H ($p < 0.001$) <i>Propionibacterium</i> : H > U > L ($p < 0.001$)	<i>Propionibacterium acnes</i> : H > U > L ($p < 0.001$) <i>Staphylococcus aureus</i> : H > U ($p < 0.001$)

L, lesional skin from psoriasis; U, unaffected skin from psoriasis; H, skin from healthy control.

1.3.1.2 *Staphylococcus*

A majority of studies have manifested elevated levels of *Staphylococcus* on skin of psoriatic subjects. According to a meta-analysis involving 21 eligible studies, the presence of *Staphylococcus aureus* colonization in psoriatic patients is approximately 4.5 times higher than that of healthy controls (57). In the trial of Balci et al. (58), *S. aureus* was cultivated from lesional skin in approximately 64% of psoriatic patients, significantly higher than about 30% from non-lesional and healthy control samples, and 60% of patients were detected with *Staphylococcus enterotoxins* (*se*) and toxic shock syndrome toxin-1 (*TSST-1*). Genes encoding *sea*, *seb*, *sec*, *sed*,

Panton-Valentine leukocidin (*PVL*), exfoliative toxin b (*etb*), *TSST-1*, and their carried accessory gene regulatory (*agr*) locus that regulates protease secretion and promotes *S. aureus* aggregation to the skin probably act as superantigen for psoriatic attack (59). Keratinocyte expression of HLA-DR that indirectly acting as a mediator binds superantigens, along with its secreted TNF concurrently trigger inflammatory cascades. In the murine experiment performed by Chang et al. (39), strong Th17 polarization was detected in mice colonized with *S. aureus* while absent in those with *Staphylococcus epidermidis* or un-colonized controls. Moreover, high PASI scores are significantly correlated

TABLE 3 | Summary of published clinical trials involving skin fungus microbiota in psoriasis.

Study	Psoriasis Patients			Healthy Controls			Psoriasis type	Psoriasis severity	Sampling	Method	Diversity	Relative Abundance
	Number	Mean or Median Age	Sex ratio (M: F)	Number	Mean or Median Age	Sex ratio (M: F)						
(45)	12	63.8 ± 10.3 (53–78)	12: 0	12	59.3 ± 11.6 (55–75)	–	–	–	Scales collection	26S rRNA (D1 and D2)	α: L > H (p < 0.05)	<i>Filamentous fungi</i> : L > H <i>Malassezia</i> : H > L <i>M. restricta</i> : L > H (p < 0.05) <i>M. globosa</i> : H > L <i>Non-Malassezia yeast</i> : L > H <i>Malassezia</i> : H > L
(46)	6	35.8 ± 9.2 (23–50)	2: 4	6	42.8 ± 18.9 (27–70)	3:3	–	PASI: 7.6 ± 2.6	Swab	26S rRNA (D1 and D2)	–	<i>Malassezia</i> : H > L
(47)	50	39 (9–76)	28: 22	50	–	–	Psoriasis vulgaris Palmoplantar psoriasis Psoriatic erythroderma	BSA: <3%: 3 subjects 3%–10%: 18 subjects >10%: 29 subjects	Scotch tape	26S rRNA	–	<i>Malassezia</i> : L > U > H (not significant) (Scalp: L > U, p = 0.03) <i>M. japonica</i> : BSA 3%–10% <i>M. globosa</i> : BSA 10%–20% <i>M. slooffiae</i> : BSA 10%–20% <i>Candida</i> : L > U > H
(48)	100	40.47 ± 11.03 (12–72)	44: 56	50	39.90 ± 11.45 (13–63)	22:28	Psoriasis vulgaris	–	Swab Biopsy	26S rRNA (D1 and D2)	–	
(49)	2	33 (F), 58 (M)	1: 1	–	–	–	Mild psoriasis	–	Swab	5.8S rRNA	α: Not significant	Not significant
(34)	3	47.7 ± 11.8 (34–55)	3: 0	5	35.2 ± 11.3 (21–54)	2:3	–	–	Swab	18S rRNA 5.8S rRNA	α: Not significant (p = 0.78)	Not significant

PASI, Psoriasis Area and Severity Index; BSA, Body Surface Area score; PGA, Psoriasis Global Assessment score; L, lesional skin from psoriasis; U, unaffected skin from psoriasis; H, skin from healthy control.

with toxin-positive *S. aureus* colonization (58, 60). Similar to *Streptococcus*, staphylococcal PG could also be recognized by psoriatic T-cell lines through IFN- γ (56).

Paradoxically, in the trial of Elfatoiki et al. (61), *S. aureus* colonization was significantly lower in the lesional psoriatic skin than in controls (3% vs. 27.3%) and indicated that *Staphylococcus* may not be indispensable in provoking psoriasis.

1.3.1.3 Other Bacterial Communities

Consistent with most clinical trials, Yan et al. (62) reported a decreased level of *Propionibacterium* in psoriasis lesions compared to controls. *Propionibacterium* can produce propionate and radical oxygenase (RoxP) that reduce oxidative stress and prevent skin inflammation (59). And its immunomodulatory constituents could protect skin barrier against external aggression (44). Hence, the underrepresentation of *Propionibacterium* may confer incapability to regulate the balance in the oxidant–antioxidant system, resulting in a disordered redox homeostasis. Moreover, *Propionibacterium acnes* strains have been demonstrated to differentially modulate Th17 cells of varied phenotypes in the presence of IL-2 and IL-23 to maintain homeostasis (63).

Corynebacterium is displayed with decreased abundance in trials. Plasmacytoid dendritic cells (pDCs) may have a direct pathological role through IFN production in psoriasis (64). It is speculated that *Corynebacterium* possesses an anti-inflammatory capability for negatively regulating “interferon signaling,” thus, its reduction causes a higher propensity to develop psoriasis onset or exacerbation (50).

With preclinical reports indicating that *Rhodobacter* has the anti-inflammatory capability to produce lycogen to prevent procollagen downregulation and inhibit NF- κ B pathway, its decreased abundance is speculated to influence skin barrier and be involved in the pathogenesis of psoriasis (41).

1.3.2 Fungus

Antifungal agents have yielded great efficacy in scalp psoriasis, suggesting the potential role of skin fungus in provocation or deterioration of psoriasis. Imiquimod (IMQ), a TLR7 agonist, has been applied to promote psoriasis-like skin inflammation via the IL-23/IL-17 axis in murine experiments (65). Hurabielle et al. (66) compared two experimental psoriatic models respectively associated with fungus/IMQ (*Candida albicans*, *Malassezia furfur*, and *Trichophyton mentagrophytes*) and IMQ alone, with the findings

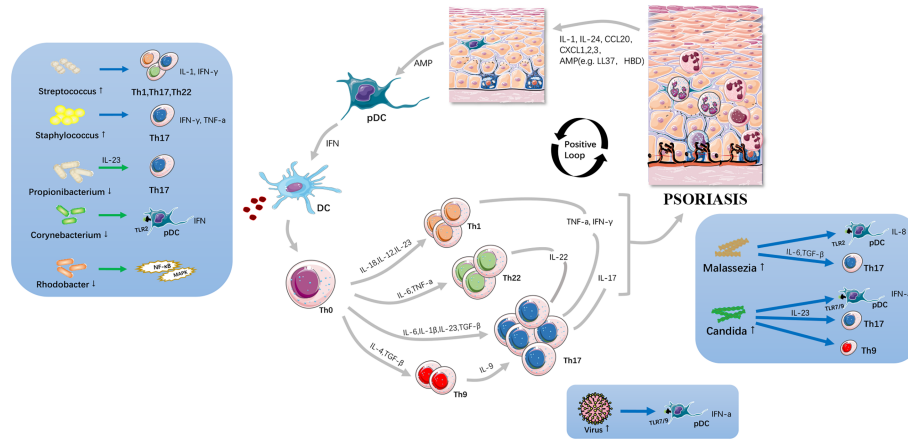


FIGURE 1 | Potential immunopathogenesis of psoriasis. The altered skin microbiota cause skin barrier disruption and act on innate immune system including Toll-like receptors etc.; and, subsequently drive Th17-associated inflammatory cascades. Large amounts of cytokines are secreted, resulting in immunocyte infiltration, angiogenesis and keratinocyte proliferation thus resulting in initiation and progression of psoriasis. Skin microbiota is viewed as a significant trigger and exacerbator in psoriatic inflammation loop.

suggesting that fungal preexposure could significantly allow a better psoriatic model, depending on Th17 responses and neutrophil extracellular traps (NETs) (Table 3).

1.3.2.1 *Malassezia*

Patch testing with inactivated *Malassezia* has been demonstrated to be capable of inducing clinically and histologically psoriasis-like lesions (67). *Malassezia* produces lipases and phospholipases that impair epidermal barrier, chemoattractants for polymorphonuclear leukocytes, as well as cross-reactive allergens leading to sensitization. In the study of Rudramurthy et al. (47), *M. furfur* is the predominant species (70.6%). *Malassezia* yeasts could do damage to the skin and stress predisposed keratinocytes then secondarily amplify AMPs. On the other hand, the study of Baroni et al. (68) showed a TLR2-dependence of IL-8 and HBD-2 in *M. furfur*-treated keratinocytes. Additionally, TLR2 can pair with TLR1 or TLR6, thus leading to large amounts of cytokine induction and ultimately chronic systemic inflammation in psoriasis (68).

Higher serum levels of IgG and significantly lower IgA against *M. furfur* were reported in patients developing psoriasis vulgaris. Antibodies to some constituents of *Malassezia* are also found in psoriatic lesions. It is also suggested that *M. furfur* can upregulate the expression of transforming growth factor (TGF)- β 1, integrin, and heat shock protein 70 (HSP70) in an AP-1-dependent manner in human keratinocytes, thereby modulating cell cycle acceleration and favoring the exacerbation of psoriasis (69).

Previous studies showed that *M. furfur* could invade skin barrier and modulate immunomodulatory cytokine synthesis by downregulating IL-1 α and by inhibiting IL-6 and TNF- α and by upregulating IL-10 and TGF- β 1, thereby enhancing inflammatory responses (70).

1.3.2.2 *Candida*

A meta-analysis revealed that *Candida* possesses significantly higher detection rates on mucosal membranes in psoriasis

compared with controls (71). Another evaluation manifested that *Candida* could be isolated from 15% of psoriatic patients while 4% in controls. The serum IgM, IgG, and IgA against *C. albicans* were also prominently less in patients ($p < 0.05$), whereas no definite evidence has demonstrated the association between serum antibodies and its colonization with PASI ($p > 0.05$) (48). Whereas recent study holds that *Candida* colonization is positively associated with PASI (72).

In a murine experiment, neutrophil infiltration is notably observed in groups with preexposure to *C. albicans*. It is proposed that driven by candidal colonization, polarized IL-17-producing T cells including Th17, Tc17, and $\gamma\delta$ T cells accumulate to concurrently promote IMQ pathology and exacerbate psoriasis-like skin inflammation in a dectin-1/Langerhans cell-dependent manner (66). In response to the skin barrier disruption, LCs recognize *C. albicans* yeasts through the C-type lectin receptor (CLR) dectin-1 and induce Th17 immune responses in the context of IL-6 (69, 70). *C. albicans* would stimulate nociceptors and could induce the neuropeptide calcitonin gene-related peptide (CGRP) via CLR dectin-1, and as a result drive dermal DCs and T cells to produce IL-23 and IL-17, which may lead to the occurrence of psoriasis (73, 74). The study found that in mice deficient in LCs, *C. albicans* is incapable of promoting neutrophil recruitment and IMQ-induced Th17 cell accumulation. Similarly, in mice deficient in dectin-1 or the gene encoding its downstream adaptor molecule CARD9, enhanced inflammation associated with preexposure to *C. albicans* was also abolished. Therefore, a Langerhans cell/dectin-1 axis plays a central role for the activated Th17 pathway in *C. albicans*/IMQ-treated mice (66).

It is also acknowledged that *C. albicans*-associated experimental psoriasis is characterized by enhanced neutrophil response and NET-mediated pathology. NET, the aberrant neutrophil activation/death, could be triggered by skin microorganisms through various downstream effector proteins (75). In the absence of NETosis

inhibitor, psoriatic symptoms are exacerbated (76). NETs activate pDC accumulation to sense microbial DNA *via* TLR9 and TLR7 signaling, thus promoting type I IFN expression and may constitute a fundamental trigger of autoimmune pathology (77); in this process, LL-37 also potentiates TLR9 activation (78). In the clinical trial conducted by Hu et al. (79), NET parameters were positively correlated with PASI.

Nakajima et al. (80) also found that in murine models, *C. albicans* topical association significantly enhanced skin inflammation *via* promoting IL-17A production from CD4+ effector T cells in the skin and lymph nodes. It is also indicated that the surface proteins of *C. albicans* may act like superantigens and trigger Th17 activation through pro-inflammatory cytokines especially IL-23, which are essential for host defense against *C. albicans*. Additionally, IL-17 recruits neutrophils to resist *Candida* through direct phagocytosis, NET formation, and a substantial number of AMPs (81). Th9 cell populations, which produce large amounts of IL-9, increase in psoriatic skin lesions and connect the innate and adaptive immune system against *C. albicans* infection (82). In *C. albicans*/IMQ-treated samples, functional analysis manifested more significant enrichment for cytokine–cytokine receptor interaction along with positively regulatory genes associated with MAPK cascade, which could be seen enriched in human psoriasis as well.

1.3.3 Virus

The role of virus in psoriasis is more obscure. PDCs infiltrate inflammatory psoriatic skin and produce large amounts of IFN- α on viral stimulation *via* TLR-7 and TLR-9, subsequently triggering T-cell cascade to potentiate Th1 cell bias and initiate psoriasis (20).

Previous cohort studies have revealed that people obtaining human papillomavirus (HPV) infection exhibited a 1.177 times greater risk of subsequently developing psoriasis particularly inverse psoriasis than did those in the healthy population, in which age acted as a prominent modifier (83). In the trial of Favre et al. HPV DNA was detected in 91.7% of 48 psoriatic skin samples. HPV5, HPV36, and HPV1 were 89.4%, 84.2%, and 42.1%, respectively, disclosing that psoriasis may be a reservoir for HPV5 (84). Simeone et al. (85) performed a clinical trial on 11 psoriatic patients, with the results showing the presence of HPV5 in 64% psoriatic keratinocytes, and concluded that viral replication in the psoriatic keratinocytes may trigger epidermal hyperproliferation along with antigen stimulation and lead to an autoimmune cascade. In hairs of psoriatic patients, the most prevalent HPV type in all tested samples was HPV-38, followed by HPV-25 (86).

With regard to psoriatic patients infected with hepatitis C virus (HCV), Chun et al. (81) found significantly higher LL37, TLR9, and IFN- γ expression in lesional skin. It has been proposed that the cutaneous load of HCV infection is positively associated with PASI *via* detecting HCV protein and RNA expression in serum (82, 87).

For another, Teng et al. (88) proposed that the inverted CD4+/CD8+ ratio could induce keratinocytes aberrantly to express HLA-DR through IFN- γ production in human immunodeficiency virus (HIV)-associated psoriasis.

1.3.4 Other Microorganisms

In addition to the aforementioned skin microbiota, evolving knowledge indicates that there is still a wide range of microorganisms predisposing patients to developing psoriasis, such as *Helicobacter pylori*, *Porphyromonas gingivalis*, *Chlamydiae*, coronavirus disease 2019 (COVID-19), which presumably function as superantigens to initiate T-cell responses (89).

2 DISCUSSION

Given the concern that the efficacy of off-the-shelf treatment products for psoriasis is limited hitherto, fully understanding the pathogenesis of psoriasis remains a priority for future research. Microbiome research is very prevalent at present. Whether the skin dysbiosis consists in the primary etiological significance or is secondary to psoriasis (or both) has yet to be completely characterized. Moreover, no consensus microorganisms have been directly identified. The generally accepted viewpoint holds that the altered microbiota probably serves potentially as a trigger or exacerbator for psoriasis. This review summarizes the outcome of multiple preceding clinical trials relevant to the altered skin microbiome in psoriatic patients, with a primary focus on mechanisms underlying how they interplay with the host immune system.

The field of the psoriatic skin microbiome is relatively new, and there are few studies on the specific and novel therapies targeting skin microbiome, thus leaving us considerable room to excavate. The manipulation of skin microbiome for treatment efficacy that preliminary research mentioned mostly refers to the conventional therapeutic options such as topical or systemic antibiotics that reduce susceptible bacterial species. Additionally, narrow-band ultraviolet radiation (NB-UVB) and balneotherapy have been demonstrated to induce an alteration of lesional skin microbiota and the improvement of psoriatic progression (90, 91). On the other hand, there is a direct link between gut and skin microbiota (92). Human skin microbiome composition can also be modulated through manipulated therapy of the gut microbiome (93). Researchers hold that probiotics may exert immunomodulatory effects on skin and can strengthen its barrier function against hazardous flora (94). Navarro-López et al. (95) had performed probiotic therapy on 80 psoriatic patients, with PASI75 reaching 66.7% and lower risk of relapse during follow-up compared to placebo group. Moreover, skin microbiome transplantation to diseased skin has yet to be regarded as another possible approach (96). Given the aforementioned encouraging efficacy on blocking disease progression, it is expected that more skin microbiome-related intervention to alleviate or cure this dermatosis would be developed in future research. For example, transdermal drug delivery must produce a milder side effect profile than current systemic medications. Besides, complement therapeutics are under investigation to potentially modulate the skin microbiota and even treat psoriasis (97).

Unlike atopic dermatitis, it is more than likely that the potential pathogens of psoriasis involve multiple species. Much about the potential role of viruses in psoriatic inflammation remains unclear. In future research, the utmost challenge might be to identify the extent to which skin microbiome plays a role in psoriatic

pathogenesis and be modulated, and we should also identify one or several microbes that exert predominant influence on psoriasis, therefore enhancing the accuracy of modulation. Nevertheless, the heterogeneous parameters including genetics, diet, treatment exclusion, and taxonomic levels probably render the results reported in clinical trials less authentic and comparable. Furthermore, even in a single specific trial, the site- and microenvironment-based matching between lesion and control samples might be absent. As discussed, the preliminary studies only elaborate the correlative relationship between skin microbiome and psoriatic state as a whole. In the forthcoming decades, further experimentation to validate their definite association, and performed on isolated microbes, presents a principal direction. For one thing, a new set of standardized analysis protocol, including study population, sampling and processing methodology, would be a useful first step to interpret microbiome data. For instance, healthy people who have a common living background with psoriatic patients ought to be enrolled in a control group to reduce the bias. For another, in terms of taxonomic levels, it is critical to apply strain-level rather than species-level resolution approaches to unravel the microbial signatures associated with psoriasis; particularly, there are still vast unprofiled and undetermined regions about cutaneous viruses. It is proposed that gene transcriptomics is a suitable predictor of disease severity. Nevertheless, there is another tough problem regarding whether the sequence reads in skin swabs could map to specific functional genomes, thus making microorganisms classifiable (98). It still remains difficult to identify the specific driven genes. A substantial number of large-scale prospective longitudinal clinical trials and proof-of-concept experiments in murine models are also required to trace the dynamics of microbial populations during the onset and progression of psoriasis, which may give some enlightenment to predictive approaches for therapeutic responses through particular transcriptomic and microbial biomarkers with disease severity.

Notably, it is hypothesized that skin microbiome composition is associated with the development of psoriatic comorbidities. Initial studies show that its reduced diversity, which may weaken the skin protective function to trigger an immune response, might be a signature for psoriatic patients with a higher risk to develop PSA. It also showed that antibiotics have the potential to reduce the risk of comorbidities in psoriatic patients (96, 99). Whether the skin microbiota is involved in its comorbidity association remains to be further explored. It is expected to develop preventative measures to intervene to halt the progression of PSA.

Taken together, endeavors should be made in seeking out the deeper association between skin microbiome and developing

microbiota-related interventions to mitigate psoriasis, such as selective modulation of isolated microbiota *via* intraindividual or interindividual skin microbiota transplantation, facilitating gut-skin cross-talk *via* prebiotics, and manipulating microbial pathways by targeting microbial metabolites through pharmacologic inhibitors, and hence, eventually improving clinical outcomes of psoriatic patients. In addition, the characteristics of chronic inflammation, along with its relevant metabolic comorbidity, concurrently indicate the significance of metabolomics in psoriasis. The extent to which skin microbiota play a role in the pathogenesis in psoriasis and which it can be modulated is certainly a critical consideration, and the potential function of skin microbiota on regulating global metabolism in psoriasis is a promising field. Hopefully, microbiome-specific targeted treatments or even curative paradigms for this dermatosis will come true in the upcoming period.

3 CONCLUSION

Psoriasis is mediated by immunological and external factors as a commonly seen chronic dermatosis in the population. Given the previous findings, the existing immunopathogenesis for psoriatic inflammation mainly involves IL-23/Th17 axis, along with large amounts of cytokines and immunocytes. Also, skin microbiota could regulate the cutaneous immune tolerance. In psoriatic skin, it is observed that the microorganism composition has altered, which interplays with host innate and adaptive immunity and potentially constitutes the pathogenesis of psoriasis. Some treatments regarding modifying the skin microbiome have been manifested to yield certain efficacy in psoriasis, whereas this field is relatively new and there is a series of challenges existing in future research. It is expected that this potential pathogenesis could be verified and that novel therapeutics targeting the skin microbiome could be figured out to improve the clinical outcome of psoriatic patients.

AUTHOR CONTRIBUTIONS

This study was conceived and designed by YC. Screening of papers and data extraction were performed by XL and CO. Writing of the first draft of the article was performed by XL, CO, JZ, and JL. Tables and figure were prepared by XL, CO, FZ, and YZ. All authors contributed to the article and approved the submitted version.

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