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The Role of the Skin and Gut Microbiome in Psoriatic Disease

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Abstract

Purpose—To understand the changes in the microbiome in psoriatic disease, we conducted a systematic review of studies comparing the skin and gut microbiota in psoriatic individuals and healthy controls.

Findings—Our review of studies pertaining to the cutaneous microbiome showed a trend towards an increased relative abundance of *Streptococcus* and a decreased level of *Propionibacterium* in psoriasis patients compared to controls. In the gut microbiome, the ratio of *Firmicutes* and *Bacteroidetes* was perturbed in psoriatic individuals compared to healthy controls. *Actinobacteria* was also relatively underrepresented in psoriasis patients relative to healthy individuals.

Summary—Although the field of the psoriatic microbiome is relatively new, these first studies reveal interesting differences in microbiome composition that may be associated with the development of psoriatic comorbidities and serve as novel therapeutic targets.

Keywords

microbiome; skin microbiota; gut bacteria; mycobiome; psoriasis; psoriatic arthritis

Introduction

The microbiome refers to the collection of genomes of microbes in an ecosystem, or microbiota. The human microbiome, or the collection of genomes of the microbial community that is on and within us, plays an important role in providing us with nutrients, regulate our immune system, and maintain overall human health.[1] The microbiome has increasingly become a topic of interest with its implication in various inflammatory and systemic autoimmune diseases such as type 1 diabetes mellitus, rheumatoid arthritis, inflammatory bowel disease, psoriasis, etc.[2-4] With extremely broad range of organisms, dysregulation of the microbiome and the symbiotic relationship that we have with the microbiota may allow disease-causing population to accumulate and consequently

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predispose us to certain diseases. For example, the gut microbiota is shaped by several environmental factors, including dietary habits, infectious agent, antibiotic use, etc.[5, 6] and alterations the microbiota (dysbiosis) are factors associated with the development of inflammatory and systemic autoimmune diseases.[7, 8] Although highly variable interpersonally, the microbiota has a “core” microbiome that encodes unique bacterial gene products that is common to over 90% of individuals.[1] Intrapersonally, microbiome is also variable depending on the body site. Most of the human microbiota is in the gut. In the skin, specific microbes are associated with moist, dry, and oily microenvironments.[9, 10] Vaginal microbial profiles generally fall into colonization by Lactobacillus.[11] In 2012, advances in sequencing technologist allowed for the Human Microbiome Project (HMP),[12] funded by the National Institute of Health (NIH), with the goal of describing the human microbiome was completed and it characterized the core microbiome composition of 18 different body sites in 200 healthy individuals in the United States.[13] Through microbiome studies, characterization of human microbes in disease may open up a new realm of potential strategies for diagnosis, prevention and therapy in personalized medicine.

Techniques for Studying the Microbiome

The gut microbiome can be obtained from stool, while the skin microbiome can be sampled by biopsy,[14] curette,[15] or skin swabs with or without culturing.[16] Biopsy captures internalized bacteria and bacteria in deeper skin layers.[14] Culturing can result in loss of fastidious bacteria.[17]

After sample collection, the bacterial DNA is extracted and analyzed to identify the bacteria and their relative abundance. There are two main approaches for genetic analysis- 16s rRNA and whole genome shotgun (WGS) sequencing. In the former, differences in the nine hypervariable regions of bacterial 16s rRNA genes can be used to cluster sequences by comparison to a database or *de novo* into operational taxonomic units (OTU's).[18] The V4 region is used to distinguish enteric microbiota,[18] while the V1-V3 regions are better for cutaneous microbes.[17]

In contrast to 16S rRNA sequencing, WGS allows for high-resolution classification of bacteria, fungi as well as viruses. Briefly, WGS entails DNA purification, fragmentation, plasmid cloning, sequencing, alignment and, ultimately, assembly, which is a computationally sophisticated and expensive process. Taxonomy is dependent on available reference genomes rather than small gene sequences such as 16S rRNA. Compared to 16S rRNA sequencing, WGS was superior in identifying microbial species strains, but equivalent in genetic functional predictions.[19] Although WGS is currently more expensive than 16S rRNA sequencing, the cost of WGS is predicted to decrease as the technology matures.

Psoriatic Disease and the Microbiome

New evidence suggests that the microbiome may play a pathogenic role in psoriatic disease. In mouse models, germ-free and antibiotic treated conventionally reared mice were more resistant to inflammation in the imiquimod-induced model of psoriasis than conventionally reared mice who received no intervention.[20] In humans, skin and non-skin infections are

associated with the development of pediatric psoriasis.[21] These studies have prompted efforts to profile the microbiome in patients with psoriatic disease. While there is no consensus on the composition of the psoriatic microbiome, the first collection of studies in this burgeoning field provides promising insights into the pathogenesis of psoriasis and its comorbidities [Table 1, Table 2].

Skin microbiome

Alpha diversity—The alpha diversity describes the variety of the microbial community in each sample and is described in terms of evenness, the distribution of species in a sample, and richness, the number of species in a sample. The earliest study by Gao and colleagues compared skin swabs from lesional and non-lesional sites on 6 psoriatic individuals with those from unmatched areas of healthy skin from 6 controls in a prior study.[16] They found that psoriasis lesional skin had a significantly higher Simpson's diversity index than non-lesional and control skin.[16] In contrast to Gao's approach, Fahlen's study examined biopsies from the lesional skin of 10 psoriasis patients and normal skin of 12 controls who had lesions removed by wide excision. They found no difference in the Shannon index, a commonly used measure of evenness, but did observe a wider range of Shannon index values in controls compared to psoriasis samples.[14] This may reflect a more normal distribution of alpha diversity in the control samples, while the lesional psoriatic microbiome is relatively uniform in alpha diversity.[14] The largest study, by Alekseyenko and colleagues used site-matched swabs of lesional and non-lesional skin from 75 psoriasis patients and healthy skin from 124 controls and found a trend toward decreased richness in lesional and non-lesional psoriasis samples compared to controls. The Shannon index was significantly lower at the phylum, class, order, family, and genus levels in lesional samples compared to non-lesional and control samples.[22] Alekseyenko and colleagues also followed the cutaneous microbiota of a subset of 15 healthy controls and 17 psoriasis patients who were on a variety of systemic therapies, including methotrexate and TNF-alpha inhibitors. With systemic treatment, the richness initially declined in lesional and unaffected skin at 12 weeks.[22] At 36 weeks, the richness of the unaffected skin rebound to baseline levels, while that of the lesional skin did not.[22] Similarly, the Shannon index declined in lesional and unaffected skin at 12 weeks, but returned to baseline levels at 36 weeks in unaffected skin.[22] This pattern of decreasing richness and evenness suggests an increase in the abundance of some taxa, which leads to a decrease or elimination of others.[22] Overall, these studies reveal conflicting differences in alpha diversity, which may be due to different sampling techniques and the use of site-matched and not site matched sampling.

Beta diversity—Beta diversity describes how similar microbial communities of psoriatic individuals are to one another. Using UniFrac and principal coordinate analysis, Fahlen and Gao found that the psoriasis lesions shared many OTUs, suggesting lower beta diversity, while the OTU composition of controls varied more between individuals, indicating higher beta diversity.[14] Conversely, Alekseyenko and colleagues found that beta diversity was lowest in the control skin, greater in the non-lesional microbiota, and highest in the lesional microbiota.[22] However, in the longitudinal component of their study, which may have been limited by insufficient power, the beta diversity was not significantly different between lesional, un-affected, and control skin at either the 12 week or the 36 week time points.[22]

Microbiome composition—Studies have also compared compositional differences between the microbiomes of psoriatic and healthy individuals [Table 1]. At the phylum level, *Firmicutes, Proteobacteria*, and *Actinobacteria* were the three most prevalent phyla in psoriatic and normal skin.[14, 16, 22, 15] In psoriatic lesions, both Gao and Fahlen found that Firmicutes was the most common phylum. Using another approach, Alekseyenko and colleagues were able to separate samples into two different clusters, representing distinct cutaneotypes. Consistent with the findings of Gao and Fahlen, Alekseyenko found that psoriatic lesions were more likely to belong to cutaneotype 2, which was dominated by Firmicutes and Actinobacteria. In contrast, Drago and colleagues profiled the cutaneous microbiota of three first cousins with healthy skin, psoriasis, and atopic dermatitis and found that psoriasis lesions were dominated by Proteobacteria and Bacteroidetes. There are conflicting conclusions about the most dominant phylum in healthy skin. Gao and colleagues found Actinobacteria to be the most abundant phylum, while Fahlen and Drago's studies found that control samples were dominated by Firmicutes. Alekseyenko's team observed that control samples were more likely to belong to cutaneotype 1, which was dominated by Proteobacteria. Overall, the lesional psoriatic microbiome differs significantly compared to control and unaffected skin, but the changes in particular phyla differ depending on the study. For example, Gao and colleagues found that psoriasis lesions had a significantly greater relative abundance of Firmicutes and less Actinobacteria and Proteobacteria than control and non-lesional skin. Similarly, Fahlen's study found that lesional skin was significantly lower in Actinobacteria than normal skin. However, lesional trunk samples had a lower abundance of Proteobacteria than site-matched samples from healthy controls.[14] Drago and colleagues noted that psoriasis lesions had a higher proportion of Proteobacteria and a lower proportion of Firmicutes. The differences between these studies may be due to variations in sampling sites as dry, moist, and sebaceous sites have different microbial compositions.[17] The microbiome also varies over time. In the small cohort followed by Alekseyenko and colleagues, cutaneotype 2 continued to be the most common in psoriasis subjects even after treatment. However, some controls switched from cutaneotype 1 to 2 and there was a trend towards increasing prevalence of cutaneotype 2 over the course of 36 weeks, which may have been due to a decreasing number of available samples over time.[22] Unlike lesional skin, non-lesional sites were not significantly different from healthy control skin at the phylum level,[22, 15, 16] indicating that changes in unaffected skin may be more subtle.

Beyond the phylum level, researchers have taken a more in detailed look at differences in the cutaneous microbiome [Table 1]. At the family level, Drago and colleagues discovered that psoriasis lesions had a higher relative abundance of *Streptococcaceae*, *Rhodobacteraceae*, *Campylobacteraceae*, and *Moraxellaceae* than eczema lesions and control skin. At the genus level, several studies have suggested an underrepresentation of *Propionibacterium*,[16, 14, 15] an overabundance of *Streptococcus*,[16, 14, 22] and mixed changes in *Staphylococcus* in psoriasis lesions compared to healthy skin. The decrease in *Propionibacterium* may be driven in part by significant reductions in the species *Propionibacterium acnes*. Interestingly, Gao and colleagues noted that *P. acnes* was lowest on lesional skin, intermediate on non-lesional psoriasis skin, and highest in skin from healthy controls. Changes in *Staphylococcus* were less straight forward. For instance, Drago and colleagues observed the lowest levels of

S. Aureus in psoriasis lesions, intermediate levels in control skin, and highest levels in atopic dermatitis lesions. Fahlen also noted lower *Staphylococcus* in lesional skin compared to control skin at limb sites, but saw no significant increase in the aggregate analysis of all sites. Similarly, Alekseyenko and colleagues found no significant difference in *Staphylococcus* abundance. This is concordant with Gao's study, which observed an increase in *S. aureus* in lesional psoriatic skin compared to unaffected and healthy skin. However, the increase in the combined relative abundance of *Corynebacterium*, *Staphylococcus*, *Streptococcus* in psoriasis lesions compared to control skin was significant.[22] Other changes at the genus and OTU level include a decrease in anaerobic species in the lesional psoriatic microbiome relative to unaffected and control skin.[16] Alekseyenko's study found significant decreases in *Cupriavidus, Flavisolibacter, Methylobacterium, Schlegelella*, while the presence of *Acidobacteria* positively correlated with PASI.

Although these early studies suggest a potential role for cutaneous dysbiosis in the development of psoriasis, there are currently no studies of the skin microbiome in psoriatic arthritis. Further research is needed to determine if patients with psoriatic arthritis have cutaneous bacteria that differ from those with skin only psoriasis.

Gut microbiome

Microbiome composition—Two studies have looked at the gut microbiome in psoriasis [Table 2]. In a study by Scher and colleagues, fecal samples revealed decreased alpha diversity in the gut microbiome of DMARD-naïve, recently diagnosed individuals with psoriatic arthritis (PsA) and skin-limited psoriasis (Pso) compared to healthy controls.[23] At the phylum level, Scher's study found that PsA individuals had a lower abundance of *Firmicutes, Clostridiales, Verrucomicrobiales* and higher *Bacteroidetes* relative to Pso patients. Subjects with Pso had lower levels of *Actinobacteria* compared to controls. In a separate study using fecal samples from 45 psoriasis patients and 45 controls, Masallat and colleagues found a decreased abundance of *Actinobacteria* in psoriasis patients versus healthy controls. The prevalence of *Actinobacteria* was negatively correlated with disease severity, measured by PASI score.[24] Masallat's group also observed an increase in the *Firmicutes/Bacteroidetes* ratio in psoriasis subjects which was positively correlated with PASI score.[24]

At the genus level, Scher and colleagues found a decreased abundance of *Akkermansia, Ruminoccocus, Pseudobutyrivibrio* in psoriatic arthritis compared to controls, which was positively correlated with fecal medium chain fatty acids, heptanoate and hexanoate.[23] *Akkermansia* was also inversely correlated with fecal levels of soluble IgA and the SCFA's, acetate and butyrate.[23] In addition, compared to Pso subjects, PsA patients had higher *Coprobacillus*. Pso patients had lower *Parabacteroides* and *Coprobacillus* than healthy controls.[23] While the effects of *Parabacteroides* and *Coprobacillus* on the host are not fully understood, they may help distinguish psoriatic arthritis from skin only psoriasis and controls. Further studies must be done to confirm the findings of Scher and colleagues and to elucidate the role of microbial metabolites in psoriatic disease and its comorbidities.

The Psoriatic Mycobiome

To date, only one study has investigated the entirety of the mycobiome in psoriatic skin [Table 1] Takemoto et al. found that psoriatic skin had higher fungal diversity and decreased abundance of *Malassezia* compared to controls, although *Malassezia* was the most abundant phylum in both groups.[25] In addition, the ratio of *M. globosa* to *M. restricta* was lower in psoriatic patients relative to control.[25] Takemoto and colleagues were also able to use principal coordinate analysis to separate psoriatic and healthy participants based on fungal species distribution. Other studies have focused solely on cutaneous *Malassezia* species in psoriasis [Table 1]. For example, two studies by Paulino et al., found that *Malassezia restricta, globosa* and *sympodialis*, in decreasing order of abundance, were not significantly different between healthy and psoriatic skin[26] and there was no consistent dichotomous variation between psoriasis and healthy participants.[27] In contrast, Jagielski et al. detected M. furfur only in psoriatic skin compared to atopic dermatitis (AD) and healthy skin.[28] Interestingly, *M. sympodialis* was the predominant species in all patients, but was more prevalent in AD and normal skin than psoriatic skin.[28] These results reveal potential differences in *Malasezzia* species, but more unbiased studies profiling the entirety of the skin mycobiome are needed to understand the importance of these changes in psoriatic disease.

The Psoriatic Virome

Viruses have long been implicated in the etiology of cutaneous neoplastic[29-31] and inflammatory diseases.[32] The role of viruses in psoriasis is more controversial. To date, there are no studies that have profiled the cutaneous virome in psoriasis as a whole. However, multiple studies have looked specifically at HPV and have implicated several HPV subtypes (e.g. HPV5 and HPV38) in psoriasis [Table 1].[33-39]

Conclusions

While data on alpha and beta diversity are conflicting, studies of the cutaneous microbiome have revealed interesting compositional trends in the microbiome of psoriatic skin. Decreased relative abundance of *Propionibacterium* in psoriatic lesional skin was seen in 3 out of 4 studies.[16, 14, 15] *Propionibacterium*, are a major component of normal skin microflora[40] as well as prolific producers of the SCFA, propionate, which modulates the immune system.[41, 42] Loss of *Propionibacterium* can therefore lead to decreased immune tolerance and increased propensity for psoriatic inflammation.[16] These studies have also found higher levels of Streptococcus on psoriasis lesions.[16, 14, 22] The observed increase in *Streptococcus* may play a pathogenic role in psoriasis as streptococcal infections have been associated with the later development of guttate psoriasis and the worsening of chronic plaque psoriasis.[43] Changes in the abundance of *Staphylococcus* in psoriatic skin are less consistent. The differing results may be due to variations in sampling sites since *Staphylococcus* is more prevalent in moist areas such as the navel and antecubital fossa.[17] In addition, *Staphylococcus* is a diverse genus in which some species, such as *S. epidermidis* appear to have a commensal role enhancing the innate immune barrier,[44] while others, like

S. aureus evoke a pathogenic Th17 response.[45] Consequently, changes in *Staphylococcus* may be better understood at the species level.

Despite the interesting differences between psoriatic and healthy skin, none of these studies address the cutaneous microbiome in psoriatic arthritis and how it may differ from skin limited psoriasis. This is an important gap in knowledge as 30% of psoriasis patients develop psoriatic arthritis and 70% of psoriatic arthritis cases psoriasis are preceded by psoriasis.[46] The potential recognition of a microbiome profile associated with a high risk for developing psoriatic arthritis may provide a target for the development of preventative measures to intervene to halt the progression to joint involvement in patients with psoriasis.

Already, the two studies of the psoriatic gut microbiome have suggested shifts in the microbiome that may herald the development of psoriatic comorbidities. For instance, Scher et al found that psoriatic arthritis patients had a gut microbiome composition that differed significantly from that of patients with skin limited disease.[23] Other changes observed in gut microbiome studies include a decrease in *Actinobacteria*.[23, 24] This may suggest a protective role of *Actinobacteria*, a phylum which includes *Bifidobacterium* species that have been shown to reduce intestinal inflammation, suppress autoimmunity, and induce Tregs.[47, 48] Of interest, Groeger and colleagues were able to demonstrate that oral administration of *Bifidobacteria infantis* 35624 for 6-8 weeks in a randomized, double-blind, placebo-controlled clinical trial reduced plasma CRP and TNF-a in psoriasis patients who had elevated inflammatory markers at baseline.[49] Perturbations in the balance of *Firmicutes* and *Bacteroidetes* were also observed in psoriasis and psoriatic arthritis.[23, 24] This has intriguing implications for cardiovascular disease, a major psoriatic comorbidity. For example, certain bacteria in the gut microbiome are especially prolific converters of dietary carnitine from red meat and eggs to trimethyl amine (TMA), the precursor of the proatherosclerotic metabolite trimethylamine-N-oxide (TMAO).[50] TMAO alters host cholesterol metabolism and promotes macrophage activation, leading to increased risk of CVD, myocardial infarction, stroke, and death.[51, 50, 52] A cross over feeding trial in healthy men found more *Firmicutes* than *Bacteroidetes* within the stool of participants who were high-TMAO producers.[53] Increased levels of *Firmicutes* with a decrease in *Bacteroidetes* has also been associated with a higher body mass index, while successful weight loss led to a subsequent increase in *Bacteroidetes* and a reduction in *Firmicutes*.[54] At the same time, obesity is a common comorbidity of psoriasis and psoriatic disease severity has been positively correlated with body mass index and waist to height ratio.[55, 56] Adipocytokines have also been posited to contribute to the systemic inflammation in psoriasis.[57] Thus, an imbalance in the *Firmicutes/Bacteroidetes* ratio in the psoriatic gut microbiome may reflect the relationship between psoriasis and its cardiovascular and metabolic comorbidities.[58, 59] At the genus level, Scher and colleagues found a decrease in *Akkermansia* and *Ruminoccocus*.[23] Similar changes in the gut microbiome are seen in inflammatory bowel disease, a known comorbidity of psoriasis.[23, 60] Both *Akkermansia* and *Ruminoccocus* are mucin-degrading bacteria that produce SCFA's and are integral to the maintenance of the gut mucosal barrier.[23, 61] Loss of their protective effect in PsA may weaken immune tolerance and serve as a marker of more severe disease. In fact, dysbiosis of the skin and gut microbiome resulting in an inflammatory response involving the joints has been proposed as a potential model for the pathogenesis of psoriatic arthritis.[62]

It is essential to acknowledge some limitations of the microbiome studies discussed in this review. For example, with the exception of the small study by Drago et al., no other study accounts for sex, ethnicity, and diet, which have been found to affect human microbiome composition.[63-66] Thus, differences in patient demographics combined with varied techniques for sampling and analysis of bacterial DNA can complicate comparisons between studies and lead to conflicting results.[22, 14, 16] Additionally, the studies reviewed primarily utilized cross-sectional methodology, which limits our understanding of the temporal relationship between microbial changes and psoriasis pathogenesis. It remains unclear whether the observed differences in the microbiota have a causal role in psoriasis or are a consequence of alterations in the environmental milieu from psoriasis. Further research involving large-scale, prospective studies in humans and proof-of-concept experiments in mouse models are needed to validate differences in psoriatic microbiome composition and reveal the role of these changes in psoriasis.

Ultimately, a better understanding of the psoriatic microbiome can lead to the development of new therapeutic modalities that target the shifting microbiota. These can include antibiotics, prebiotics, probiotics, and fecal transplant therapy. Antibiotics alter the composition of the microbiome by reducing susceptible bacterial species and allowing others to take their place. Randomized controlled studies have found improvement in rheumatoid arthritis patients following antibiotic monotherapy and therapy with concomitant antibiotic use,[67, 68] suggesting a possible role for antibiotics in the management of autoimmune disease. Interestingly, large prospective study found a decrease in TMAO following antibiotic administration and a return to baseline following antibiotic cessation.[52] Thus, antibiotics also have the potential to reduce the risk of cardiometabolics comorbidities in patients with psoriasis. In contrast to therapies aimed at directly reducing certain bacterial species, other therapies aim to alter the microbiome through the growth of specific taxa. Probiotic and prebiotic therapies are commonly used to promote specific bacteria, the former through direct colonization and the latter through nutrient formulations aimed to promote the survival and proliferation of specific bacterial species. Limiting factors in the use of probiotics and prebiotics lies in the poor understanding of effective dose, duration, and interaction with dietary intake. As future studies elucidate the role of the microbiome in psoriasis and psoriatic arthritis, more effective probiotic and prebiotic therapies can be developed. A recent approach to intestinal microbiota modulation includes fecal microbiota transplantation where successful results have been observed in *Clostridium difficile*.[69] The success of this therapy may be extended to other inflammatory conditions; however implementation may be challenged by cost, transporting logistics, and measures to prevent infection. An alternative approach involves targeting pathogenic bacterial metabolites or microbial pathways through diet modification or pharmacologic inhibitors. For example, oral administration of dimethylbutanol (DMB) suppressed TMAO production in mice.[50] A Mediterranean diet, which is low in carnitine-containing red meat, has also been found to reduce the risk of cardiovascular events.[70] Such diet-based and nutraceutical approaches to targeting the microbiome may produce a milder side effect profile than current systemic medications.[71] Thus, interventions aimed at the microbiome may be a valuable adjunct for preventing or managing psoriatic disease and its comorbidities. These novel

therapeutic approaches demonstrate that although the psoriatic microbiome is still a nascent field, it has the potential to yield important insights into disease pathogenesis and treatment.

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[i]Here Alekseyenko et al. report the results of the largest study profiling the cutaneous microbiome in psoriasis to date. This study is also the only one to profile changes in the cutaneous microbiome after treatment for psoriasis.

[ii]The study by Scher et al., is the only comprehensive, genus-level, profiling study of the gut microbiome in psoriatic disease to date. This study is also significant in that it correlates fecal metabolites with shifts in gut microbiome composition, providing the foundation for a mechanistic understanding of how bacteria can influence the host.

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Table 1
Summary of studies of the skin microbiome, mycobiome, and virome in psoriatic disease

Bacteria			
Study	**Study Design**	**Methods**	**Major findings**
Alekseyenko et al.	Cross-sectional - 75 Pso, 124 C - Site matched skin swabs of L, NL, C from dry or sebaceous cutaneous areas from extremities, trunk, head Longitudinal - 17 Pso, 15 age, gender, ethnicity matched C -Skin swabs at baseline, 12 wks, 36 wks after treatment	Cross-sectional 16s rRNA (V1-V3) Longitudinal 16s rRNA (V1-V3), parallel analysis using V3-V5	Alpha diversity: L Pso < NL Pso and C Beta diversity: C<NL Pso <L Pso Phyla C more likely to be cutaneotype 1 (dominated by *Proteobacteria*), Pso L more likely to be cutaneotype 2 (dominated by *Actinobacteria, Firmicutes*) Genera ↑ Combined relative abundance of *Corynebacterium, Staphylococcus, Streptococcus* in Pso L vs. C Species Presence of *Acidobacteria, Schlegelella* strongly associated with Pso *Acidobacteria* positively correlated with PASI ↓ *Cupriavidus, Flavisolibacter, Methylobacterium, Schlegelella* in Pso vs. C
Drago et al.	- 3 adult first cousins- 1 AD, 1 Pso, 1 C on Mediterranean diet for 1 mo, living in same neighborhood, all vaginally delivered - Skin samples by curette from L, NL in AD, Pso and NL in C	16s rRNA (V2, V3)	Alpha diversity: N/A Beta diversity: N/A (only 1 per group) Phyla ↓ *Firmicutes*, ↑ *Proteobacteria* in L Pso vs. L AD and C Family ↑ *Streptococcaceae, Rhodobacteraceae, Campylobacteraceae, Moraxellaceae* in L Pso vs. L AD and C ↓Staphylococcaceae, Propionibacteriaceae in L Pso vs. L AD, C Species ↓ *Propionibacterium acnes* in L skin of Pso vs. AD and C ↓ *S. aureus* L skin of Pso < C< L in AD, no difference in NL No difference in NL skin of Pso, AD vs. C
Gao et al.	Skin swabs of multiple sites on 6 C (from prior study) and multiple sites on NL and L skin of 6 Pso not on systemic or topical treatment	16s rRNA (nearly full length)	Alpha diversity: L Pso >NL Pso and C Beta diversity: L Pso > C Phyla ↑ *Firmicutes* Pso L vs. Pso NL, C ↓ *Actinobacteria*, *Proteobacteria* in Pso L vs. Pso NL, C Genera ↓ *Propionibacterium* in Pso L vs. Pso NL, C ↑ *Streptococcus* in Pso L vs. Pso NL, C Species ↓ *Propionibacterium acnes* in L skin of Pso vs. Pso NL and C ↓ Anaerobic species in L Pso vs. Pso NL and C
Fahlen et al.	- Skin biopsies from L skin in 10 Pso, 12 C at unmatched, non-flexural sites - Pso off topicals for 2 wks, light and systemic therapies for 4 wks - C skin from terminal end of elliptical wide excisions of skin lesions	16s rRNA (V3, V4)	Alpha diversity: No difference in Shannon Index Beta diversity: L<C Phyla ↓ *Actinobacteria* in Pso L skin vs. C ↑ *Proteobacteria* in trunk samples from L Pso vs. C Genera Trend towards ↓ *Propionibacterium* in Pso L vs. C from all sites ↓ *Propionibacterium* in Pso L vs. C at limb sites ↓ Staphylococcus in Pso L vs. C ↑ Streptococcus/Propionibacteria ratio
Fungus			
Paulino et al. (2006)	5 C, 3 Pso Site: swab of NL forearm, various L sitess	rRNA clone library	No consistent variation in Pso vs. C

Bacteria			
Study	**Study Design**	**Methods**	**Major findings**
Paulino et al. (2008)	1 C, 1 Pso Site: swabs of NL on forearms, forehead, scalp, upper back, lower back; L on elbow, finger	PCR	No consistent variation in Pso vs. C
Jagielski et al. (2014)	6 C, 6 Pso, 6 AD Site: swabbed scalp, face, interclavicular region, interscapular region	PCR	↑ Malassezia furfur in Pso patients
Takemoto et al. (2015)	12 C, 12 Pso Site: trunk; L scales via tweezers, and OpSite transparent dressing for NL/C skin	Pyrosequencing	↑ Malassezia restricta in Pso patients ↑ Malssezia globosa in C
Virus			
Wolf et al. (2004)	81 Pso total comparing: Group A (Pso + Hx PUVA + Hx skin cancer), Group B (Pso + Hx PUVA), Group C (Pso) Site: plucked hairs from NL skin	PCR	↑ HPV (esp. HPV-38) in plucked NL body hairs in Pso patients with hx PUVA irrespective of skin ca hx
Simeone et al. (2005)	11 Pso patients Site: biopsies from L skin	Cultured primary keratinocytes and PCR	↑ HPV-5 in Pso patients
Cronin et al. (2008)	20 Pso patients, 23 C Site: plucked eyebrow hairs and forearm scrapes	PCR	↑ HPV DNA in Pso patients, but no specific HPV type predominated
Salem et al. (2010)	20 Pso (untreated), 20 Pso (nb-UVB), 20 Pso (PUVA), 10 C Site: skin biopsy	PCR	↑ HPV DNA in Pso patients on PUVA HPV ubiquitous in normal and diseased skin
de Koning et al. (2011)	27 Pso patients, 17 AD Site: plucked eyebrow hairs	PCR	↑ HPV DNA in Pso patients compared to AD patients
Bellaud et al. (2014)	151 Pso patients (48 anti-TNF-α , 21 MTX, 82 no treatment) Site: plucked eyebrow hairs	PCR	High overall of HPV across all Pso patients with no significant difference (genus or subtype level) between treatment groups
Prignano et al. (2005)	54 Pso patients, 20 C Site: L and NL skin scales	PCR	↑ HPV-5 in Pso patients L and NL skin

Abbreviations: Pso = Psoriasis, PsA = Psoriatic arthritis, C = control, L = lesional, NL = non-lesional, AD = atopic dermatitis, HPV = Human papillomavirus, PASI = Psoriasis Area Severity Index, PCR = Polymerase chain reaction, MTX = Methotrexate, PUVA = Psoralen and ultraviolet A radiation; DMARD = Disease-modifying antirheumatic drug

Table 2
Summary of studies of the gut microbiome in psoriasis

Bacteria			
Study	**Study Design**	**Methods**	**Major findings**
Masallat et al.	- Fecal samples from 45 PsO, 45 age and sex matched C	16s rRNA using 3 sets of specific primers for 3 phyla (Bacteroidetes, Firmicutes, and Actinobacterial)	Phyla ↓ Actinobacteria in Pso vs. C, negatively correlated with PASI ↑ Firmicutes/Bacteroidetes ratio in Pso vs. C, positively correlated with PASI
Scher et al.	- Fecal samples from 17C, 16 PsA, 16 Pso who were recently diagnosed and had never been treated with DMARD's, oral or systemic therapies - Secretory Ig A, pro-inflammatory proteins, fatty-acids from fecal supernatant and serum	16s rRNA (V1, V2)	Phyla ↓ *Firmicutes, Clostridiales, Verrucomicrobiales* in PsA vs. Pso ↑ *Bacteroidetes* in PsA vs. Pso ↓ *Actinobacteria* in Pso vs. C Genera ↓ *Akkermansia, Ruminoccocus, Pseudobutyrivibrio* in PsA vs. C ↑ *Coprobacillus* in PsA vs. Pso ↓ *Parabacteroides* and *Coprobacillus* in Pso vs. C

Abbreviations: Pso = Psoriasis, PsA = Psoriatic arthritis, C = control, L = lesional, NL = non-lesional, AD = atopic dermatitis, HPV = Human papillomavirus, PASI = Psoriasis Area Severity Index, PCR = Polymerase chain reaction, MTX = Methotrexate, PUVA = Psoralen and ultraviolet A radiation; DMARD = Disease-modifying antirheumatic drug