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The role of the microbiome in psoriasis: moving from disease description to treatment prediction?

Short title: Microbiome in psoriasis

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What's already known

The human integument plays host to an extensive microbial ecosystem, under-estimated due the reliance on bacterial culture for its identification

16S ribosomal RNA sequencing has shed new light on both the extent, diversity (both inter- and intra-individual) of the cutaneous microbiome and its potential role in health and chronic inflammatory diseases, including psoriasis.

The mechanisms underpinning the interactions between our resident skin flora and the immune system are incompletely understood.

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What this review adds

The review outlines the evidence for, and clinical relevance of, differences in the composition of cutaneous microbiota in terms of inflammatory skin disease.

In the age of personalized medicine, the integration of cutaneous microbiome signatures, combined with comprehensive geno- and phenotyping of patients and their diseases may facilitate treatment selection and consequently optimize treatment efficacy.

Abstract:
With several million microbes per cm^2 of skin, the task of mapping the physiological cutaneous microbiome is enormous. Indeed, the reliance on bacterial culture to identify cutaneous bacterial communities has led to a systematic under-appreciation of cutaneous microbial diversity, potentially limiting our understanding of common inflammatory skin diseases including psoriasis.
However, based heavily on developments in molecular biology and bioinformatics, including next generation sequencing, the last decade has witnessed a marked increase in our understanding of the extent and composition of the cutaneous microbiome. It is already clear that skin-specific (skin site and skin microenvironment), individual-specific (hygiene, sex, age, and hormonal status), disease-specific (atopic eczema, acne) and genetic factors can all influence the cutaneous microbiome, albeit to varying and, as yet ill-defined, extents. This review briefly describes the process of 16S ribosomal RNA sequencing, before charting our current understanding of the cutaneous microbiome in health and the alterations (dysbiosis) associated with chronic inflammatory diseases with particular reference to psoriasis. The possibility and clinical relevance of intra-individual cross-talk between the various microbiomes is discussed and potential mechanisms underpinning the interactions between resident skin flora and the immune system are highlighted. We outline how the power of microbiome studies can be harnessed to provide new insights into disease pathogenesis and treatment selection. Ultimately, in the age of personalized medicine, the integration of cutaneous microbiome signatures and comprehensive disease and drug response endotypes will herald a novel approach in the clinical management of chronic, multi-system inflammatory diseases.

Introduction:

With a surface area of approximately 2 m^2 and containing an estimated 5 million hair follicles,[1] human skin plays host to a bewildering microbial ecosystem. It has been claimed that each square centimetre of skin may contain up to 2 million bacteria.[2] However, due to a reliance on bacterial culture to demonstrate its existence, the extent and diversity of the cutaneous microbiome has been profoundly underestimated; reportedly identifying only 10% of the bacteria present on skin.[3]

Advances in molecular biology, coupled with the development of complex bio-informatics tools, have revolutionised our understanding of the extent and composition of the cutaneous microbiome.[4,5] Specifically, the use of high-throughput sequencing, exploiting the highly conserved bacterial 16S ribosomal RNA gene, has shed new light on the bacteria with whom we share our cutaneous interface. Indeed, we are only now beginning to discover ways in which the cutaneous microbiome can influence and perhaps shape the immune system. The corollary, namely the extent to which host genetic factors and environmental influences regulate the microbiome, perhaps via antimicrobial peptide and cytokine expression, is of special interest in efforts to better understand the pathogenesis of chronic inflammatory skin disorders particularly psoriasis.

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This review briefly describes the technology underpinning research into the cutaneous microbiome before charting our current understanding of its physiological composition. Drawing on lessons from chronic inflammatory skin and bowel diseases, specifically highlighting psoriasis, we illustrate how the concept of dysbiosis (bacterial imbalance due to an breakdown in tolerance to commensal bacteria [6]) may underpin a range of chronic diseases. We conclude by presenting an integrated concept of how resident bacteria can be used to provide new insights into disease pathophysiology, but more importantly, how the microbiome can be exploited to develop novel therapeutic targets; harnessing the power of sequencing in the clinic.

High throughput next generation sequencing made simple

The use of 16S rRNA next generation sequencing, taking advantage of both the highly conserved and hyper-variable regions of the prokaryotic 16S ribosomal gene, has facilitated a marked expansion in our understanding of the range of bacteria which colonise human skin.[7,8] The Human Microbiome Project [9] was a large international collaborative effort which used 16S rRNA sequencing to chart the human microbiome, sampling diverse body habitats in almost 250 individuals. This study provided the basis for a dramatic expansion in metagenomic data.[10] The basic sequencing process initially involves obtaining skin swabs, washings, scrapings or biopsies. The majority of published skin microbiome data is based on results obtained from skin swabbing, with only a handful of studies utilizing skin biopsies.[11,12] Whilst sampling technique may theoretically affect the bacterial species identified, Grice et al. found little evidence of a significant effect when comparing skin swabs, scrapes and biopsies.[12] Chng et al. have favoured tape-based skin sampling but reported concordance between several sampling approaches.[13] Nevertheless, the possibility remains that skin compartment-specific microbial signatures exist.

Subsequently, DNA is isolated and the 16S rRNA gene amplified using PCR and bar-coded primers. Importantly, specific hypervariable regions of the 16S gene, for example V1-V3, may be most suited to skin microbiome research based on its ability to identify members of the *Firmicutes* phyla, down to the species level.[14-16] It is important to bear in mind that binding of the primers used to target regions of the 16S gene may also effect which bacteria are identified, leading to under- or over-representation of specific bacterial groups.[17] The product is then confirmed and isolated using gel electrophoresis before being sequenced on a commercial platform, for example the MiSeq sequencer (Fig 1).

The vast amount of data generated is subsequently analyzed using a range of bioinformatics programs, for example MOTHUR, [18] QIIME[19,20] or SEQUENCE MATCH at RDP II[21] to identify which bacteria are present, in terms of phyla, genera and even species. This classification is based on the degree of sequence similarity (usually over 97%), termed the operational taxonomic unit (OTU). In addition, information can be obtained about bacterial prevalence, abundance and diversity and whether specific species are associated with disease phenotypes. Importantly, causal relationships cannot be determined by next generation sequencing at single time points. Additionally, whilst using 16S as the sequencing target the abundance of bacterial species within the microbiota can be determined, the dynamic content of bacterial genomes, including virulence factors and resistance mechanisms, is more difficult to capture.

The cutaneous microbiome: remarkable levels of complexity

Given the sheer structural complexity of human skin, it is perhaps unsurprising that this is reflected in the composition and regulation of the cutaneous microbiome. Whilst skin-site and cutaneous microenvironment (dry, wet or sebaceous) are recognised as the key factors determining the composition of the microbiome [7,9,12,21-23] a raft of additional factors have been reported to influence it. For example, age,[24,25] sex,[26,27] hygiene,[28] ethnicity [24,29] and

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hormones [30] may all influence the microbiome to varying extents. The identification of transient and/or pathogenic skin bacteria (for example *Staphylococcus aureus*) versus resident skin bacteria (for example *Micrococcus luteus*) further complicates the picture.[21] It does appear likely that an individual's physiological cutaneous microbiome is surprisingly stable over time.[22,23,29,31] Indeed, individuals can actually be identified based on the microbial fingerprint they leave on the environment, for example on computer keyboards.[32]

In the clinical context, the most interesting aspect of microbiome research is the extent to which skin disease alters the cutaneous microbiome, or even results from dysregulation and/or disruption of the resident bacterial flora. The initial focus of skin microbiome research was centered on atopic eczema [33,34] given the prominent role of *staphylococci* in disease pathogenesis, but more recent efforts have focused on psoriasis as a useful model of chronic, inflammatory disease.

Psoriasis pathophysiology: the role of bacteria

The role of bacteria, in particular *Streptococci*, as a potential trigger factor for psoriasis was reported over half a century ago [35,36] and led to the hypothesis that the disease itself was a T-cell mediated autoimmune disease mediated by group *A beta-haemolytic streptococcal* superantigen.[37] Moreover, while *streptococci* are most readily associated with the guttate subtype of psoriasis, recent evidence has suggested that *streptococca*l throat infections are also associated with exacerbations of chronic plaque psoriasis.[38] *Streptococci* have been isolated from the blood of patients with chronic plaque as well as guttate psoriasis, albeit with varying frequency.[39] Indeed, the role of tonsillectomy as a therapeutic intervention in psoriasis has recently been reviewed.[40]

Although the role of bacteria in general, and *streptococci* in particular, in the pathogenesis of psoriasis remains unsolved, the association invites speculation that the disease is at least associated with changes in the composition of the microbiome. Whether changes in the cutaneous microbiome are an effect of *streptococcal* antigens present in the tonsils or are a primary event in the development of psoriasis remains unclear. Moreover, another interesting association between the microbiome and psoriasis has been suggested by Fry et al. [6,41] drawing on lessons from chronic inflammatory bowel disease, leading the authors to propose that psoriasis may reflect an abnormal innate immune response (e.g. IL-23, IL-17) to the skin microbiome rather than being an autoimmune disease.[6,41]

Psoriasis, particularly severe disease, may be associated with an increased risk of inflammatory bowel disease, both Crohn disease and ulcerative colitis.[42,43] This association is supported by genetic evidence suggesting shared susceptibility loci.[44,45]More recently, associations between Crohn disease and alterations in the gastrointestinal microbiome have been reported.[46-48] Interestingly, a reduction in *Faecalibacterium prausnitzii*, a member of the gastrointestinal *Firmicutes* phyla, was associated with an increased risk of postoperative disease relapse.[49] Decreased *Faecalibacterium prausnitzii* prevalence in stool has recently been reported in patients with psoriasis.[50] This observation supports the possibility that psoriasis is also associated with important shifts in the composition of the gastrointestinal microbiome.

To what extent is psoriasis associated with a dysregulated skin microbiome?

Turning attention to the skin itself, the site of the characteristic plaques of psoriasis, what evidence exists that the cutaneous microbiome is altered in psoriasis? One of the seminal studies which aimed to characterise the cutaneous microbiome in psoriasis was performed by Gao et al.. [51] Drawing on results from an antecedent study in healthy skin,[21] the authors reported that plaques of psoriasis had the most diverse taxa, with *Firmicutes* forming the most abundant phylum. In fact, *Firmicutes* were significantly over-represented when comparing involved and uninvolved psoriasis skin with control skin.

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Actinobacteria were the most prevalent and diverse phylum in healthy and uninvolved psoriasis skin, but were significantly reduced in involved skin. In contrast, Grice et al. reported *Proteobacteria* were the most abundant phylum in healthy skin,[12] although in a later study the reported abundance was reduced.[22] Nevertheless, Gao et al found that *Proteobacteria* were more readily detected in healthy skin compared to psoriasis plaques.[51]

Clones representing the genus *Streptococcus* were detected significantly more frequently from involved psoriasis skin when compared to uninvolved skin. This contrasted with a significant reduction in *Propionibacterium* in involved skin.[51] Overall, double principal coordinate analysis revealed that intra-individual variation within the microbiome was less than inter-individual variation. Notwithstanding several methodological factors (the relatively small numbers in the study, the lack of stringent matching of psoriasis patients to controls, the diverse extent of the psoriasis involvement (body surface area 5-20 %) and the varied duration of disease (1-24 years), significant differences in the cutaneous microbiome between healthy subjects and patients with psoriasis were readily detectable. Importantly, analysis of the microbiota by sequencing the 16S microbiome only describes the relative abundance of bacterial species, genera and phyla within the microbiota. Relative changes of abundance in the microbiome do not necessarily represent changes in the actual number of all subpopulations. Future studies combining sequencing and culture data may address this limitation.

As part of the Human Microbiome Project,[52] a smaller cohort which formed a longitudinal sub-study, by Alekseyenko et al. [53] sought to determine the extent to which changes in the cutaneous microbiome were associated with psoriasis and whether these were influenced by systemic treatment. The microbiome was determined using high-throughput 16S rRNA gene sequencing and ultimately included skin swabs from 54 patients with moderate to severe psoriasis and 37 healthy controls, on a site-, ethnicity-, and gender-matched basis. Controls were of a similar age to the psoriasis patients. The final analysis was based on 51 triplets (healthy control, involved and contralateral uninvolved skin swabs).

Although there was a trend towards decreased bacterial diversity in psoriasis, particularly in involved skin, *Firmicutes, Actino-* and *Proteobacteria* were the dominant phyla in all groups. However, in terms of bacterial genera, there were significant differences in the combined relative abundance of the major taxa (*Propionibacterium, Corynebacterium, Streptococcus*, and *Staphylococcus*) between involved and uninvolved psoriasis and control skin. The scalp harboured the most distinct microbial community and skin site was a significant variable, consistent with the literature.[7,12,22]

The mean combined relative abundance of *Corynebacterium, Streptococcus*, and *Staphylococcus* actually increased from control to uninvolved to involved skin and two specific operational taxonomical units (OTUs), namely *Acidobacteria Gp4* and *Schlegelella* were strongly associated with psoriasis status. Whilst the authors concluded that the correlation between psoriasis severity and cutaneous microbial composition was weak, psoriasis status was a major source of variability in the microbial communities and two "cutaneotypes" were identified. Healthy control skin was dominated by *Proteobacteria*, whilst psoriasis skin had a higher relative abundance of *Actinobacteria* and *Firmicutes*. In terms of temporal changes associated with systemic therapy, involved psoriasis skin consistently contained a higher proportion of *Corynebacterium, Propionibacterium, Staphylococcus*, and *Streptococcus* and this actually increased slightly over time. The changes in uninvolved skin were more dynamic, with the abundance of these bacterial genera similar to control skin at baseline, before increasing, and remained increased, during treatment.
Whilst confirming the association between psoriasis and altered microbial colonisation, several factors need to be borne in mind. Approximately 5% of the control population had a positive family history for psoriasis. Due to the lack of long-term follow up, and the bi-modal peak of psoriasis incidence, it is possible that some of these subjects may have developed psoriasis after the study had been performed. The contribution of genetic factors to the

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cutaneous microbiome and whether changes within it are present before the clinical manifestation of psoriasis remain unclear. Interestingly, genetic polymorphisms resulting in altered filaggrin expression have recently been associated with changes in the cutaneous microbiome, with underrepresentation of gram-positive anaerobic cocci.[54] It remains unclear whether genetic polymorphisms in the genes associated with psoriasis may also result in changes in the microbiome. However, given the increased beta-defensin genomic copy number reported in psoriasis,[55] the extent to which genetically determined differences in antimicrobial peptides may alter the cutaneous microbiome in psoriasis is worth exploring. Moreover, given the recently reported antimicrobial activity of psoriasis-associated late cornified envelope (LCE) proteins, the role of LCEs in host defence and their effects on the cutaneous microbiome warrant further investigation.[56]

It is interesting to note that despite the typical symmetrical pattern of psoriasis, unaffected matched sites on the contralateral body surface could be identified. This raises the question of the contribution of psoriasis phenotype to the composition of the skin microbiome. Finally, given the propensity for psoriasis to affect the extensor surfaces of the upper limbs, the use of the inner aspect of the elbow as a control skin site could be criticised. Despite these limitations, including the small sample size in the longitudinal sub-study, Alekseyenko [53,57] confirmed the association between psoriasis and altered composition of the cutaneous microbiome. Moreover, they also highlighted the difficulties of performing psoriasis microbiome studies, including, but not limited to, antibiotic use, systemic and topical therapy, family history of psoriasis, psoriasis phenotype, co-morbidities (including inflammatory bowel disease and psoriatic arthritis), and the selection of skin sites, and the inclusion of both involved and uninvolved skin in a dynamic disease process. Indeed, these factors are crucial to both standardise and inform the methodology for future microbiome studies in psoriasis.

In contrast to Alekseyenko et al. [53] Fahlen et al. examined the cutaneous microbiome using skin biopsies and targeted the V3-V4 regions of the 16S rRNA gene using pyrosequencing. In a comparatively small study of 10 patients with psoriasis and 10 healthy controls, psoriasis plaques were biopsied and compared to control skin obtained during dermato-surgical procedures.[11]Bacterial diversity (Shannon Diversity Index) was increased in the control group compared to the psoriasis group, albeit not reaching statistical significance. Unifrac analysis revealed clustering of the psoriasis samples, while the control samples had a more diverse skin flora. Consistent with other studies [53] *Firmicutes, Proteobacteria* and *Actinobacteria* were the predominant phyla in healthy and psoriasis skin. In fact, *Actinobacteria* were significantly more abundant in normal than in psoriasis skin (16% and 5%, respectively) and the abundance of *Proteobacteria* was significantly higher in psoriasis samples from the trunk compared to those of the control group. At the genera level, the prevalence of *streptococc*i exceeded that of *staphylococc*i in psoriasis skin whilst the reverse was seen in healthy skin. Again, site- and psoriasis-associated differences were identified, for example in the abundance of *Propionibacteria,* [11] although to a lesser extent than in other studies. [51,53,57] As outlined above, targeting the V3-V4 region of the 16S rRNA gene may have contributed to an underestimation of *Propionibacteria.*[17] Perhaps the most interesting difference reported by Fahlen et al. [11] was the abundance of *Proteobacteria* in psoriasis skin and the overrepresentation of *Streptococci* in both psoriasis and healthy skin.

In order to attempt to reconcile these seemingly divergent results, it is important to consider the methodologies used. Fahlen et al.[11] compared whole skin biopsies to control skin, derived from dermato-surgical procedures obtained during removal of skin lesions. The extent to which this skin had a microbial composition similar to completely healthy skin is unclear. Moreover, the previous use of antibiotics, in either group, was not specifically commented upon. Finally, the study concentrated on involved and healthy skin, perhaps missing more dynamic changes that may occur in uninvolved skin.

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However, given that Fahlen et al.[11] did not specifically match specimens by skin site, the detection of site-specific differences becomes even more significant. Furthermore, the attempt by Fahlen et al.[11] to capture a more complete picture of the cutaneous microbiome, by specifically including the dermis and the key adnexal structures, for example the pilosebaceous unit, should be recognised. In fact, the skin microbiome has recently been reported to include bacteria in the dermis and subcutaneous fat. [58] Ultimately this may contribute to the development of a more nuanced understanding of the cutaneous microbiome and reveal potential skin compartment-specific regulation. Any dysregulation of this may conceivably contribute to the development of disease or altered wound healing.[20]Furthermore, given the aforementioned association between Group *A ß-haemolytic Streptococci* andpsoriasis,[39] the increased prevalence of *Streptococci* in psoriasis skin, consistent with the original findings of Gao et al.,[51] deserves further attention.

Utilising microbiome data: bringing sequencing into the clinic

With these at times seemingly divergent data, at both the level of bacteria phyla and genera, Statnikov sought to move the field forward by determining feasibility of identifying the "molecular signature(s)" of psoriasis.[57] Using high-throughput sequencing, in combination with generalised local learning multivariate analysis techniques, three genera from the *Proteobacteria* Phylum, *Cupriavidus, Methylobacterium* and *Schlegelella*, could be used to statistically differentiate between healthy, and involved and uninvolved psoriasis skin. It should be noted that both the V1-V3 and V3-V5 regions of the 16S rRNA gene were targeted.

Moving from the "cutaneotypes" described in earlier work [53] to specific microbiome psoriasis signatures is a promising concept that awaits replication. If substantiated, such an approach would not only improve characterisation of psoriasis phenotypes or endotypes, but would also hold promise as a biomarker of response to treatment i.e. a drug response endotype. Specifically, changes in the microbiome signature may be used to predict treatment response, or even serve as a basis for treatment selection; much needed at a time when the therapeutic armamentarium in psoriasis has rapidly expanded.

Can microbiome research reveal insights into the pathophysiology of inflammatory disease?

Drawing lessons from the largely descriptive studies of the cutaneous microbiome in psoriasis, attention should focus on translating these findings into developing an integrated model of the pathogenesis of psoriasis; potentially unveiling new therapeutic targets. To this end Fry et al. [6,41] have charted the key aspects of the immune system which may be influenced by the microbiome. For example, they highlighted the potential two-way interaction between anti-microbial peptides, toll-like receptors, peptidoglycan-recognition proteins and cytokines on commensal cutaneous bacteria. [59] Indeed, it is known that antimicrobial peptides, including cathelicidins (LL-37), play a role not only in regulating the composition of the cutaneous microbiome, but also in the regulation of bacterial function, for example biofilm formation and may also act as a potential autoantigen in psoriasis.[60-62] (Figs. 2 and 3).

Recognising that treatments for psoriasis and other immune-mediated inflammatory diseases, particularly inflammatory bowel disease, may target shared cytokine pathways, [63] an interesting question is the extent to which microbiome research can reveal insights into the pathophysiology of inflammatory disease in general. The paradoxical development of psoriasis is well-recognised during tumour necrosis factor inhibitor therapy for Crohn disease.[64] Exacerbations of Crohn disease may be induced by anti-interleukin-17 therapy in patients with psoriasis.[65] It is at least conceivable that the site-specific effects of biologic therapies may be mediated by differences in the microbiome, or more intriguingly, by affecting skin-gut microbial cross-talk. Given the potential interplay between the

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gastrointestinal and cutaneous microbiomes,[50,66] and affected patients' respective immune systems, future studies would be advised to investigate both.

Conclusion and open questions

Given the myriad of factors which can influence the cutaneous microbiome, a major challenge confronting this area of research remains the establishment of standardised experimental design so as to enable valid comparisons between the wealth of published data. Such an approach should be built on best experimental practice and must be adaptable following technological advances. Perhaps a set of basic, but detailed, reporting criteria, including study population, methods of sample procurement and processing, and data analysis, would serve as a useful first step in helping to interpret microbiome data. As outlined, microbiomes differ and future work should also concentrate on which regions of the hypervariable 16S gene are best targeted for specific ecological niches and to address specific research questions.

Cutaneous microbiome research to date has captured the complex nature of bacterial colonisation of human skin. The complexity is highlighted by the observation that disparate bacterial communities are supported and sustained in regions of skin sometimes only a few centimetres apart. The regulation of the microbiome in anatomically distinct skin locations (even within skin compartments), its effect on the cutaneous immune system and its potential role in disease pathogenesis will likely form the basis of intense research activity over the next decade. Only carefully designed, large, prospective controlled longitudinal studies will help address the perennial cause and effect question, which often overshadows microbiome studies. Clearly establishing the extent to which bacteria play a role in psoriasis pathogenesis is crucial to provide a rationale for antibacterial therapy in an age of increasing antibiotic resistance.

Acknowledging the largely descriptive nature of human cutaneous microbiome research to date, the key challenge is now to utilise this wealth of data to improve patient care. Future studies should address the extent to which the skin microbiome contributes to, or indeed is protective against the development of disease. In addition, the potential of the microbiome to aid treatment selection or even predict treatment response, in the age of personalized medicine, remains an exciting possibility. A comprehensive and nuanced understanding of the cutaneous microbiome in health and disease, including bacteria but also fungi (especially *Malassezia* [67]) and viruses, recognising that there is in fact no single "skin microbiome," but site- and skin microenvironment-dependent cutaneous bacterial populations, may deepen our understanding of cutaneous (patho-) physiology and identify new therapeutic strategies and targets. Therefore, perhaps the major challenge facing research on the cutaneous microbiome is to establish the extent to which it can be modulated. In addition to modulation with antibiotics (topical or systemic) or antiseptics, such modulation can either be direct intra- or even inter-individual skin microbiome transplantation or indirect via cross-talk with the gastrointestinal microbiome (pre- and probiotic application), as novel strategies in the management of psoriasis.

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Figure Legends

Figure 1. From swabbing to sequencing; the workflow. An overview of the various steps involved in cutaneous microbiome research, from swabbing to sequence analysis, is illustrated.

Figure 2. Bacterial-Host interactions at the cutaneous interface. The potential mechanisms underpinning the bidirectional communication between the cutaneous microbiome and host immune systems are illustrated. Cutaneous innate immune defences, including Toll-like receptors, Pattern recognition receptors, Proteoglycan recognition proteins and anti-microbial peptides may all contribute to the regulation of the cutaneous microbiota. Dysregulation of the cutaneous microbiota, resulting from colonization by pathogenic bacteria and/or altered innate immune response, may result in the acquired immune system promoting a Th1/Th17 response and the subsequent development of inflammatory skin lesions, for example in psoriasis.

Figure 3. Potential roles for bacteria in the transition from healthy skin to psoriatic plaques. The interplay between genetic, environmental and microbiological factors are likely to mediate the effect on the microbiome on the development of inflammatory skin disease. The central question is to what extent each of these factors plays a role in molding the composition of the cutaneous microbiome? With a better understanding of the checks and balances regulating the skin's bacterial flora, new therapeutic strategies can be developed to modulate the microbiome to restore bacterial diversity to healthy levels and avoid down-stream pro-inflammatory responses from the innate and acquired immune systems.

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From swabbing to sequencing; the workflow

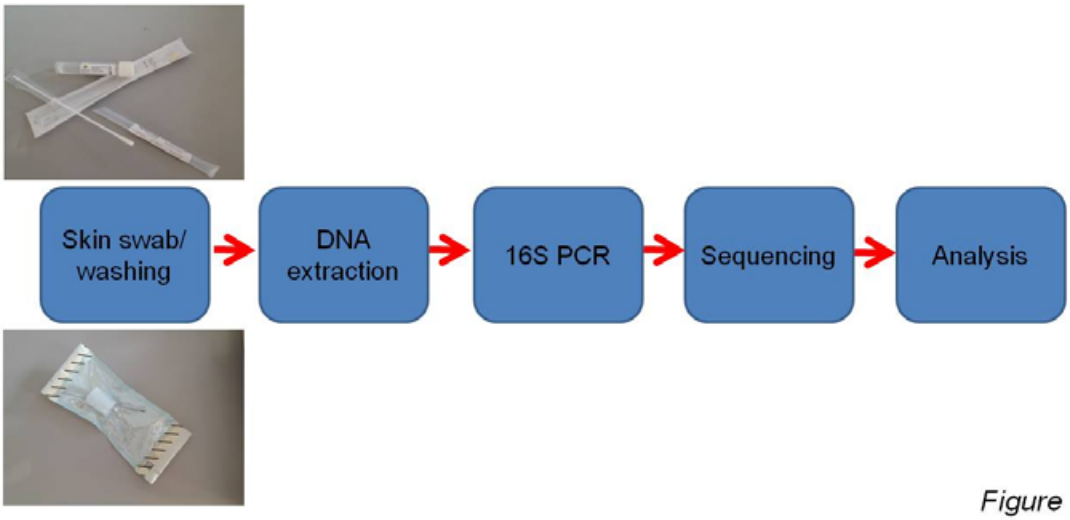

Figure 1

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Potential Bacterial-host interactions at the cutaneous interface

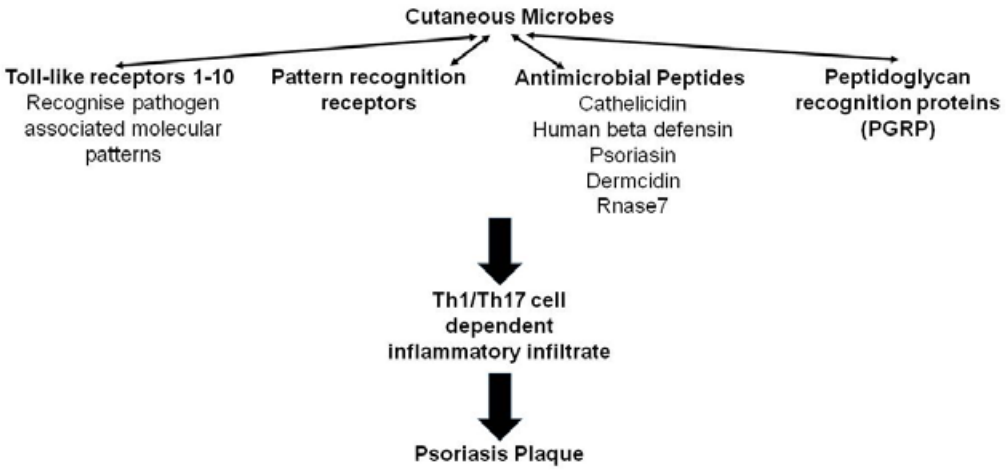

Figure 2

Potential roles for bacteria in the transition from healthy skin to psoriatic plaques

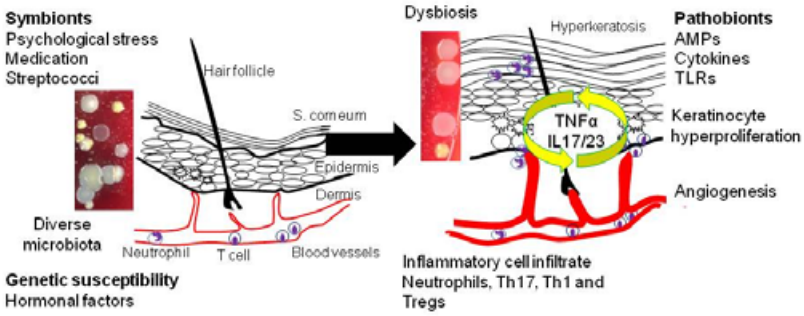

Figure 3

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