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# What Lives On Our Skin: Ecology, Genomics and Therapeutic Opportunities Of the Skin Microbiome

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## Abstract

Our skin is home to a rich community of microorganisms. Recent advances in sequencing technology have allowed more accurate enumeration of these human-associated microbiota and investigation of their genomic content. *Staphylococcus*, *Corynebacterium* and *Propionibacterium* represent the dominant bacterial genera on skin and illustrate how bacteria adapt to life in this harsh environment and also provide us with unique benefits. In healthy states, our skin peacefully co-exists with commensal bacteria while fending off potentially dangerous invaders. Disruption of this equilibrium, termed “dysbiosis”, can result from changes in the composition of our skin bacteria, an altered immune response to them, or both and may be a driving factor in certain types of inflammatory skin disease. Engineering topical therapeutics to favourably influence the composition of our skin flora and optimize interactions with them represents a real therapeutic opportunity for the field of dermatology and warrants additional investigation into skin microbial ecology and disease mechanisms related to host-microbe dysbiosis.

## Introduction

The human body is covered with microorganisms; in fact, bacteria outnumber our own cells 10:1 [1]. Moreover, despite being a uniquely inhospitable environment each square centimeter of our skin is home to approximately $10^6$ bacteria [2]. Recent advancements in sequencing technology have enabled more accurate identification of these human-associated microbiota and their genomic content - the human “microbiome.” Having co-evolved with our microbiota over millennia, we do not just tolerate but also benefit from the presence of microbiota in ways that are suspected but poorly understood.

Our skin acts as a physical barrier and is armed with surveillance mechanisms, e.g. langerhans cells and toll-like receptors (TLRs), and a molecular and cellular defence arsenal, e.g. anti-microbial peptides (AMPs) and T cells [3]. To maintain health we must navigate a



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delicate balance that allows symbiosis with our commensal bacteria while fending off potentially dangerous invaders. Disruption of this equilibrium or "dysbiosis" can result from a change in the composition of skin bacteria, or an alteration of the host immune response, or both; in either case the end result is excessive inflammation (Figure 1). Subtle dysbiosis with our skin microbiota likely contributes to inflammation seen in a number of disease states, though more work is needed to better define the nature and extent of this phenomenon. Here we will review recent key findings in the field of skin microbiome research, with an emphasis on introducing current techniques, identifying the key bacterial players, exploring what is known about the skin's relationship with these bacteria and highlighting key challenges that lie ahead in this field.

## Enumerating who's there

Historically, microbial ecology has relied on the ability to isolate bacteria from a niche and cultivate them *in vitro* for identification and characterization of phenotypes such as antibiotic resistance. However, culture-based approaches are prone to biased results such as over-estimating the abundance of bacteria that grow easily and quickly in the lab or failing to identify important species that require unique growth factors not easily replicated *in vitro* [4].

Over the last several years, researchers have begun to take advantage of culture-independent molecular techniques and next generation sequencing to enumerate bacterial communities [5]. One of two approaches is generally employed. The first, called 16S rRNA gene sequencing, relies on conserved sequences in the region encoding the 16S ribosomal RNA to amplify this gene segment from all bacteria in a given sample. The resulting mixture of 16S amplicons can then be sequenced and compared to existing databases in order to make phylogenetic assignments, enumerating a community's constituent microbial genera and their relative abundance. By comparison, shotgun metagenomic sequencing is a technique by which the total metagenomic DNA from a sample is isolated and sequenced en masse. Depending on the DNA purification method, this yields information not only about bacteria but also viruses, fungi, and host cells present in a sample. The resulting sequences are mapped to reference genomes or stitched into larger fragments by de novo assembly methods. Phylogenetic assignments can then be made as they are for 16S rRNA gene sequencing, but there is also the capacity to collect information about microbial function based on genomic content. Metagenomic sequencing can therefore be used not only to generate a species roster but to predict the functional capacity for a given bacterial population. An important caveat is that metagenomic sequencing cannot confirm gene expression or verify that a particular microbe is performing a specific function. To date, most skin microbiome surveys have been performed using 16S, since metagenomic sequencing can be more difficult on skin than other body sites with higher bacterial loads and a greater number of reference genomes such as the gastrointestinal tract [6].

Surveys of skin sites using 16S rRNA gene sequencing have uncovered a rich and highly diverse bacterial community [7, 8, 9, 10]. These studies have confirmed key bacterial players that have long been considered important components of the human skin microbiota, and also identified novel species that had not been discovered by culture-based techniques. Molecular methods can also be used to characterize yeast [11, 12] and viral communities [13]. Efforts to better define the skin "mycobiome" and "virobiome" are ongoing but we will focus here on skin bacteria.

Our skin microbiota is acquired at birth [14] and its composition is highly dynamic early in life [15, 16]. These communities stabilize as we approach adulthood, but continue to evolve in response to various host and environmental factors. Variation in our skin microbiota can

be defined in terms of several parameters: topographical, interpersonal and temporal diversity [17]. Compared with other body sites, the skin microbiome has greater complexity based on variation across different topographical skin niches: i.e. the forearm bacterial community is very different in composition from the axilla community. In fact, similarities between microbial communities are more dependent on the particular skin site than on the individual from which they are sampled. This suggests that our skin bacteria are highly adapted to live in their particular body niche.

The skin microbiome is also notable for having more interpersonal variation than is generally seen at other body sites; this is particularly true for exposed sites such as the hand and less so for moist or sebaceous sites such as the inguinal crease or external auditory canal [7, 18, 19]. Additionally, the community composition of an individual site can fluctuate over time. Further studies are needed to better define the degree and nature of these temporal fluctuations [20] but early evidence suggests that exposed sites which also demonstrate greater microbial diversity tend to fluctuate more over time than occluded sites [17]. Despite these variations by age, site, individual and time, our skin microbiome is dominated for the most part by just four phyla: Actinobacteria, Proteobacteria, Bacteriodetes and Firmicutes. In particular, three genera – *Staphylococcus*, *Corynebacterium* and *Propionibacterium* – account for over 60% of the bacterial species present [7].

## The Key Players

Our skin is a remarkably inhospitable environment for bacteria; it is acidic, low in moisture, coated in salt-laden sweat, and replete with antibacterial molecules such as free fatty acids, sphingosine, nitric oxide, immunoglobulins and antimicrobial peptides [21, 22]. Despite this, many different types of bacteria have found a way not only to live but also to thrive on skin. The topographical variation of skin is important in determining microbial inhabitants at each site; for example, differences in hair density, sebaceous, apocrine or eccrine activity, pH, and degree of occlusion provide distinct microenvironments that are presumably advantageous for certain species (Figure 2). While a broader discussion of these factors and the different types of skin bacteria can be found elsewhere [23], we would like to highlight here three key bacterial genera and how they have adapted to life on our skin (Table 1).

### Staphylococcus

*Staphylococci* are gram-positive cocci belonging to the Firmicutes and have long been recognized as members of the skin flora since they grow so easily in laboratory culture. *S. epidermidis* is the most prevalent skin strain but many others including *S. hominis, S. capitis,* and *S. saprophyticus* are also present. *Staphylococci* are highly adaptable; they have a propensity for occluded areas such as the axilla, groin or interdigital webspace with relatively higher moisture content, temperature and pH, but are also found on exposed, dry sites such as the palm and volar forearm. As both aerobes and facultative anaerobes, they can colonize the skin surface but also survive the low oxygen environment of the hair follicle.

*Staphylococci* employ a range of strategies for surviving on skin. They are halotolerant, meaning that they can withstand the high salt content of sweat, and may even use urea present in sweat as a source of nitrogen. They possess a variety of adhesins that likely facilitate attachment to skin as well as proteases that may help re-model the stratum corneum and liberate additional nutrients. Over 80% of *S. epidermidis* strains also produce an enzyme for esterifying fatty acids to cholesterol, a function that might protect them from the effects of these abundant bactericidal lipids [24].

*S. aureus* is usually thought of as a pathogen, but the methicillin-resistant strain USA300 is increasingly found colonizing moist skin sites of healthy people [25]. Unlike other *S. aureus* strains, USA300 contains the arginine catabolic mobile element (ACME), which it appears to have acquired horizontally from *S. epidermidis* [26]. ACME encodes several genes including a second copy of arginine deimidase, an enzyme capable of converting arginine to ornithine. Since arginine is an abundant amino acid in the stratum corneum and can otherwise be used to generate nitric oxide or to acidify the skin pH, depleting this pool of arginine may optimize growth conditions for *Staphylococci*. ACME also includes an oligopeptide permease operon that has been hypothesized to facilitate uptake of short peptides for nutrients [27]. The verdict is still out on whether or how ACME confers an advantage for growth on skin, but today's genomic tools provide an opportunity to investigate this mystery.

### Corynebacterium

*Corynebacteria* are gram-positive aerobes or facultative anaerobes belonging to the Actinobacteria. They have a propensity for growth on moist and sebaceous skin sites, and have been implicated in skin conditions such as erythrasma and pitted keratolysis. Several members of the genus are abundantly found on skin, including *C. accolens, C. jeikeium, C. urealyticum, C. amycolatum, C. minutissimum,* and *C. striatum* [28]. *Corynebacteria* are "lipid-loving" bacteria; more specifically many are lipophilic (i.e., lipid auxotrophs), which means they cannot produce their own lipids and must obtain them from their environment. Not coincidentally, both sebum and the stratum corneum are rich in lipid components. *Corynebacteria* utilize these for nutrients as well as to generate corynomycolic acids that coat their cell surface. Most *Corynebacteria* are also halotolerant -- capable of growing in the presence of high salt concentrations -- explaining their ability to colonize sites rich in eccrine glands, and some rely on vitamins in sweat for survival [22].

### Propionibacterium

*P. acnes* is the best known member of this genus of gram-positive anaerobic bacilli, but several others are found regularly on skin. *P. acnes* and *P. granulosum* live in areas rich in sebaceous secretions, while *P. avidum* favors regions rich in eccrine sweat [29]. *Propionibacteria* tend to localize to hair follicles where oxygen content is low but can be cultured from the skin surface. *P. acnes'* affinity for sebaceous sites is explained by the multitude of lipases found in its genome, which it likely uses to acquire nutrients from lipid-rich sebum [30]. *P. acnes* also produces proteases capable of liberating arginine, a key carbon and energy source, from skin proteins [31]. Lastly, *P. acnes* is known to produce large quantities of porphyrins, which is sometimes exploited in treatment of acne [32]. Why *Propionibacteria* choose to spend so much energy generating these porphyrins remains unclear, but their production could have implications for its relationship with other skin bacteria or the host.

## Host-microbe interactions

### Microbe-microbe dynamics

Resident skin bacteria provide the first line of defence against potentially dangerous pathogens and also produce small molecules that influence growth and behavior of their microbial neighbors. Certain strains of *S. epidermidis* secrete *Esp*, a protease that inhibits biofilm formation and colonization by *S. aureus* in the anterior nares [33]. AMPs of the lantibiotic and phenol soluble modulin classes are also produced by *Staphylococci* and have activity against skin pathogens, though their clinical relevance remains undetermined [34, 35, 36]. The abundance of *Corynebacterium* spp. in the nares is inversely correlated with

that of *S. aureus* [37], suggesting that they too may serve a protective function against skin pathogens.

### Immune function

Skin is a powerful immune organ replete with AMPs, TLRs, langerhans cells, and effector and regulatory T cells. It is important to recognize that our skin bacteria can have a synergistic as opposed to purely antagonistic relationship with this immune arsenal [38]. For example, *S. epidermidis* can upregulate production of the AMP human beta defensin 2 via activation of TLR2 [39] and amplify the immune response of keratinocytes to pathogenic bacteria [40]. Conversely, *S. epidermidis* can also inhibit TLR3-dependent inflammation after skin wounding via activation of TLR2 by surface lipoteichoic acid [41].

The skin of germ-free mice harbors increased numbers of regulatory T cells and demonstrates reduced production of IFN-γ and IL-17A by effector T cells. Colonizing the skin of these mice with *S. epidermidis* is sufficient to restore IL-17A production in an IL-1R dependent manner, suggesting that commensal skin bacteria are necessary for optimal skin immune function [42]. Whether bacterial populations at remote body sites, such as the colon, might also influence inflammatory patterns in the skin is another intriguing and unanswered question. The study discussed above in germ-free mice could not confirm any such effect, but clinical observations such as neutrophilic skin disorders associated with inflammatory bowel disease or bowel bypass surgery as well as preliminary work examining the effect of probiotics on atopic conditions suggest that further investigation is warranted [43].

### Barrier function

Mechanisms by which skin flora interact with or influence our physical skin barrier are less well defined but likely important. *S. aureus* has the ability to convert histidine, an abundant skin amino acid, to trans-urocanic acid (unpublished data), a molecule that both contributes to the skin's natural moisturizing factor and serves a natural UV-protectant [44]. As discussed earlier, *Corynebacterium* spp. have the capacity to modify lipids from their surrounding environment; this has the potential to impact the lipid composition in the stratum corneum or sebum. We know that the skin's permeability and antimicrobial barriers are co-ordinately regulated and interdependent [45]. Bacteria are known to stimulate production of AMPs but it remains to be seen whether their presence might also augment pathways contributing to keratinocyte differentiation and cornification.

## Challenges and opportunities ahead

How will dermatology capitalize on recent advances in the field of microbiome research to improve understanding of skin disease? An important first step is already underway: to revise our thinking about inflammatory skin disease to include potential host-microbe interactions as factors that can potentiate or even initiate inflammation without the prerequisite of overt infection. To date, acne vulgaris, acne rosacea, psoriasis and atopic dermatitis have received the most attention in this regard [38], but this list will likely grow much longer as we learn more. Genetics and other host factors are of course central to pathogenesis in these inflammatory conditions but our cutaneous immune system does not operate in a vacuum. Shifts in the skin microbiota may act cooperatively with host susceptibility factors to perpetuate a pathogenic pro-inflammatory state. Rather than the blunt approach of conventional antibiotics, future therapies to address microbial contribution to disease will hopefully involve more subtle manipulation of the host-microbiome ecosystem. Engineering topical therapeutics to favourably influence the composition of our

skin flora and optimize interactions with them represents a real opportunity but will require additional groundwork.

Advancing the concept of "host-microbe dysbiosis" towards a set of concrete mechanisms will require further attention to both the "host" and "microbe" pieces of this puzzle. Having now enumerated the types of bacteria on healthy skin, our next mission is to explore through bioinformatics how their collective genomes complement and augment the processes we consider critical to skin biology and health. Efforts by the NIH Common Fund's Human Microbiome Project to sequence entire genomes from human bacterial isolates will facilitate this effort [5]. Studies using 16S rRNA gene sequencing to characterize microbiota shifts in the setting of skin disease are already underway [46, 47, 48]. Continuing such efforts should be a priority with the caveat that we are likely to learn most from studies that include large numbers of subjects, employ whole-genome shotgun metagenomic sequencing, and incorporate a prospective longitudinal approach to sampling in order to help distinguish instrumentative shifts in microbiota from secondary changes due to inflammation, disordered cornification or ulceration inherent to many skin diseases. These sorts of studies are large undertakings and should be paired appropriately with mouse or human skin models in which the specific effects of bacterial shifts can be validated.

Recent attention to human microbiome research in the lay media has touted its potential importance in treating a wide-array of medical conditions, from obesity to diabetes. This enthusiasm is well founded but needs to be paired with discussion of realistic near-term goals. Microbiome research has a bright future in the field of dermatology and is sure to gather steam in years to come. Whether topical probiotics to treat skin disease will ever become a reality remains to be determined [49], but engineering topical therapeutics to favourably influence the composition of our flora and optimize their interaction with our skin is a real possibility.

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Molecular techniques have uncovered a diverse community of skin microorganisms uniquely adapted to colonize human skin.

Topographical variation in the skin microenvironment is important in determining microbial inhabitants at each skin site.

“Host-microbe dysbiosis” can result from changes in the composition of skin bacteria, an altered immune response to them, or both

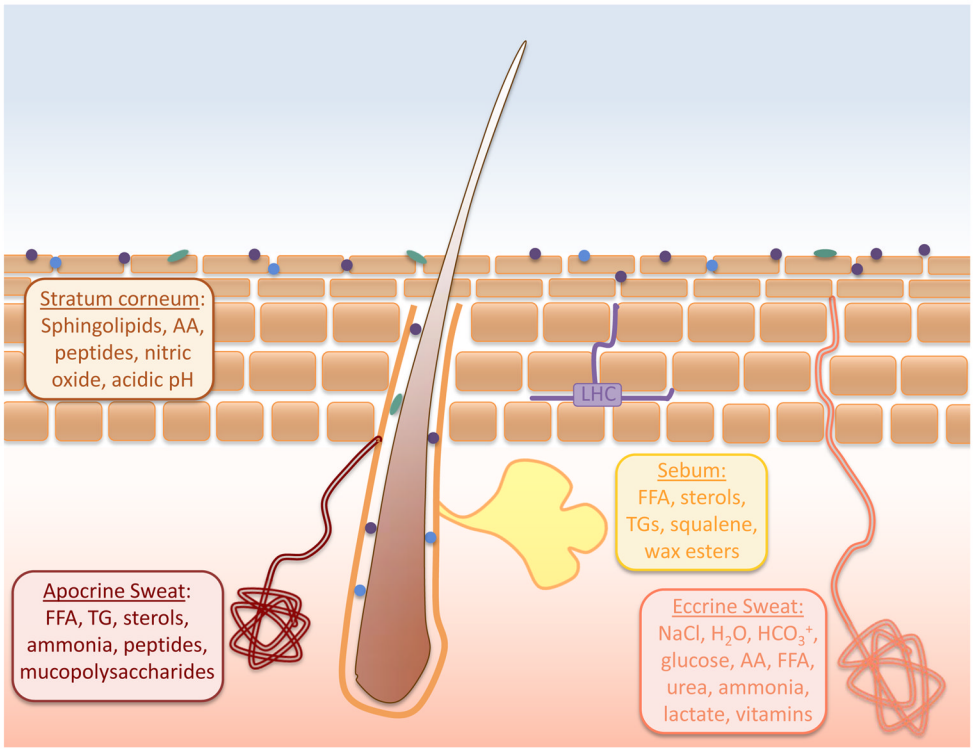


**Figure 1.**

Skin microenvironment shapes composition of cutaneous flora: Bacteria derive nutrients from components of the stratum corneum, sebaceous, eccrine and apocrine secretions, examples of which are detailed here. Relative abundance of these skin nutrients varies by skin site and the composition of the bacterial flora fluctuates accordingly. *Staphylococcus* spp, which can tolerate high salt concentrations and utilize urea and amino acids in sweat as a source of nitrogen, are favored in areas with a high density of eccrine glands. By comparison, *Propionibacterium* spp have lipases and favor areas rich in sebaceous lipids. (AA = amino acids; FFA = free fatty acids; $HCO_3^+$ = bicarbonate; $H_2O$ = water; LHC = langerhans cell; NaCl =sodium chloride; TG = triglycerides)

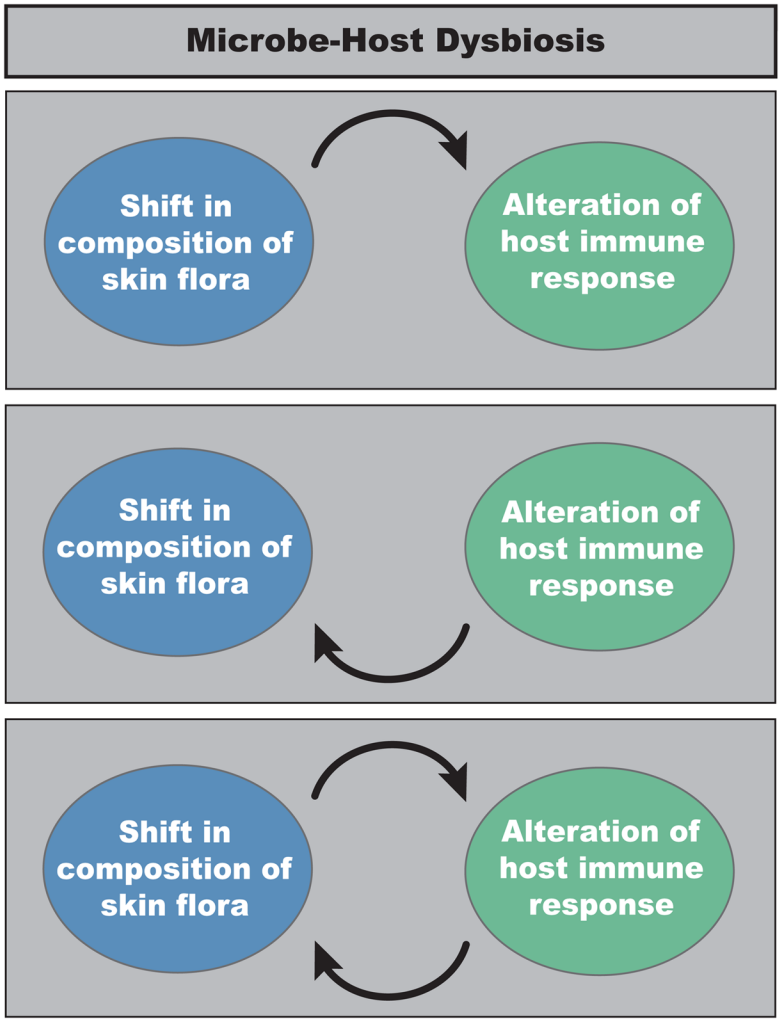


**Figure 2.**
Microbe-host dysbiosis refers to a state of imbalance with the microbiota that negatively impacts the host. This can occur primarily as a result of exogenous factors that alter the composition of the flora towards a more pro-inflammatory population. Alternatively, host susceptibility factors such as polymorphisms in innate or adaptive immune elements can lead to excess inflammation prior to any significant microbial shift. Either case can lead to a state where both the microbiota and host immune response are altered and contribute to a vicious cycle of detrimental inflammation.

**Table 1**

Overview of the three major skin bacterial genera [22, 23]

| Genus | Phylum | Primary Nutrient Sources in Skin | Molecules that may mediate microbe-microbe or microbe-host interactions |
|---|---|---|---|
| *Staphylococcus* | Firmicutes | Sweat: Urea, ammonia, AAs, glucose<br>Sebum: AAs<br>SC: peptides | Lantibiotics, phenol-soluble modulin, adhesins, proteases |
| *Corynebacterium* | Actinobacteria | Sweat: Urea, ammonia, vitamins, glucose<br>Sebum: lipids<br>SC: lipids | Corynomycolic acids, free fatty acids |
| *Propionibacterium* | Actinobacteria | Sweat: AA, glucose<br>Sebum: lipids, AA<br>SC: peptides, lipids | Porphyrins, propionic acid, lipases, proteases |

AA = amino acids, SC = stratum corneum