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What lives on our skin: ecology, genomics and therapeutic opportunities of the skin microbiome

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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 favorably 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.

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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, for example, Langerhans cells and toll-like receptors (TLRs), and a molecular and cellular defence arsenal, for example, anti-microbial peptides (AMPs) and T cells [3]. To maintain health we must navigate a 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

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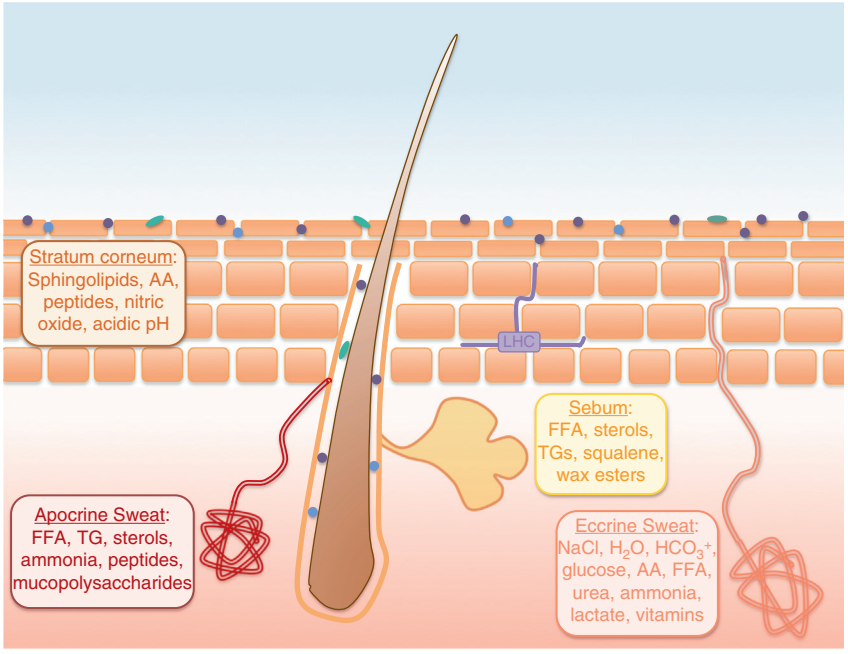

Figure 1. Skin microenvironment shapes composition of cutaneous flora: Bacteria derive nutrients from components of the stratum corneum, sebaceous, eccrine and apocrine secretions, examples of which are detailed here. Relative abundance of these skin nutrients varies by skin site and the composition 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).

result is excessive inflammation (Fig. 1). Subtle dysbiosis with our skin microbiota probably contributes to the inflammation seen in several disease states, although 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 past 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 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, because 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].