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TOPICAL REVIEW

Shaping of cutaneous function by encounters with commensals

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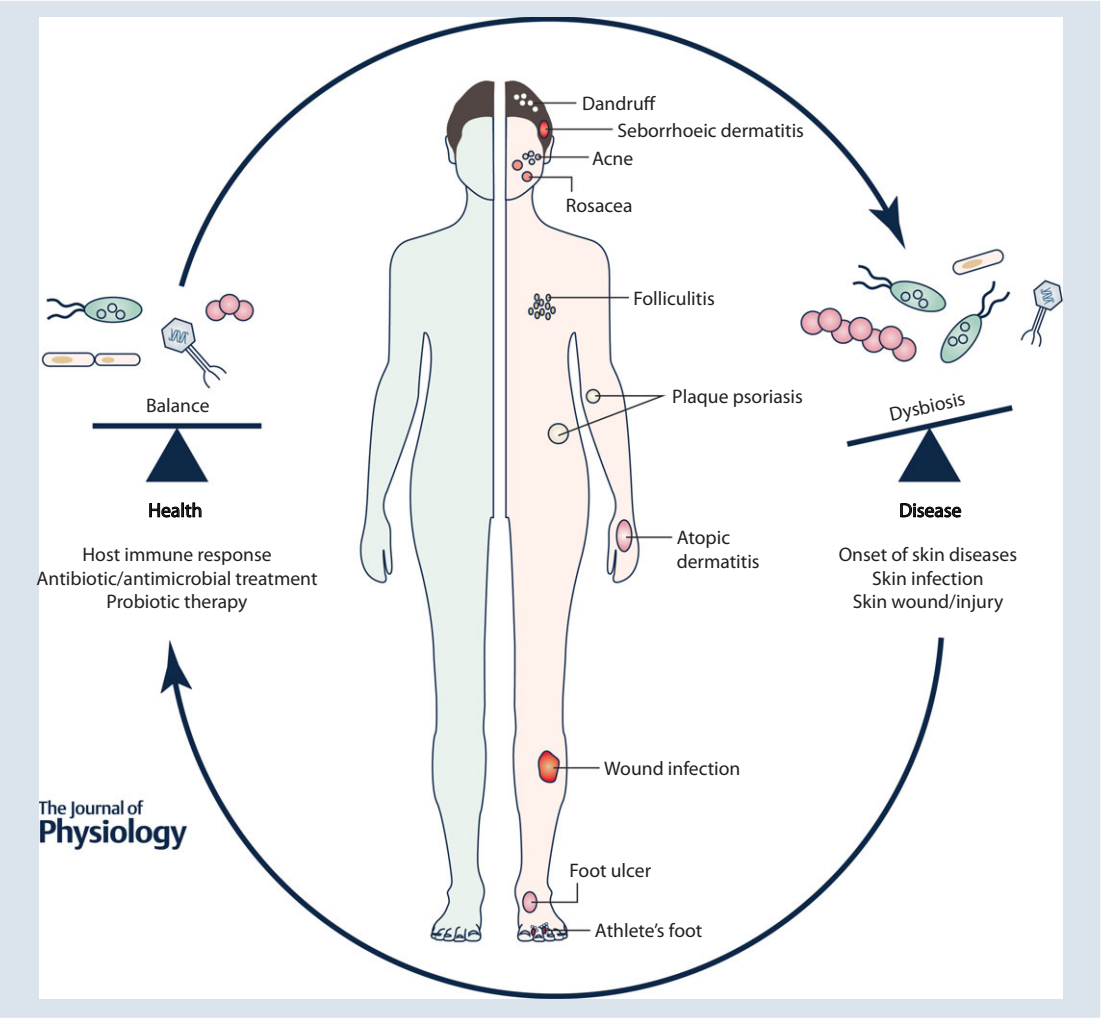

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Abstract The skin is the largest organ in the human body and provides the first line of defence against environmental attack and pathogen invasion. It harbor multiple commensal microbial communities at different body sites, which play important roles in sensing the environment, protecting against colonization and infection of pathogens, and guiding the host immune system in response to foreign invasions. The skin microbiome is largely variable between individuals and body sites, with several core commensal members commonly shared among individuals at the healthy state. These microbial commensals are essential to skin health and can potentially lead to disease when their abundances and activities change due to alterations in the environment or in the host. While recent advances in sequencing technologies have enabled a large number of studies to characterize the taxonomic composition of the skin microbiome at various body sites and under different physiological conditions, we have limited understanding of the microbiome composition and dynamics at the strain level, which is highly important to many microbe-related diseases. Functional studies of the skin microbial communities and the interactions among community members and with the host are currently scant, warranting future investigations. In this review, we summarize the recent findings on the skin microbiome, highlighting the roles of the major commensals, including bacteria, fungi and bacteriophages, in modulating skin functions in health and disease. Functional studies of the skin microbiota at the metatranscriptomic and proteomic levels are also included to illustrate the interactions between the microbiota and the host skin.

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Abstract figure legend Hundreds of microorganisms colonize the human skin at various sites. They form complex communities that function with the host immune system together to defend against pathogens and to maintain skin health. Microbial dysbiosis impairs normal skin function, and is a feature typical of diseased and injured skin.

Abbreviations AMP, antimicrobial peptide; GAS, Group A *Streptococcus*; ITS, internal transcribed spacer; SCFAs, short chain fatty acids; TLR, Toll-like receptor.

Introduction

The skin is the largest organ in the human body and plays important roles in human physiology. Organized as an assembly of cells in highly structured layers including the epidermis, dermis and subcutaneous regions, the skin acts as the physical barrier protecting the internal organs from environmental changes and pathogen invasion (Madison, 2003).

The skin is also a host for hundreds of microorganisms, including bacteria, eukaryotes and viruses. Immediately after birth, diverse microbial communities colonize the skin at different sites with unique physiological and immunological niches. The resident microorganisms sequester nutrients from skin secretions and form a dynamic ecological system with the host skin through complex interactions within the microbial communities and with the host. The composition, dynamics and function of the skin microbiota have a significant impact on skin health and function.

Skin microorganisms have been recognized mostly in their role in various skin diseases, and the emphasis in medical implication has been on how to remove the pathogenic organisms. The research in recent years through microbiome studies has revealed that the microorganisms on the skin are an essential part of the host–microbiota symbiotic system, suggesting that skin commensals play important roles in maintaining skin health and proper function (Sanford & Gallo, 2013). This new view calls for paradigm-shifting recognition of the functions of the skin microorganisms in skin health and new treatment strategies for microorganism-associated skin diseases.

Taxonomic composition of the human skin microbiome

Studies investigating the composition of the human skin microbiome have revealed the presence of hundreds of microorganisms including bacteria, fungi, parasites and viruses (Grice & Segre, 2011). To date, the majority of culture- and sequencing-based microbiome studies have focused on characterizing the skin bacterial and fungal communities. Based on sequencing analysis of phylogenetic marker genes, such as the bacterial 16S ribosomal RNA (rRNA) and fungal internal transcribed spacer (ITS), the bacterial residents identified mainly belong to four phyla: Actinobacteria, Firmicutes, Proteobacteria and Bacteroidetes (Gao *et al.* 2007; Grice *et al.* 2009), while the majority of fungal species

identified are from a single genus, *Malassezia* (Findley *et al.* 2013).

While the taxonomic composition of the skin microbiome has been well characterized at the genus or sometimes species level, its strain-level composition and dynamics are still poorly understood. Two studies have shown that two of the most abundant skin bacterial species, *Propionibacterium acnes* and *Staphylococcus epidermidis*, exhibit strain-level diversity between individuals, skin status, and the skin site sampled (Fitz-Gibbon *et al.* 2013; Oh *et al.* 2014). Fitz-Gibbon *et al.* identified strain-level differences in the skin microbiota between acne patients and healthy individuals. Certain *P. acnes* strains were highly associated with acne while some other strains were enriched in healthy skin (Fitz-Gibbon *et al.* 2013). Genome comparison based on the single nucleotide polymorphisms (SNPs) observed in a large number of sequenced *P. acnes* strains revealed that strains isolated from the same individuals were often more closely related to each other than to the strains isolated from different individuals, suggesting individuality of the skin microbiota at the strain level (Tomida *et al.* 2013). Consistently, metagenomic shotgun sequencing analysis by Oh *et al.* revealed that *P. acnes* strain types and abundances were primarily driven by individuality as opposed to body site. *S. epidermidis* strains, on the other hand, exhibited less individual specificities. Instead, the strains were correlated with the body sites from where they were collected (Oh *et al.* 2014).

In contrast to bacterial and fungal compositions, only a few studies have described the remaining skin inhabitants such as the viral and parasitic components. Metagenomic shotgun sequencing analysis and culture-based studies have started to unfold the composition and function of the skin viral community. Double stranded DNA (dsDNA) eukaryotic viruses, including herpesviruses, papillomaviruses, polyomaviruses, circoviruses, adenoviruses, anelloviruses and paroviruses, were identified in the healthy skin microbiota (Foulongne *et al.* 2012; Ma *et al.* 2014; Wylie *et al.* 2014). In addition, prokaryotic viruses of the major skin bacteria, in particular *P. acnes* and *S. epidermidis* phages, were found at multiple skin sites (Oh *et al.* 2014; Liu *et al.* 2015). These initial studies suggest the existence of a complex and dynamic virome on the human skin.

Microscopic analysis of skin samples has revealed the presence of parasitic mites on the human skin (Crosti *et al.* 1983; Kligman & Christensen, 2011). However, further investigation of the skin viral and parasitic communities has thus far been hampered in part due to the low abundances of these organisms. Limited cultivation methods, a lack of genomic reference databases, and few molecular tools to enrich and identify these organisms also pose challenges in studying these communities on the skin. Future developments in molecular methods and sequencing technologies will improve our understanding of the role of the less abundant skin microorganisms and their interactions with others in the community and with the host in shaping the function of the human skin.

Factors influencing the composition of the skin microbiome

The composition of the human skin microbiome is influenced by multiple factors. Similar to the microbial communities at other body sites, individual variation is the major factor differentiating the skin microbiome among the populations (Gao *et al.* 2007; Costello *et al.* 2009). Age, sex and hygiene practice have been suggested to contribute to the individual variation of the skin microbial composition (Larson, 2001; Fierer *et al.* 2008; Song *et al.* 2013).

The spatial site is another factor affecting the skin microbiome composition. The skin is composed of a number of compartmentalized regions with distinct physiological properties such as pH, temperature, moisture, sweat level and lipid content. Each site represents an ecological niche that favours the growth of its own unique collection of microorganisms. The microbial communities at dry, moist and lipid-rich sites are largely different (Fig. 1). The most diverse skin microbial communities are found on the dry and exposed skin sites, such as the forearm and palm (Gao *et al.* 2007; Costello *et al.* 2009; Grice *et al.* 2009). The skin microbiota of the moist and sweat-rich axilla (underarm) is dominated by aerobic *Corynebacterium* and *Staphylococcus* species, which prefer conditions of higher temperature and humidity (Costello *et al.* 2009; Grice *et al.* 2009). The lipid-rich areas of the skin, such as the sebaceous sites of the face and upper trunk, exhibit the lowest microbial diversity, colonized primarily by lipophilic microorganisms including *Propionibacterium* and *Malassezia* species, as well as the demodex mite, *Demodex folliculorum* (Costello *et al.* 2009; Grice *et al.* 2009; Kligman & Christensen, 2011; Fitz-Gibbon *et al.* 2013). In an attempt to transplant the skin microbial community from different topographical sites, Costello *et al.* found that over an 8 hour period, forehead and forearm bacterial communities inoculated onto forearm and forehead, respectively, deviated from the original composition and became more similar to the community of the inoculated site. This suggests that the physiological properties of the skin site are a strong driver in defining the composition of the microbial community (Costello *et al.* 2009).

Open to continual contact with surroundings, the skin microbiota is influenced by environmental factors. It has been suggested that human-to-human (Hamburger, 1947; Pittet *et al.* 1999; Meadow *et al.* 2013; Song *et al.* 2013), human-to-pet (Song *et al.* 2013), and even human-to-object (Lax *et al.* 2014; Wood *et al.*

2015) contacts shape the composition of the skin microbial community. Song *et al.* showed that skin bacterial communities can be shared among co-habiting family members, while pet ownership could also lead to the transfer of skin microorganisms between human and animals (Song *et al.* 2013). Diversity analysis of *P. acnes* phages on the skin revealed that the same phage strains were shared among related individuals, suggesting transmission of either phage or the phage-associated bacterial host can occur between individuals (Liu *et al.* 2015).

Transfer of microorganisms between human and surfaces has also been shown in a number of different settings including the computer keyboard, mobile phone, home, classroom, restroom and hospital wards (Hambraeus, 1973; Fierer *et al.* 2010; Flores *et al.* 2011; Lax *et al.* 2014; Meadow *et al.* 2014*a*,*b*). These studies indicate common microbial pools existing in the population, which is important to issues regarding pathogen transmission, health care and hygiene practices (Pittet *et al.* 1999; Flores *et al.* 2011; Meadow *et al.* 2014*b*), and also suggest a potential application of individual microbiome signatures in forensic science (Fierer *et al.* 2010).

In addition to individual differences, topographical variation, and environmental influences, the host health status and the skin condition can also affect the composition of the microbiota. Shifts in skin bacterial and fungal communities have been linked to a number of skin diseases and conditions including psoriasis (Gao *et al.* 2008; Alekseyenko *et al.* 2013; Statnikov *et al.* 2013), atopic dermatitis (Dekio *et al.* 2007; Zhang *et al.* 2011; Kong *et al.* 2012), acne (Fitz-Gibbon *et al.* 2013), dandruff (Clavaud *et al.* 2013), and damaged or wounded skin (Robson, 1997; Price *et al.* 2009; Gontcharova *et al.* 2010; Misic *et al.* 2014). The parasitic mite *Demodex folliculorum*, as well as its own associated microbiota, has been implicated in rosacea (Bonnar *et al.* 1993; Murillo *et al.* 2014).

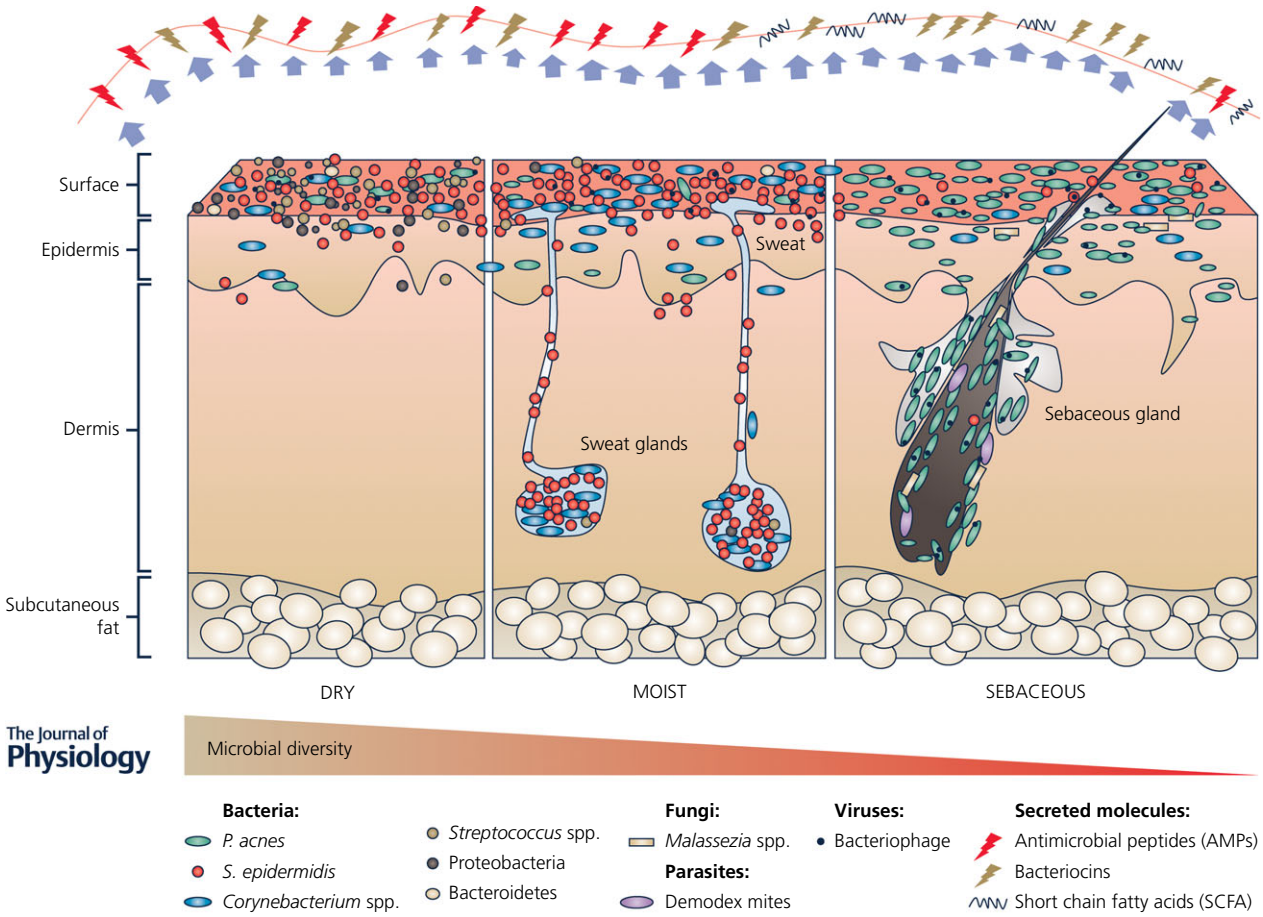

Figure 1. The composition and function of the human skin microbiota
Driven by physiological properties of the skin, the microbial communities at dry, moist and sebaceous skin sites are largely different with various species dominating at each site. *Staphylococcus epidermidis*, *Propionibacterium acnes* and *Malassezia* spp. metabolize skin nutrients, produce physiologically important molecules, such as antimicrobial peptides, bacteriocins and short chain fatty acids, and play a role in defending against pathogen colonization and infection.

Table 1. The functions of the major skin commensals in health and disease

Microorganism	Function in skin health	Disease association	References
Staphylococcus epidermidis	Producing antimicrobial peptides and bacteriocins Promoting host immune responses via TLR signalling	Hospital-acquired, open wound, skin burns and medical device infections	Wisplinghoff *et al.* 2004; Fontana *et al.* 2006; Li *et al.* 2007; Bastos *et al.* 2009; Rogers *et al.* 2009; Cogen *et al.* 2010; Lai *et al.* 2010; Coates *et al.* 2014
Propionibacterium acnes	Metabolizing sebum and producing SCFAs Maintaining acidic skin pH Producing bacteriocins Promoting commensal growth	Acne, SAPHO syndrome, sarcoidosis, sciatica, endophthalmitis, prostate cancer	Ushijima *et al.* 1984; Schaeverbeke *et al.* 1998; Eishi *et al.* 2002; Cohen *et al.* 2005; Schmid-Wendtner & Korting, 2006; Javey *et al.* 2010; Fitz-Gibbon *et al.* 2013; Rollason *et al.* 2013; Shu *et al.* 2013
Corynebacterium spp.	Commensal organisms	Atopic dermatitis	Kong *et al.* 2012; Oh *et al.* 2012
Streptococcus spp.	Commensal organisms	Atopic dermatitis	Oh *et al.* 2012
Malassezia spp.	Producing antimicrobials, such as azelaic acid	Dandruff, atopic dermatitis, folliculitis, psoriasis	Nazzaro-Porro & Passi, 1978; Leeming *et al.* 1986; Brasch & Christophers, 1993; Xu *et al.* 2007; Gaitanis *et al.* 2012
Bacteriophage	Specific lytic activities against bacterial species and strains Modulating skin bacterial populations		Soothill, 1994; Vieira *et al.* 2012; Mendes *et al.* 2013; Liu *et al.* 2015; Pincus *et al.* 2015

Despite variations in the skin microbiome due to multiple contributing factors, skin microbial communities of healthy individuals appear relatively stable over at least several months (Costello *et al.* 2009; Grice *et al.* 2009). The stable nature of the human skin microbiome and persistence of core skin microorganisms suggest important functions of the commensal microbiota in skin health.

Key players of the commensal skin microbiota

Taxonomic studies have identified a number of key players in the healthy skin microbiota. Resident skin microorganisms are often considered commensal or mutualistic; however, with changes to the condition of the skin, including injury or the introduction of medical devices such as implants or catheters, some of the resident microorganisms can behave as opportunistic pathogens. To date, the dominant and most extensively studied members of the healthy skin microbiota include *Staphylococcus*, *Propionibacterium*, *Streptococcus*, *Corynebacterium* and *Malassezia*. Changes in the abundances of these organisms are often linked to diseased states (Paulino *et al.* 2006; Gao *et al.* 2008; Kong *et al.* 2012; Alekseyenko *et al.* 2013; Clavaud *et al.* 2013; Fitz-Gibbon *et al.* 2013) (Table 1). Studies have also implicated phages as potential modulators of the skin bacterial community (Soothill, 1994; Vieira *et al.* 2012; Mendes *et al.* 2013; Liu *et al.* 2015; Pincus *et al.* 2015). Although these skin microorganisms are believed to be beneficial residents of the healthy skin microbiota, their functions in protecting against the action of pathogenic species and in maintaining skin health are not yet fully understood. Below we discuss the roles of the most representative skin commensals, *S. epidermidis*, *P. acnes*, and eukaryotic microorganisms *Malassezia* species, as well as phages, in skin health.

***Staphylococcus epidermidis*.** The Gram-positive bacterium *S. epidermidis* is a dominant skin resident found at multiple body sites. Multi-locus sequence typing (MLST) of *S. epidermidis* has revealed a high level of strain diversity, with nearly 600 sequence types currently identified (http://sepidermidis.mlst.net). Unlike its coagulase-positive relative *Staphylococcus aureus*, coagulase-negative *S. epidermidis* is widely accepted as a beneficial skin microorganism of low pathogenicity. Genomic analysis of *S. epidermidis* has revealed a reduced virulence potential of this species compared to other staphylococci (Zhang *et al.* 2003). The roles of commensal *S. epidermidis* in skin health are twofold. Firstly, *S. epidermidis* produces and secretes a number of antimicrobial peptides (AMPs), such as phenol soluble modulins (PSMs) and bacteriocins, which can directly prevent the colonization of skin pathogens including Group A *Streptococcus* (GAS), *S. aureus* and even other *S. epidermidis* strains (Fontana *et al.* 2006; Bastos *et al.* 2009; Cogen *et al.* 2010) (Fig. 1). Secondly, *S. epidermidis* functions as a bacterial primer on the skin, regulating and promoting host inflammatory responses via Toll-like receptor (TLR) signalling. Wanke *et al.* showed that when co-colonized with pathogenic *S. aureus*, commensal *S. epidermidis* not only upregulated AMP expression but also abolished the inhibition of NF-κB signalling

asserted by *S. aureus*, leading to amplified host immunity in response to pathogen invasion (Wanke *et al.* 2011). *S. epidermidis* can enhance host immune responses in defence against other bacterial pathogens in addition to *S. aureus*, such as GAS, as well as against viral infections, such as vaccinia virus and human papillomavirus (HPV), while maintaining its own colonization on the skin (Li *et al.* 2007; Lai *et al.* 2010). Despite being typically considered a commensal organism, *S. epidermidis* can act as an opportunistic pathogen, with biofilm formation as a pathogenic mechanism (Cogen *et al.* 2010). The ubiquitous nature of *S. epidermidis* on the human skin and its ability to form biofilms have resulted in a high incidence of *S. epidermidis* in hospital-acquired infections, medical device failure and even bacteraemia (Wisplinghoff *et al.* 2004; Rogers *et al.* 2009).

***Propionibacterium acnes*.** Gram-positive lipophilic *P. acnes* is a dominant skin resident species, particularly at sebaceous sites, such as the face, neck and upper trunk. Other *Propionibacterium* species, including *Propionibacterium granulosum*, *Propionibacterium avidum* and *Propionibacterium humerusii*, have also been identified on the human skin, but at a much lower prevalence and abundance than *P. acnes*. Propionibacteria are believed to play a beneficial role in maintaining skin health via their ability to metabolize triglycerides in sebum to short chain fatty acids (SCFAs). SCFAs exhibit antimicrobial properties and contribute to the acidic skin pH, thus preventing the colonization of pathogenic skin species including *S. aureus* (Ushijima *et al.* 1984; Shu *et al.* 2013) (Fig. 1). In addition to the production of SCFAs, some *Propionibacterium* species are capable of producing bacteriocins (Faye *et al.* 2011). *P. acnes* bacteriocins have been shown to inhibit the growth of some *P. acnes* strains as well as other bacteria (Fujimura & Nakamura, 1978). Consistent with their role in skin health, studies have revealed reduced relative abundance of Propionibacteria in skin diseases including psoriasis (Gao *et al.* 2008) and atopic dermatitis (Kong *et al.* 2012). Historically, *P. acnes* has been implicated in the pathogenesis of the common skin disease, acne, mostly due to a high frequency of isolation of the species from acne lesions (Marples *et al.* 1973; Gehse *et al.* 1983). Yet this association remains a topic of much debate due, in part, to the dominance of the species on healthy, non-acneic skin. Analysis of the first *P. acnes* genome highlighted the virulence potential of this organism (Brüggemann *et al.* 2004). Sequencing and comparative genome analysis of large collections of *P. acnes* strains isolated from acne patients and healthy individuals have since revealed significant phylogenetic diversity within this species (McDowell *et al.* 2005, 2008; Kilian *et al.* 2012; Fitz-Gibbon *et al.* 2013; Tomida *et al.* 2013). Certain lineages of strains have been associated with disease while others are associated with health (Lomholt & Kilian, 2010; McDowell *et al.* 2011; Fitz-Gibbon *et al.* 2013; Kasimatis *et al.* 2013). While a causal relationship is yet to be determined, it has been increasingly recognized that communities of microorganisms colonize the skin. Mere presence or absence of disease-associated strains may not be sufficient in determining the clinical outcome of disease or health. The presence and activities of other strains and species in the community may also contribute to skin health and disease and need to be considered when defining disease association.

***Malassezia* species.** Recent metagenomic analyses have revealed that bacteria represent the main fraction of the skin microbiota; however, the skin also harbor eukaryotic species. Metagenomic shotgun sequencing and ITS-based analysis of the fungal community from healthy skin have revealed low fungal diversity at most core body sites, with *Malassezia* species being the predominant colonizers (Paulino *et al.* 2006, 2008; Findley *et al.* 2013; Oh *et al.* 2014). *Malassezia* are lipophilic yeasts that colonize sebaceous areas of the skin and degrade sebum. *Malassezia,* in particular *M. restricta* and *M. globosa*, are generally recognized as commensal fungi, due to their prevalence on healthy skin (Ashbee & Evans, 2002). Genome analysis of *M. restricta* and *M. globosa* has revealed an abundance of lipases and phospholipases that are believed to aid in fatty acid metabolism (Dawson, 2007; Xu *et al.* 2007). One of the by-products from fatty acid metabolism by *Malassezia* species is azelaic acid (Nazzaro-Porro & Passi, 1978), which exhibits antimicrobial properties against skin bacteria and fungi (Leeming *et al.* 1986; Brasch & Christophers, 1993). Similar to other skin commensal microorganisms, *Malassezia* species have also been linked to a number of skin diseases. *M. sympodialis* has been implicated in atopic dermatitis, whereby it contributes to skin inflammation via the release of allergens (Selander *et al.* 2006). *M. restricta* has been controversially associated with dandruff, an inflammatory scalp disorder (Gaitanis *et al.* 2012). Despite associations with skin inflammatory conditions, the prevalence of *Malassezia* species on healthy skin suggests that these species are commensals and may become harmful when unfavorable conditions are presented. Further understanding of the functions of these fungal species will provide important insight in skin health and disease.

Bacteriophages. Phages are prokaryotic viruses that infect bacterial hosts, and are a dominant part of the skin virome. They are commonly found at multiple skin sites, naturally co-occurring with their preferred bacterial hosts. Metagenomic shotgun sequencing analysis suggested that *Propionibacterium* and *Staphylococcus* phages are the most abundant skin phages, while other phages, such as *Streptococcus* and *Corynebacterium* phages, are also present but at lower relative abundances (Oh *et al.* 2014).

Using culture-based approaches and genome analysis of skin samples, Liu *et al.* revealed an increased frequency of *P. acnes* phages isolated from healthy individuals compared to acne patients, and suggested that phages may play a role in modulating the skin bacterial populations (Liu *et al.* 2015). Despite being used for over a century in Eastern European countries to treat bacteria-associated diseases (Sulakvelidze *et al.* 2001), the interest in phage therapy to modulate bacterial communities in health and disease has recently generated substantial interest (Nobrega *et al.* 2015). Skin pathogens, such as *S. aureus* and *Pseudomonas aeruginosa*, can colonize the open wound upon skin injury, and subsequently cause skin infections that can be difficult to manage and treat (Church *et al.* 2006). Phage therapy, demonstrated *in vitro* and *ex vivo*, was found to be an efficient and promising treatment strategy to clear skin infections caused by *P. aeruginosa* (Soothill, 1994; Vieira *et al.* 2012; Pincus *et al.* 2015). With the emergence of many drug-resistant pathogens and the increased failure rate in common skin antibiotics and antimicrobials, phage therapy presents a promising approach to treat bacterial infection and to maintain a healthy state of the skin microbial community.

Beyond the taxonomy and metagenome of the skin microbiota

Despite the existence of many microorganisms on the human skin, the limited microbial biomass available from skin samples has hindered the study of the functional role of the skin microbiota as a whole. To date, only a few published studies have characterized the skin microbiome at the metagenomic level (Human Microbiome Project Consortium *et al.* 2012; Mathieu *et al.* 2013; Oh *et al.* 2014). Metatranscriptomic, metaproteomic, and metabolomic analyses of the skin communities are not quite on a par with the success shared by the microbiome studies at other body sites such as the gut and oral cavity. Continued advances in molecular methods and next-generation sequencing technologies have allowed 'omic'-based analysis of the skin microbiota from limited biological materials, and as a result, researchers have begun to expand their focus from taxonomic characterization to the functional determination of the skin microbiota and how they interact with the host. To understand the role of the skin microbiota in health and disease beyond the metagenomic level, recently Kang *et al.* performed the first skin metatranscriptomic analysis and revealed significant differences in the transcriptional activities of the skin microbiota between healthy individuals and acne patients (Kang *et al.* 2015). A host–bacteria interaction mechanism via metabolites was discovered from the study, providing one molecular explanation for acne pathogenesis. In the presence of externally available vitamin B_{12}, *P. acnes* was shown to repress its own vitamin B_{12} biosynthesis and shunt the metabolic flow towards the production of porphyrins, a group of bacterial metabolites inducing inflammation in host tissues and leading to acne development (Kang *et al.* 2015). This suggests that the skin microbiota constantly senses the host metabolite level, reacts to its changes, and in turn plays a role in skin health or disease.

Bek-Thomsen *et al.* performed a proteomic analysis of the host and bacterial proteins identified from the skin follicles of acne patients and healthy individuals (Bek-Thomsen *et al.* 2014). Surface adhesion proteins, namely dermatan sulfate binding proteins and Christie-Atkins-Munch-Petersen (CAMP) factors (CAMP1 and CAMP2), which have both been previously linked to the virulence property of *P. acnes* (Valanne *et al.* 2005; McDowell *et al.* 2011, 2013; Nakatsuji *et al.* 2011), were found more frequently in healthy skin than in acne-affected skin (Bek-Thomsen *et al.* 2014). While these data are seemingly contradictory to the association of these factors with diseased states, further investigations of the functions of these bacterial proteins are needed to fully understand the roles of the skin microorganisms in health and disease, and to determine whether these secreted molecules are essential to the microorganisms and/or are virulent to the host.

Proteomic analysis of the *Malassezia* secretome has also revealed the functional potential of the skin fungal community. Of the 14 lipases and 9 phospholipases encoded in the *M. globosa* genome, 13 and 6, respectively, are believed to be secreted (Xu *et al.* 2007). The clustering of the genes on the chromosome and the secretion of multiple gene products are thought to aid in host specificity and imply an efficient mechanism for nutrient biosynthesis in these microorganisms. Their full health benefit to the human skin yet remains to be elucidated.

The role of the skin microbiota in shaping skin functions

The functions of the human skin include insulation, sensation, thermoregulation, absorption and synthesis. Additionally, the skin plays a central role in immune defence, preventing infection and host damage. Keratinocytes, the cells that coat the outer skin layers, constantly monitor the skin surface to recognize foreign or pathogen-associated molecular patterns (PAMPs), and in their presence, initiate an innate immune response via TLRs and Nod-like receptors, resulting in the production and secretion of cytokines, chemokines and AMPs (Heath & Carbone, 2013).

The skin microbiota plays an important role in shaping host immunity and aiding in the stimulation of host immune responses to defend against the colonization of pathogenic microorganisms. Naik *et al.* compared germ-free mice with mice raised under

specific pathogen-free (SPF) conditions to understand how the skin commensal microorganisms modulate host immunity (Naik *et al.* 2012). Compared to SPF mice, who exhibited diverse immune signalling, germ-free mice had weakened skin immune responses, producing significantly lower levels of microbial-derived signalling molecules, interferon-γ (IFN-γ) and interleukin-17A (IL-17A). Colonization of germ-free mice by commensal *S. epidermidis* restored IL-17A production on the skin (Naik *et al.* 2012). When exposed to the protozoan parasite *Leishmania major*, germ-free mice had impaired immune responses, which were rescued by colonization with *S. epidermidis* on the skin. This further supports a role for commensal skin bacteria in promoting host immunity (Naik *et al.* 2012).

Wound healing is a critical process in skin barrier function. Upon skin injury, skin cells deploy a highly efficient wound healing process involving inflammation, tissue repair and scar formation (Singer & Clark, 1999). In contrast to the many health benefits offered by the skin microbiota, in damaged or broken skin, when the physical barrier function is compromised, the otherwise commensal microorganisms can often behave as opportunistic pathogens, hindering the processes of tissue formation and wound healing. Commensal species, such as *P. acnes* and *S. epidermidis*, can infect the open wound, tightly adhering to damaged and exposed tissue via biofilm formation (Fig. 2). Biofilms are complex microbial communities encased in an extracellular polymeric substance (EPS). This encasing facilitates microbe–microbe communications and leads to increased virulence and resistance to many antimicrobial agents. As a result, biofilm formation complicates the wound healing process (Black & Costerton, 2010; Percival *et al.* 2012; Bertesteanu *et al.* 2014). Foot ulcers are chronic wounds commonly found in diabetic patients. The observation of biofilm formation from otherwise non-pathogenic skin microorganisms in diabetic foot ulcers has led to the concept of functional equivalent pathogroups, whereby alone these species are harmless but together they can elicit a virulent potential equivalent to that of a known pathogen (Dowd *et al.* 2008).

In addition, microbial colonization of wounded sites can result in the release of microbial molecules that further damage the skin tissue, promoting chronic inflammation and delaying the healing process (Eming *et al.* 2007). Wound infection with the skin pathogen *S. aureus* has been shown to cause impaired healing due to the production of extracellular adherence protein (Eap). Eap is an anti-inflammatory molecule that interferes with normal skin repair by reducing neutrophil and macrophage recruitment, and thus reducing inflammation, an important process in tissue repair (Athanasopoulos *et al.* 2006).

More recently, studies have revealed that wound healing is accelerated in the absence of the skin microbiota (Canesso *et al.* 2014). Skin wound healing was scarless in germ-free mice, with reduced infiltration of neutrophils and inflammation, compared to conventionally raised mice (Canesso *et al.* 2014).

While evidence points towards the microbiota as a cause of delayed wound healing, the ability of commensal microbes to produce AMPs and bacteriocins to prevent pathogen colonization is central to reducing wound infection by

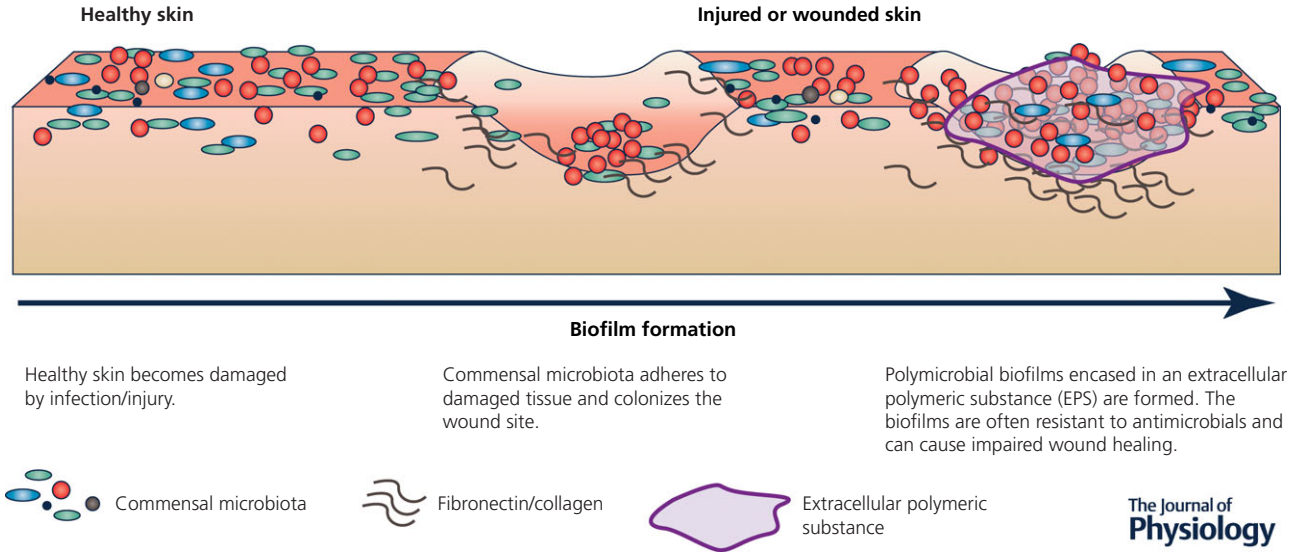

Figure 2. Schematic diagram of biofilm formation in impaired wound healing
Commensal skin microorganisms colonize the wound site and adhere to exposed substratum tissues of the wound surface. Secretions of extracellular polymeric substances facilitate biofilm maturation, leading to the formation of polymicrobial biofilms.

pathogens. Recent advances in understanding the role of the microbiota in wound healing through mouse models (Grice *et al.* 2010; Canesso *et al.* 2014; Zhang *et al.* 2015) has opened up new avenues to further investigate the role of commensals in skin healing, and thus providing insight on host–microbial interactions in this essential skin process.

Exploiting microorganisms to enhance skin function in health

With the many health benefits conferred by commensal microorganisms, research has turned towards exploiting the properties of commensal skin microorganisms, such as those with potential probiotic properties, to manipulate the skin microbiota and enhance skin health. Examples include the topical application of the commensal skin bacterium *Janthinobacterium lividum* to treat athlete's foot, a common fungal skin infection, via the control of bacterial–fungal interactions (Ramsey *et al.* 2015). Ramsey *et al.* revealed that growth of the fungal species *Trichophyton rubrum* was inhibited by *J. lividum*. The *in vitro* and amphibian animal models used in the study warrant additional research to investigate the use of *J. lividum* as a probiotic treatment in humans (Ramsey *et al.* 2015).

Commensal skin microorganisms can be exploited to correct dysbiosis in the skin microbiota in diseases. *S. epidermidis* has been suggested as a probiotic in treating acne (Wang *et al.* 2014). While *S. epidermidis* and *P. acnes* naturally co-exist on the skin, Wang *et al.* found that commensal *S. epidermidis* can inhibit the overgrowth of *P. acnes*, which has been linked to acne. On the other hand, the health-association of certain *P. acnes* strains implies that supplementation with health-associated strains may help to treat acne and to maintain skin health (Fitz-Gibbon *et al.* 2013). While typical acne treatments include antibiotic administration, the extensive use of antibiotics has led to the emergence of antibiotic-resistant strains and thus increased rate of treatment failure (Ross *et al.* 2003). Exploiting probiotic and prebiotic therapeutics will ultimately reduce the prevalence of antibiotic resistance in the population and potentially result in better treatment outcomes.

Additionally, non-pathogenic microorganisms that are not usually part of the normal skin microbiota have been investigated for their potential applications in enhancing immune responses. *Vitreoscilla filiformis*, a Gram-negative bacterium recognized by keratinocytes, can stimulate antioxidant and antimicrobial defence mechanisms via TLR-2 signalling (Mahe *et al.* 2013; Volz *et al.* 2014). Application of topical *V. filiformis* to lesional skin significantly improved the skin condition in atopic dermatitis patients by inducing high levels of the anti-inflammatory cytokine IL-10 (Guéniche *et al.* 2008; Volz *et al.* 2014).

Conclusion

An increasing number of studies have shown that the human microbiome exhibits a high level of individuality (Schloss *et al.* 2014), and at the strain level it can be used as 'individual fingerprints' (Schloissnig *et al.* 2013). While we have gathered ample knowledge of the taxonomic composition of the skin microbiome at the phylum, genus and sometimes species level, our current understanding at the strain level is limited. A few studies have highlighted associations of specific strains of skin bacteria with disease pathogenesis, such as the increased prevalence of specific *P. acnes* lineages on acneic skin compared to healthy skin (Fitz-Gibbon *et al.* 2013), and the increased prevalence of multi-drug-resistant *S. epidermidis* strains isolated from prosthetic joint infections (Hellmark *et al.* 2013). Therefore, strain-level differentiation is important in defining the role of the resident microorganisms in skin health and disease. Recently, new methods have been developed to infer the strain-level composition of a microbial community from metagenomic shotgun sequencing data, such as PathoScope and ConStrains (Francis *et al.* 2013; Luo *et al.* 2015). Improved methods for strain-level identification and analysis will enable future studies to reveal the population structure and dynamics of the skin microbiome at the strain level and the complex interactions between strains, species, bacterial prey and viral predators, microbiota and human host. Strain-level understanding of the microbiome will provide unprecedented insight into the role of the skin microbiota in health and disease.

The core skin microbiota consists of a number of key commensals, including species from *Staphylococcus*, *Propionibacterium*, *Streptococcus* and *Corynebacterium*, as well as fungi and viruses, which are dominant and prevalent among healthy individuals. Despite the health benefits that these key players confer, a number of studies have implicated a role for these same species in diseases, mainly due to frequent detection and isolation of these species at diseased sites (Marples *et al.* 1973; Gehse *et al.* 1983; O'Gara & Humphreys, 2001; Ramage *et al.* 2003; Jahns *et al.* 2012). With the dominance and prevalence of these organisms on the healthy skin, one must question if these skin microorganisms are truly representative of a diseased state, or if they are nothing more than normal constituents of the resident skin microbiota, innocent bystanders in skin disease and guilty by association. A key issue in determining a role for the skin microbiota in disease pathogenesis is to establish whether alterations in the healthy skin microbiota are a cause or consequence of the diseased state. Additionally, sample contamination due to the ubiquitous nature of skin microorganisms presents another challenge when defining a pathogenic role for skin commensals found outside their normal environment.

Factors influencing the role of commensal microorganisms in skin health and disease include changes in the environmental niche that they colonize or the host status. While these organisms are typically considered commensal, when they find residence outside of their preferred environmental niche or when opportunistic conditions are presented, they can often pose a pathogenic threat. Such examples include the cases of *P. acnes* and *S. epidermidis* found in medical device and implant infections (Tunney *et al.* 1998; Sampedro *et al.* 2009), and the high incidence of infection from common skin species, such as *Malassezia*, in immuno-compromised patients (Tragiannidis *et al.* 2010). The microbial properties that allow these commensal microorganisms to benefit the host, for example biofilm formation or host-adhesion mechanisms, are often the traits linking them with virulence in diseased states (O'Gara & Humphreys, 2001; Ramage *et al.* 2003; Jahns *et al.* 2012). Understanding their environmental niche and molecular mechanism in host interactions will provide significant insight in treating commensal-associated infections and diseases.

Advances in modern technologies have allowed researchers to expand from the studies of individual microorganisms in human health and disease to investigations of the role of the microbial community as a whole in human physiology. Given the multitude and complexity of the microbiota residing on the human skin, investigating the molecular interactions between microbe and microbe and between microbe and host, in addition to taxonomic characterizations, will advance our knowledge of the role of the commensal skin microbiota in health and disease. Future functional studies of the skin microbiota at the metatranscriptomic, metaproteomic and metabolic levels are vital to our understanding of disease mechanisms involved with the microbiota and potential future manipulations of the microbiota in disease therapeutics and skin health maintenance.

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Additional information

Competing interests

None declared.

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