Review

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Human Microbiome

Structure and function of the human skin microbiome

Nina N. Schommer and Richard L. Gallo

Division of Dermatology, University of California, San Diego, La Jolla, CA, USA

An abundant and diverse collection of bacteria, fungi, and viruses inhabits the human skin. These microorganisms vary between individuals and between different sites on the skin. The factors responsible for the unique variability of the skin microbiome are only partly understood, but results suggest that host genetic and environmental influences play a major role. Today, the steady accumulation of data describing the skin microbiome, combined with experiments designed to test the biological functions of surface microbes, has provided new insights into links between human physiology and skin microbiota. This review describes some of the current information regarding the skin microbiome and its impact on human health. Specifically, we summarize the present understanding of the function of microbe–host interactions on the skin and highlight some unique features that distinguish skin commensal organisms from pathogenic microbes.

Skin microbial community

It has long been known that bacteria, viruses, and eukaryotes such as fungi and arthropods inhabit the skin. However, the community of microorganisms on human skin is more complex than once thought. Understanding the composition of the skin microbial community is a significant advance from older classifications of cutaneous microbiota that focused on skin microbes only as pathogens or opportunistic pathogens, and has come from the development of methods based on sequencing technologies that are independent of the need for cultivation of microbes. This new information has revealed that the composition of the skin microbiome is diverse and loosely organized and varies for different skin locations. Most importantly, more recent descriptions of the composition of the skin microbiome have inspired new work towards understanding the functional significance of resident microbes on the skin, and have led to important new advances in our understanding of both normal physiology and disease.

Corresponding author: Gallo, R.L. (rgallo@ucsd.edu).
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First and foremost, the ecological system under normal physiological conditions must maintain homeostasis between the microbiome and host. The mechanisms responsible for this balance remain largely unknown, and have been complicated by observations showing that the exact composition of skin microbes varies from individual to individual, but remains somewhat stable over time [1,2]. Furthermore, the relevant interactions that define this cutaneous system are not limited to those between the microbe and the host. The skin is unique among epithelial surfaces in terms of complex ecological interactions with the environment. In addition, competition within and between microbial species is important for the development and maintenance of a healthy microbiome. This review provides an update on some of the current information describing the skin microbiome and experimental advances towards better understanding of the biology and significance of this important system.

The skin is a unique and variable ecosystem

The skin provides many niches in which large populations of microbes are subjected to variable ecological pressures including humidity, temperature, pH, and the composition of antimicrobial peptides and lipids. In addition, skin structures such as hair follicles and sebaceous, eccrine, and apocrine glands constitute discrete niches that harbor unique microbiota [3]. Analyses of the topographical diversity of microbes that inhabit these niches of the human skin using 16S rRNA gene phylotyping revealed that the habitats have large effects on the microbial composition. At least 19 phyla are known to be part of the bacterial skin microbiome. Major examples are Actinobacteria (51.8%), Firmicutes (24.4%), Proteobacteria (16.5%), and Bacteroidetes (6.3%). The majority of the identified genera are *Corynebacterium*, *Propionibacterium* and *Staphylococcus* [4]. The abundance of each group is strongly dependent on the characteristics of the appropriate niche. For example, sebaceous sites on the face are predominated by *Propionibacterium* and *Staphylococcus* species. In moist sites such as the axilla, *Corynebacterium* species predominate, although *Staphylococcus* species are also present. By contrast, in dry sites mixed populations of bacterial species of β-Proteobacteria and Flavobacteriales are part of the resident microbiota [4,5]. Findings from classical cultivation methods largely coincide with the findings from new sequencing technologies. For example, older reports on cultures from the skin describe a carriage rate of

Staphylococcus aureus among different individuals of approximately 4%, whereas its close phylogenetic relative *Staphylococcus epidermidis* is found much more frequently. This is similar to the results from DNA sequencing [1,6].

However, sequencing and culture methods are not identical. DNA sequencing techniques can detect organisms that cannot be cultured. This limitation may exist partly because many of the organisms detected on the skin surface have already been killed by the antimicrobial actions of the skin. In fact, species detected by both techniques tend to be those most resistant to killing by the epidermal environment. In addition, a genomic approach in which samples from different body sites on 129 males and 113 females were tested revealed that diversity within single samples (alpha-diversity) differs from diversity between samples from the same habitat among subjects (beta diversity). This study indicated that skin is intermediate in alpha diversity and highest in beta diversity compared to other epithelial surfaces [1]. Thus, because of the variability in microenvironments for different sites on the skin and the great variability in external treatment of the skin by different individuals, it has been more difficult to establish clear relationships between the presence of specific organisms and skin functions. Importantly, the uniqueness of the microbial composition for each individual seems to be stable over time, suggesting consistency for the individual subject and study.

Most microbiome studies concentrate on understanding bacterial composition, but the microbes present in human skin habitats are not limited to bacteria. Viruses, fungi, and arthropods are also important parts of the skin microbiota. In a small study, the predominant fungi detected using phylogenetic markers such as18S rRNA belonged to the species *Malassezia*, including the most frequent isolates *Malassezia globosa*, *Malassezia restricta*, and *Malassezia sympodialis* [7–9]. *Malassezia* species are lipophilic microbes that are frequently associated with sebum-rich areas of the skin [10]. Similar to the bacterial distribution on the skin, the distribution of *Malassezia* is dependent on the characteristics of the habitat. For example *M. globosa* predominates on the back and occiput and in the inguinal crease, whereas *M. restricta* is found on the scalp [11] and in the external auditory canal, retroauricular crease, and glabella [8]. Differences between the species may reflect different lipid requirements [12]. Other areas of the skin, such as foot sites, are colonized with greater diversity (e.g., *Aspergillus*, *Rhodotorula*, *Cryptococcus*, and *Epicoccum*) [8].

Other eukaryotes that colonize the human skin belong to the phylum Arthropoda. Like *Malassezia* species, *Demodex* mites favor lipids of the sebum [13]. To date, two of the 0.2–0.4-mm-long mite species are known to inhabit human skin. *Demodex folliculorum* is found in hair follicles in clusters with other mites of the same species. The smaller mite *Demodex brevis* resides alone in sebaceous glands or in meibomial glands located at the eyelid rim [14].

Less is known about the human virome. This is because of difficulties in amplifying viruses in cell culture, limited antigenic/serological cross-reactivity, and the lack of nucleic acid hybridization to known viral sequences. Detection methods have also largely focused on metagenomic sequencing of total DNA, making detection of RNA viruses unlikely. Their minuscule genomic size also argues against easy virus detection in metagenomic approaches. One approach to facilitate viral discovery is enrichment of small viral particles and removal of contaminating bacterial and human nucleic acids, leaving viral nucleic acids protected within their virion shells [15,16]. Despite methodological difficulty, a recent high-throughput metagenomic sequencing study of skin from five healthy individual and one patient with Merkel cell carcinoma revealed a high diversity of DNA viruses on the human skin [17]. However, because this was a small study it is not yet clear if these viruses are actually part of the human skin microbiota or if they involve some mutual benefit to the host. Interestingly, it has been hypothesized that even recognized pathogenic viruses such as human papillomavirus are a normal part of the skin microbiome [17–21].

Host interactions with skin microbiota

It is still too early to say with confidence what the exact assembly of the complex network of human microbiota looks like. From sequencing information we know that microbial communities are more complex than previously expected from culture-based studies. These findings raise many new and important questions about interactions among hosts and microbes and their relevance to health and disease. Individuals can carry similar microbial compositions, so it is highly likely that microbes and their hosts have co-evolved. Microbes profit from their host in terms of nutrients and a stable ecological niche. Advantages for the host may include the capacity of the microbe to evolve quickly and therefore help individuals to respond to changes in their environment.

As mentioned, although there are variations in microbial composition between individuals, the microbial composition of each individual appears to remain relatively stable. Conversely, shifting of microbial communities that alter host–microbiome interactions has been associated with disease [22–24]. To better understand such changes in microbial composition, we briefly discuss the dynamics of microbial interactions at the skin surface.

Interactions of microbes within or on a host can be divided in three relationship categories. The relationship can have a negative impact, a positive one, or no impact at all on one of the species involved. The possible combinations of these categories allow classification into various types of interaction [25,26]. For instance, commensalism describes the situation whereby only one species benefits from the relationship and the other one is unaffected. The term mutualism implies that both partners are in a win–win situation. These types of interaction are an important part of the skin immune shield. By contrast, in detrimental relationships, only one organism benefits and the other is harmed (Figure 1). Cooperative interactions between microbes and their hosts involve microbial participation in host functions.

An example of a beneficial relationship between bacteria and the skin involves the innate capacity of the epithelium to detect microorganisms with Toll-like receptors (TLRs). Stimulation of TLRs induces distinct patterns of gene expression that lead to activation of a variety of immune responses. Classically, these immune responses

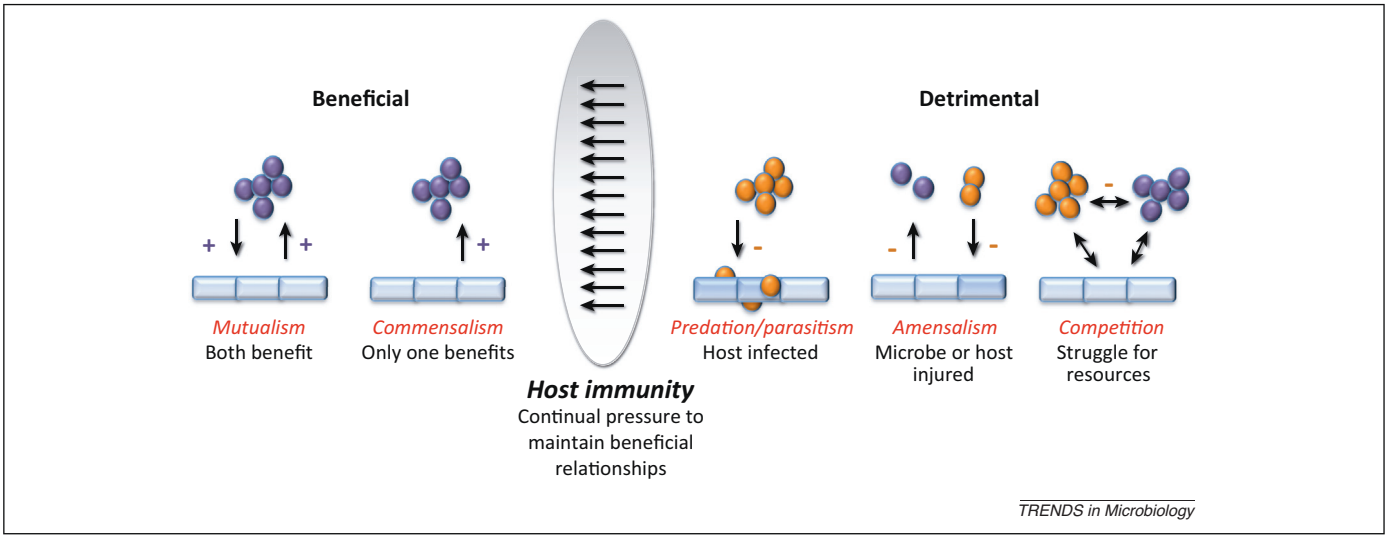

Figure 1. Dynamics of microbial interactions at the skin surface. Microorganisms form complex interaction networks. Beneficial situations include mutualistic and commensal relationships. By contrast, detrimental relationships describe correlations in which at least one interaction partner is harmed. The host immune system acts to manage microbial communities and orchestrate beneficial microbe–host relationships.

were considered to be exclusively pro-inflammatory and designed to defend against the microbe causing infection. It has been shown that the commensal bacterium *S. epidermidis* modulates TLR3-dependent inflammation by initiating a TLR2-mediated cross-talk mechanism to suppress inflammation [27]. This bacterium also induces keratinocytes to express endogenous antimicrobial peptides through a TLR2-dependent mechanism [28]. Furthermore, it has been reported that *S. epidermidis* has an autonomous function in controlling and tuning the functions of resident T lymphocytes [29]. Comparison of T cells from germ-free (GF) mice and specific pathogen-free (SPF) mice revealed that the former produce lower levels of inflammatory molecules such as interferon-γ (IFN-γ) and interleukin-17A (IL-17A). Monoassociation of the skin of GF mice with just one bacterium, *S. epidermidis*, was enough to reinstate the production of IL-17A by T cells in the skin, but not in the gut. Interestingly, this skin bacterium also allows a protective Th1 response after cutaneous infection with the protozoan parasite *Leishmania major*, because only GF mice colonized with *S. epidermidis* were able to mount a proper immune response against the parasite [29].

Various factors can drive disruption of the normal microbial composition, a state referred to as dysbiosis. Functional dysbiosis can affect host–microbe cross-talk and may result in disease. Host factors such as age, sex, use of medication, lifestyle, and hygiene play an essential role [30]. Gender-linked differences in the microbial composition of the skin could be based on physiological and anatomical differences that influence skin properties such as hormone production, sweat rate, sebum production, surface pH, skin thickness, hair growth, and cosmetic use [31]. In a recent study of the human epidermis following skin barrier disruption, women showed significantly greater microbial diversity on their hands than men, and this was linked to their less acidic skin surface and use of make-up [31].

In general, more diversity seems to be more advantageous because it is thought that a diverse ecosystem is more resilient. Studies of the gut microbiome exemplify the enormous influence of a Westernized lifestyle on microbial diversity and the pathophysiology of many diseases. Lifestyle choices such as the mode of birth delivery and feeding modality [32,33], improved sanitation, introduction of antibiotics and vaccines [34], a Western diet [35], and consumption of artificial nutrients [36] greatly impact the gut microbiota. A Western lifestyle may also have a similar impact on the skin microbiota. By comparing cutaneous bacterial communities of Amerindians in the Venezuelan Amazon with samples from volunteers in the USA, one study uncovered significant differences in forearm skin bacterial communities [37]. Using multiplexed V2-targeted 16S rRNA gene pyrosequencing for 112 samples revealed a division of the Amerindian skin microbiota into two major clusters that were not represented in the US samples. In this context, the alpha diversity of the US samples showed relative equivalence in species richness, because bacteria from only one taxon were present. By contrast, cluster B for the Amerindian samples exhibited much higher richness in comparison to the US samples, with no recognizable dominant bacterial taxon [37]. Although these observations are interesting, to better understand the impact of modern life on human cutaneous microbiota it will be necessary to sample more groups of individuals from native and Westernized cultures, and more carefully control for the effect of skincare products.

The skin microbiome in human disease

Disturbance of the homeostasis between microbiome and host has been associated with disease. For example, the antibiotic vancomycin, when used in early life, can increase the incidence and severity of allergic asthma [38]. However, only neonatal, and not adult, exposure to certain antibiotics appears to promote susceptibility to experimental allergic asthma, a time point when key immunological thresholds are established. The following section reviews current information regarding the relevance of microbe–host interactions from the perspective of specific human skin disorders.

Acne

Although this chronic inflammatory disease of the pilosebaceous unit is not yet completely understood, altered bacterial colonization is considered to be one of the main elements contributing to the development of acne [39]. The basic disease mechanism is thought to involve androgen-induced increases in sebum production, altered keratinization, inflammation, and dysbiosis of the facial skin. The primary disease-associated bacterium is *Propionibacterium acnes*. It colonizes sebaceous follicles that contain microcomedones, providing the bacterium with an anaerobic and lipid-rich environment [40,41]. Secretion of several enzymes such as hyaluronidases, lipases, and proteases, causes local injury and inflammation [42].

A comparison at the strain and genome levels of *P. acnes* for sample of nose pilosebaceous units from 49 acne patients and 52 healthy individuals showed no significant difference in the relative abundance of *P. acnes*. However, only certain *P. acnes* strains, based on their phylotype, were highly associated with acne. By contrast, those strains were less abundant on healthy skin and other strains were enriched [5]. In another study, different *P. acnes* phylotypes were visualized in sebaceous follicles from facial skin biopsies. Samples from patients with acne presented higher amounts of *P. acnes* and follicles containing *P. acnes* compared to control samples [43].

Interestingly, acne is absent in non-Westernized individuals in Papua New Guinea and Paraguay. Here, it is speculated that high glycemic loads in the Western diet could lead to increased androgens, increased insulin-like growth-factor 1, and altered retinoid signaling [44,45]. In this context, such variables may also influence the skin microbiome.

Atopic dermatitis

Atopic dermatitis (AD) is a chronic inflammatory skin disease whose prevalence is increasing in industrialized countries [46,47]. A hallmark of AD that has been well known for decades is that patients have increased bacterial colonization and are particularly susceptible to infections with *S. aureus* and viruses such as herpes and vaccinia [48,49]. It has been hypothesized that the alteration in surface microbial composition is due to dysfunction of the skin barrier. These disruptions include mutations in the gene that encodes for filaggrin, a protein involved in cornification [50]. Greater susceptibility during the course of this disease may also be attributable to decreased expression of antimicrobial proteins in the skin [51]. Once the skin barrier is impaired and antimicrobial protein expression is reduced, it is likely that homeostasis between the host and microbe is shifted.

Several recent findings in patients with AD reveal a dramatic change in microbial community structures compared to healthy volunteers [23,52]. AD patients can occasionally obtain benefit from the use of certain antibiotics in combination with corticosteroids and diluted bleach baths [23,53], but excessive use of antibiotics has also come under criticism for negatively affecting the microbiome and potentially disrupting any beneficial functions. Worsening disease and lower skin bacterial diversity are strongly associated, and microbial shifts are known to be localized to sites of disease predilection. The latter may suggest that specific ecological niches such as the anticubital and popliteal creases are not only important for disease initiation but are also influenced the microbial communities that live there. Interestingly, effective treatment against AD is associated with higher bacterial diversity, indicating that current treatments that promote bacterial diversity promote improvements in the disease. Increases in specific bacterial genera, such as *Corynebacterium*, *Streptococcus*, and *Propionibacterium*, are observed during therapy, indicating more complex species relationships during AD than known from culture-based methods [23]. Some studies have also suggested that *Malassezia* species are more often associated with AD [7,12].

Psoriasis

In comparison to AD, less is known about the role of the skin microbiome in psoriasis. Psoriasis is an idiopathic inflammatory skin disorder that affects 2% of the world population. Hallmarks of this disease include hyperkeratosis, hyperproliferation of keratinocytes, infiltration of skin by immune cells, and angiogenesis [54]. Similar to AD, psoriasis results from a combination of genetic and environmental factors. The overall ecological diversity of the microbial population overlaying psoriasis lesions is greater than for healthy skin. Firmicutes are predominant, whereas Actinobacteria are underrepresented in psoriatic lesions in comparison to healthy skin [55,56]. It is not known if these alterations in the microbiome in psoriasis are a consequence of the disease or contribute to its pathogenesis.

Rosacea

Some 3% of the world population suffers from rosacea [57]. Most patients are fair-skinned and have a Northern European ethnic origin. Clinical presentations of the disease include flushing, nontransient erythema, papules, pustules, telangiectasia, and inflammatory nodules, mainly found on the facial skin. In rosacea, microbes other than bacteria may take advantage of impaired homeostasis between the host and skin microbiota. The *Demodex* mite found on healthy skin is significantly increased on the skin of rosacea patients [58,59].

Dysregulation of the immune system has been described in rosacea, including altered TLR2 expression, high levels of the serine protease kallikrein 5 (KLK5), and abnormal expression of the cathelicidin antimicrobial peptide LL-37 [60,61]. These elements respond to and influence the composition of the skin microbiome, so it is logical to speculate that skin microbes play an important part in this disease. Skin inflammation also correlates with mite density on the skin of rosacea-affected patients [62]. Thus, mites may participate in the exacerbation of disease either by disrupting the skin barrier [14,63] or by triggering TLR2 activation through chitin in the insect cuticle [64,65]. Furthermore, it has been reported that bacteria that live in the digestive tract of *Demodex* are released into surrounding skin tissues, thereby triggering further tissue degradation and inflammation [66,67]. All of these mechanisms may participate to various degrees. However, it appears most likely that a genetic predisposition in the

host changes certain ecological characteristics of the skin that result in a shift of the microbiome. *Demodex* may take advantage of those changes and evoke a response that makes the skin susceptible to other inflammatory triggers such as UV exposure, alcohol, hormone fluctuations, and bacterial overgrowth on developing papules (e.g., *S. epidermidis*). Rosacea affects patients at a certain age, so it is also possible that age-specific modulations in TLR expression might play an essential role in the course of this disease [68].

Seborrheic dermatitis

It is postulated that the predominant fungus of the skin microbiota, *Malassezia*, is involved in seborrhoeic dermatitis (SD). This chronic inflammatory skin disorder is often first diagnosed around puberty and is caused by an increase in cutaneous lipids resulting from androgen-driven sebaceous gland development and sebum secretion. The disease also often occurs in patients older than 50 years. The prevalence of SD in the overall population is estimated at 1–5% and can affect any ethnic group; it is more often diagnosed in men than in women. High-risk populations include patients with AIDS. The clinical presentation is characterized by erythematous patches associated with greasy scaling. Commonly affected sites include the anterior hair line, eyebrows, ears, glabella, chest, and scalp [69]. The disease may also occur in combination with other skin diseases such as AD and psoriasis, leading to complications in diagnosis.

Dandruff is the common term for seborrhea of the scalp. It is mainly associated with *M. restricta* and *M. globosa* [10,11], and has a very high prevalence of nearly 50% of the population. Improvements in the disease can be achieved by therapeutic application of antifungal but not antibacterial agents. The mechanisms underlying pathogenicity are incompletely understood. Impaired skin barrier function facilitates the course of the disease [70]. The fungus secretes a lipase that splits triglycerides into irritant fatty acids that may induce hyperproliferation and scaling, or releases arachidonic acid, which is also involved in inflammation [71]. From the current literature it can be speculated that the fungus, which is part of the normal skin microbiota, switches to a pathogenic state when its growth is not controlled. What these control factors are and how they are dampened are not yet understood.

Microbe–microbe interactions on the skin

Altered ecological interactions between pathogenic microbes and their hosts can lead to disease, but the consequence of microbe interactions with each other has been underestimated and not well studied. This section provides some examples of specific microbe–microbe interactions and their impact on the skin.

Bacterium–bacterium interactions

It has been proposed that *S. epidermidis* protects the skin from pathogens by producing antimicrobial peptides such as phenol-soluble modulins (PSMs). PSMδ and PSMγ interact with lipid membranes similar to mammalian antimicrobial peptides. By secreting these peptides, *S. epidermidis* exerts selective antimicrobial action against skin pathogens such as *S. aureus* and group A streptococci [72]. Moreover, *S. aureus* biofilm formation and nasal colonization are inhibited by the serine protease Esp produced by *S. epidermidis* [73]. However, the interaction between different *Staphylococcus* species seems to be more complex. In a recent study, Kong *et al*. discovered that the proportion of *S. epidermidis* consistently increased during the AD condition when no treatment was applied [23], opening new hypotheses about the relationship between staphylococci. One possibility is that *S. epidermidis* not only has a mutualistic relationship with its eukaryotic host but also shares a mutualistic or commensal relationship with other *Staphylococcus* species such as *S. aureus* [23]. Thus, bacteria may take advantage of the specific situation. For example, the relative decrease in other bacteria such as *Streptococcus*, *Corynebacterium*, and *Propionibacterium* in AD could be due to the combined action of *Staphylococcus* species.

Interaction between species of one common genus is also observed in propionibacteria. As mentioned above, the distribution of different *Propionibacterium* strains is significantly different on the skin of healthy volunteers in comparison to acne-affected skin, indicating possible communication between bacterial strains [5].

Virus–bacterium interactions

In addition to bacterium–bacterium interactions, bacterial communities also interact with the bacteriophages that infect them. These viruses influence the bacterial community structure and function via several mechanisms, including killing of their host and mediation of genetic exchanges. Several phages are known in *Staphylococcus*, *Pseudomonas*, and *Propionibacterium* species [74–76]. So far it is not clear to what extent bacteriophages have an impact on the skin microbiome. It has been shown that phages reduce microbial colonization and pathology in a host-independent way. In the gut, they attach to specific glycoproteins in the luminal mucus via a specific capsid protein, thereby creating an antimicrobial layer that reduces bacterial attachment to and colonization of the mucus, which in turn lessens epithelial cell death [77].

Bacterium–fungus interactions

Complexes containing bacteria and fungi are varied and wide-ranging. Industry uses such interactions for the production of foods such as cheese and beer. These interactions are also found in many parts of the human body such as the oral cavity [78] and the gastrointestinal tract [79]. However, most of the clinical studies to date have focused on bacterial interaction with *Candida albicans*, a yeast that is common in the human microbiome that can cause several infections. In this context, mixed communities have virulence and resistance properties significantly different from those of single-species communities. For example, biofilms containing *S. epidermidis* and *C. albicans* in medical-device-associated infections are significantly more resistant to antimicrobials than single-organism biofilms are [80]. By contrast, *Pseudomonas aeruginosa* biofilm formation leads to death of the fungal cells. One explanation of communication between bacteria and fungi is based on quorum-sensing systems [80,81]. Furthermore, *P. aeruginosa*

is able to grow on skin at the expense of dermatophyte fungi associated with skin and nail infections [82].

These examples show that interactions between microbes have a strong influence in health and disease. However, although it is known that fungi are part of the healthy human skin, less is known about their ecological interactions in the state of health. A recent study revealed that bacterial richness and fungal richness are not linearly correlated, but both kingdoms live in clusters in close relation in the same location [8]. In accordance with their observations, the authors provided a preliminary evaluation of major fungal–bacterial associations in the skin. For example, co-occurrence analysis of foot sites revealed anti-correlation of Actinobacteria with resident Ascomycota and Basidiomycota. By contrast, Firmicutes and Proteobacteria were positively correlated with these fungal taxa [8].

From commensal organism to pathogen and unique propensities of skin microbes

Commensal microorganisms can become pathogens, and thus no microbe can really be considered to be exclusively beneficial. The most prominent and best-studied examples are *S. epidermidis* and *C. albicans*. Others are less well understood, such as *M. restricta* and *M. globosa*. How does a commensal become a pathogen? Even more importantly, what are the unique factors that allow a commensal organism to be tolerated by a host? This can be illustrated by the example of *S. epidermidis*.

Among coagulase-negative staphylococci (CoNS), *S. epidermidis* causes the greatest number of infections. It is commonly regarded as the most frequent causative agent of infections of indwelling medical devices such as peripheral or central venous catheters [83]. Staphylococci are transferred into the patient's body from the skin of the patient or that of healthcare personnel during device insertion. Once the bacteria have entered the body they use various virulence factors to facilitate interactions with host tissues and subvert the host's immune system. The most essential staphylococcal virulence factor is the characteristic biofilm formation on medical devices. Biofilms are multicellular, surface-attached agglomerations of microorganisms [84]. Their regulation involves quorum-sensing systems and is not yet completely understood. Do all *S. epidermidis* species on the skin have the potential to become a pathogen? Previous epidemiological and genetic studies suggest that *S. epidermidis* isolates in the hospital environment differ from those obtained outside of medical facilities in terms of biofilm formation, antibiotic resistance, and the presence of mobile DNA elements. For example, most disease-associated *S. epidermidis* biofilms are dependent on the expression of polysaccharide intercellular adhesin (PIA). However, the intercellular adhesion operon (*ica*) necessary for PIA production is rarely found in isolates obtained outside of hospital settings [85,86]. To date, i*caA*, *mecA*, and *IS256* are used as markers for invasive nosocomial strains. Acquisition of these markers is associated with intra- and interspecific horizontal gene transfer. In this context, *S. epidermidis* can be regarded as a highly flexible organism on an evolutionary level.

High diversity of *S. epidermidis* skin commensal and hospital infection-associated isolates was recently uncovered [87]. Comparison of specially created draft genomes from several commensal and nosocomial isolates revealed that commensal strains had an open pan-genome with 80% core genes and 20% variable genes, comprising mobile DNA elements, transcription factors, and transporters. The formate dehydrogenase gene (*fdh*) was present in 23% of the commensal strains, but in only 4% of the pathogens. These 4% of *fdh*-positive nosocomial strains were characterized by less virulence influenced by less abundant *icaA*, *mecA*, and *IS256* markers. Thus, the authors suggested that these strains could represent skin commensal contaminants from venipuncture.

Although there is less known about how skin commensal organisms and mutualistic bacteria can be distinguished from pathogens, some possibilities have been put forward. Virulence factors of the pathogen group A streptococci (GAS) mediate the *in vivo* changes from non-invasive GAS serotype M1T1 to the invasive phenotype. This process is potentiated by spontaneous mutations within a specific two-component system resulting in upregulation of numerous virulence-associated genes. One of those genes includes the operon for the synthesis of the hyaluronic acid capsule. The glucuronic-β-1,3-*N*-acetylglucosamine chain has the same structure as the human hyaluronan molecule and provides the bacterium a form of mimicry that impairs immune recognition and phagocytic clearance [88]. Hyaluronan is the most abundant glycosaminoglycan in the skin and it is plausible that commensal bacteria use a similar mechanism to mask themselves and avoid recognition by the immune system.

Epigenetic mechanisms regulate expression of the genome to generate multiple cell types during development or orchestrate cellular responses to external stimuli. It has been widely accepted that pathogenic bacteria and viruses can induce epigenetic changes in host cells by influencing various epigenetic factors to their own benefit. In this context, it is likely that commensal microbes can interfere with histone modification or DNA methylation mechanisms. Indeed, it has been reported that epigenetic control of host genes by commensal bacteria in the gut contributes to the maintenance of intestinal symbiosis [89,90]. Therefore, it would be highly interesting to test if skin commensal species can similarly regulate epigenetic mechanisms.

Concluding remarks and future perspectives

Modern technology has taught us to rethink our sense of self and consider our normal physiology to be a complex dynamic interaction between many organisms. Initial descriptions of the skin microbiota have revealed an important role for genetics and environmental variation in shaping patterns of diversity. The resulting specific microbial composition consequently determines host–microbe and microbe–microbe interactions, which in turn are strongly associated with the state of health and disease (Figure 2). Once a change in genetics or in the environment occurs, the microbiota can change rapidly. A better understanding of interactions among hosts, microbes, and disease-causing organisms may lead to better strategies against skin diseases. To this end, many details

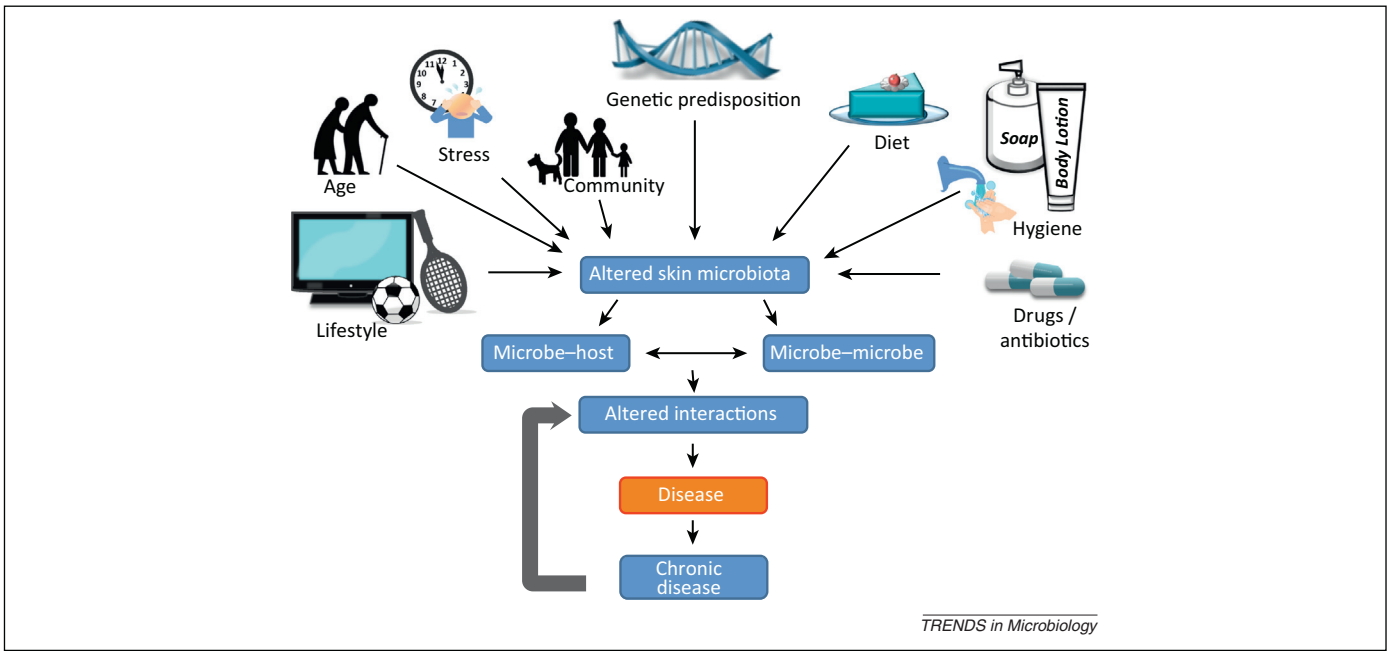

Figure 2. Environment and interactions predict functions of the skin microbiome. The ecology of the skin surface is influenced by many variables including lifestyle, age, emotion, community, genetics, diet, hygiene products, and drugs. Under unfavorable conditions, an altered community of microbes can arise on the skin, leading to conditions of dysbiosis. Both interactions between microbes and between a microbe and the host can promote disease. Dysfunction of the capacity to reestablish a normal microbial community may perpetuate chronic disease.

remain to be identified. Future research should include strategies to overcome current methodological limitations in describing microbial composition (Box 1). Such advances should reveal the microbial composition in several skin diseases and facilitate hypotheses related to their role in pathophysiology.

Differences in the genome of pathogenic and non-pathogenic bacteria at the strain level may have an important role. Subtle variations could have great consequences during interactions between the host and microbe or between microbe and microbe. The opportunity for microbes such as bacteria and viruses to cause epigenetic changes resulting in important functional changes in the host should not be underestimated.

Current available information already supports the conclusion that some treatments in dermatology medicine should be rethought. The indiscriminate use of antibiotics has a cost to the long-term health of the whole microbiota. It can take years until the normal microbiota recovers [91]. In this context, it is plausible that the application of several medications intended for acute treatments could lead to dysbiosis and therefore promote long-term susceptibility to certain diseases. Moreover, exposure to pharmacological doses of antimicrobial agents over years can alter bacterial species in the population and possibly lead to a shift in the human microbiome and higher susceptibility to pathogenic microbes [56]. *Helicobacter pylori* is such a bacterium that is becoming rarer in the Western population. The bacterium has long been regarded as exclusively pathogenic, but it is now proposed that it also has several protective functions [92]. The skin has many such microbial inhabitants whose biology and relationship to the host are incompletely understood. Some of these are associated with disease, but as long it is not clear if they belong to the normal human microbiota or not, elimination of these microbes should not be an option. Furthermore, modern lifestyles also lead to changes in the skin microbiome and therefore might represent a parameter in skin microbiome research.

Manipulation of microbial communities to enhance the abundance of beneficial species is a hot topic in human therapy. Such manipulations may aid us by directly promoting health or reducing the presence of undesirable pathogens. Although not yet described in human dermatology, addition of an antifungal bacterial species to the skin of the frog *Rana muscosa* successfully prevents morbidity and mortality caused by the pathogen *Batrachochytrium dendrobatidis* [93]. This fungus is the cause of chytridiomycosis, which has led to dramatic declines in many amphibian populations. More cause–effect experiments are needed for an understanding of whether changes in the human skin microbiome are indeed responsible for disease initiation or progression. Only the future will reveal to what extent recognition of ourselves as a colony of mutualistic organisms will aid in the treatment of disease.

Box 1. Outstanding questions

- What is the composition of the complex network of organisms that comprise the human skin microbiome?
- How do factors such as diet, stress, and lifestyle interfere with skin microbial composition?
- Can the surface microbiome be used to diagnose or predict disease?
- Is dysbiosis of the skin microbiome a causative element in the pathophysiology of some diseases?
- Can skin microbes cause differential epigenetic changes in the host?
- Can manipulation of skin microbial communities be a beneficial therapeutic approach to disease?

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