The Nature and Functions of Vertebrate Skin Microbiota

Aline Rodrigues Hoffmann, Caitlin E. Older, and Mayane Faccin

Abstract The skin is the first layer of protection from the environment, preventing pathogens from entering the body. Although the skin is often considered to be a hostile microenvironment for microbes, numerous microbes have adapted and thrived as colonizers of the skin in different animal species. Several intrinsic and extrinsic factors can contribute to the diversity and composition of the skin microbiome including skin biology, the environment, health status, and lifestyle. Despite its highly variable morphology across different animal species, the skin microbiome plays important roles that are conserved across the vertebrate phylogenetic tree. Along the evolutionary process, the microbial communities evolved with the host, building a symbiotic relationship that allowed the survival of both microbes and the host. This intricate balanced relationship between microbes inhabiting the skin and the host may easily be disrupted by damage to the skin barrier leading to microbial dysbiosis and often times development of skin lesions in the host. We are now recognizing the need to use these symbiotic microbes colonizing the skin to recover dysbiosis and improve skin health. These different aspects that can influence the cutaneous microbiome in humans and animals will be covered within this chapter.

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1 Introduction

Within the subphylum of Vertebrata are several incredibly diverse classes of animals; depending on the source, this may include up to seven classes which broadly include amphibians, birds, fish, reptiles, and mammals. Breaking these groups down to an even larger number of orders still does not fully capture the diversity of animals. The skin microbiome across the body of even a single animal can be different based on the body site; therefore, considering animals which have vastly different environments, lifestyles, anatomy, and physiology reveals an incomprehensible range of microbial communities that may be present on the skin. Within this chapter, we hope to familiarize readers with the unique communities present on the groups but also consider the conserved nature and functions of the skin microbiota across different animal species.

2 Factors Influencing the Skin Microbiome

Several factors are known to influence the skin microbiome, which we have divided between five categories: microenvironment, biology, environment, health status, and lifestyle (Fig. 1). While we attempted to divide the factors known to influence the

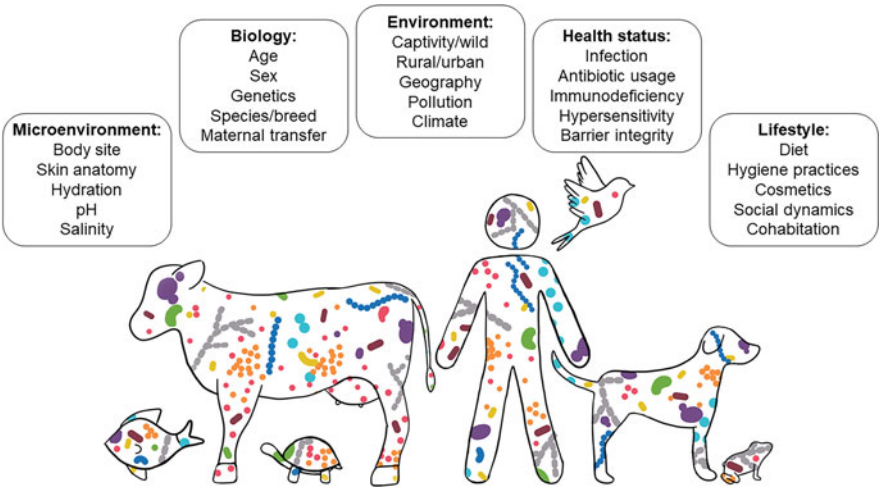

Fig. 1 Factors influencing the skin microbiome

skin microbiome in a single category, it is important to note that many of these factors are connected to each other. For example, a host's genetic makeup can inform some of the factors which we have classified as "skin physiology," including the natural pH of the skin and hydration; a host's genetics also has obvious influences on health status. Prior to describing some of the many factors that may dictate what the skin microbiome looks like on animals, it is important to first understand the diversity of environment that these microbes inhabit.

2.1 Microenvironment

While what is considered to be the "skin" of an animal may appear dramatically different depending on the animal, all animals do have an exterior organ which plays important roles that are conserved across the phylogenetic tree. The skin is the first layer of protection from the environment, preventing pathogens from entering the body and keeping internal tissues safe from the sometimes harsh environmental conditions. Each animal's skin has adapted to the environment where it lives, with some mammals having large amounts of fur to better insulate critical organs in extremely cold climates and with some fish having scales that act as a hard armor to protect against predators.

Features of the skin that are not obvious to the naked eye also exist to protect the body from microbial threats; for example, on human skin, antimicrobial peptides [1] and a low pH create a hostile microenvironment for microbes [2], directly having an influence on the composition of communities. Fish skin has a mucus layer that acts as a physical barrier to trap pathogens and prevent them from entering the skin. This mucus layer also has several molecules that act as a biological barrier, including antimicrobial peptides, proteases, and immunoglobulins [3].

2.2 Biology

In addition to the diversity of the anatomy and physiology of the skin that is seen across different animal species, there can also be numerous distinct microenvironments across the skin of a single animal. In humans, body sites that are less exposed to the external environment are usually more humid, for example, the axilla, which creates a different environment for microbes to live in compared to a more exposed body site such as the arm [2, 4]. Newborns are colonized with homogeneous microbes across different body sites, with these colonizer microbes briefly varying depending on mode of delivery. Despite the changes in the microbes colonizing infants at delivery, within a few weeks after birth, infants will start to change their cutaneous microbiome with variable community composition across different body sites and with mode of delivery no longer playing a role in the microbes colonizing their skin [5]. As infants grow, their skin microbiome continues to change as well,

resulting in significant differences from the cutaneous microbiome they were initially colonized with [6].

2.3 Environment

When thinking about the constant exposure the skin has to the exterior, it becomes easy to see that environment can play a significant role in altering the landscape and composition of the skin microbiome. The effect of environment has been well documented in humans, where individuals living in urbanized areas are much more likely to have lower skin microbial diversity compared with secluded indigenous populations that have not previously had contact with Western civilizations [7]. Furthermore, individuals living in rural areas and with exposure to diverse environments, as well as contact with animals, are much more likely to have higher skin microbiome diversity and be colonized with certain bacterial taxa, such as *Acinetobacter* sp., compared to those living in urban areas [8, 9]. Many individuals living in urbanized areas are exposed to high levels of air pollution, which can significantly affect the skin microbiome resulting in increased richness and diversity, as well as alterations in the functional capacity of the microbiome [10]. Perhaps one of the most compelling pieces of evidences that supports that the skin microbiome is affected by the environment occurs in astronauts within the international space station. These individuals can present alterations in the structure of their skin during space flight [11] which may make them more prone to develop skin lesions and infections. Remarkably, their skin microbiome can change significantly with reduction of Gammaproteobacteria and Betaproteobacteria, at the expense of increased Firmicutes. It is perhaps the constant filtration of the air within the space station or the lack of contact with natural environments that leads to these microbial changes [12].

Research has indicated that exposing individuals to green environments is a method that can be used to increase the diversity of the microbiome, which could potentially have a favorable impact on cutaneous health status [13, 14]. This has been shown by a study performed in adults [13], as well as a biodiversity intervention study, where children kept in a nature-oriented daycare facility versus an urban facility had more diverse bacterial communities, with increases in regulatory T cells and TGF-β1 levels. Similar interventions could be implemented long term aiming to increase microbiome diversity in infants and children and potentially reducing the development of immune-mediated disorders [14].

While the environment plays a role in influencing the skin microbiome of all animals, the relationship between the environment and the skin microbiome of aquatic animals is unique since the water they spend the majority of their time in has its own microbial populations [15, 16]. The microbiome of water influences the cutaneous microbiome; however interspecies variation does exist [17] and individuals of the same species living in different environments have some of the same core microbiota [18], indicating the distinct microbiome that exists on their skin. Studies

evaluating the skin microbiome of aquatic animals and the surrounding waters indicate that these microbiomes are distinct from each other [15, 17]. Remarkably, the microbial composition of human skin is also affected by swimming in the ocean, and this altered microbial composition is associated with increases in antibiotic resistance genes, with changes that can persist for at least 6 h after swimming in the ocean [19].

Seasonality is another important factor contributing to alterations of the skin microbiome. Dogs [20] and horses have been shown to have variable composition in different seasons. In horses, winter and summer were characterized by higher alpha diversity compared to spring and fall. During the winter and summer, horses were primarily colonized by Firmicutes, whereas during the autumn and spring, their skin was predominantly colonized with Proteobacteria [21].

2.4 Health Status

Health status factors are likely some of the most studied influences on the skin microbiome, given the direct implications of the skin microbiome on cutaneous health and vice versa. Antibiotics have often been the first choice for bacteria-driven disease; however clinicians and patients are becoming more concerned of the effect these drugs may have on nonpathogenic microbes [22]. In addition to antibiotic usage, the immune system and microbiome are closely linked; microbes are important for training the immune system in early life to be tolerant of commensals, and immune dysfunction can have important implications. In terms of the skin microbiome, immune abnormalities may result in inherent dysbiosis [23, 24], further putting individuals at risk for infection and exacerbation of disease. Given the wealth of knowledge with respect to health and the skin microbiome, more information is included in later sections in this chapter.

2.5 Lifestyle

Interestingly, but not unexpectedly, cohabitation is another factor that plays a significant role in the skin microbiome. Individuals that cohabit together are much more likely to share their skin microbiomes, compared to those that live in different households. Pet ownership, and in particular dog ownership, can increase the diversity of the human skin microbiome, and owners and their dogs tend to share their skin microbiomes [25]. Cohabitation also changes the skin microbiome of our pets, with strictly indoor cats that cohabit with humans presenting several bacterial taxa that predominate within human skin [26] and with dogs cohabiting together being one of the strongest effects on their cutaneous microbiomes [27]. For humans, hygiene practices, in particular the use of cosmetics and antiseptics, are important factors influencing the skin microbiome. The topical application of hygiene products

to the skin can significantly alter not only the composition of the microbiome but also the metabolites that are synthesized in the different body locations [28, 29]. The common use of hand sanitizers, in particular, within health-care workers [30], has been demonstrated to be an excellent way to reduce transmission of pathogens between hospitalized patients. These products became a necessity within the general population during the COVID-19 pandemic, and despite their benefits, these products may lead to alterations in the skin barrier and the cutaneous landscape, resulting in significant reduction in hand microbial diversity and lower production of antimicrobial peptides [31].

Hygiene products to reduce axillary malodor, including deodorants and antiperspirants, which are two of the most common cosmetic products used around the world, are associated with increased diversity, selection for bacteria that cause bad axillary odor, and selection of increased proportions of *Staphylococcus* spp. and the malodorous bacteria in the genus *Corynebacterium* spp. [32] Microbiome axillary transplantation [33] and microbially converted plant-derived products [34] have been successfully used to counter bad axillary odor, although the effects were just transient and after a few days individuals returned back to their own microbiomes. These "alternative" treatment options are likely to become potential less harmful options to reduce body malodor.

In addition to hygiene products, certain types of clothing, such as polyester, have also been associated with increase in bad body odor and overgrowth of certain bacterial types, including micrococci [35]. Since clothing can lead to changes in odor and cutaneous bacteria, why not create clothing that could actually reduce bad odor bacterial composition? Well, some researchers have begun investigating the potential of using clothing to modulate the skin microbiome to reduce malodor, as well as for other purposes such as wound healing, and it is likely that in the upcoming future we may see many clothing items that will be used to augment a "favorable" skin microbiome [36].

Strong body odor in pets is another topic in the realm of hygiene products and a concern for individuals that cohabit with indoor pets. It has been found that certain bacterial taxa, including *Psychrobacter* spp., which can be found in spoiled food and predominates in aquatic animals, and to a lesser extent *Pseudomonas* spp., have been associated with malodor in a colony of bloodhound dogs. The microbial diversity was reduced in dogs with malodor. Interestingly, the use of essential oils reduced the skin odor, as well as the bacteria that were associated with the odor [37].

Despite its constant external exposure and influence from so many extrinsic factors, the skin microbiome tends to be fairly stable within an individual, especially the facial microbiome, most likely due to recolonization from the follicles and pores, which act as special microbial reservoirs [38, 39]. Changes that occur are often transient, and healthy individuals are very likely to return to their own microbiomes after being influenced and altered by different external factors.

3 Composition of Microbial Communities in Humans and Across Different Animal Species

In humans, the skin microbiome composition varies across the different body sites which have been divided as dry, sebaceous, and moist microenvironments [2]. Each of these niches are characterized by core microbial communities. Overall, the predominant bacterial phyla on human skin include Actinobacteria, Firmicutes, Proteobacteria, and Bacteroidetes [2, 4, 40, 41]. Sebaceous regions have lower diversity and tend to be colonized with the Actinobacteria Cutibacterium acnes (formerly known as *Propionibacterium acnes*), whereas *Corynebacterium* spp. and *Staphylococcus* spp. dominate moist regions. Dry areas are the most rich microenvironment, with more even distribution of the predominant phyla [2].

Animal species tend to have much higher diversity of their microbiomes, compared to humans (Fig. 2). Host taxonomic order is the most significant factor influencing skin microbiota of animals, followed by their geographic location [26]. Studies in several animal species have found a more similar microbiome across the different body sites covered with hair, although the ear and mucocutaneous junctions are more likely to be colonized with different microbes. In dogs, the individual and to a lesser extent the body site are some of the factors playing a role in the composition of the cutaneous microbiome. Some of the most common phyla found in canine skin include Proteobacteria, Actinobacteria, Firmicutes, Bacteroidetes, and Fusobacteria [42]. In cats, similar phyla were identified; interestingly, Bacteroidetes, a phylum that predominates in the oral cavity, was one of the most common phyla found on the haired feline skin, which is likely related to their grooming behaviors [43]. Equine skin is highly diverse and influenced by the different body sites, with some of the most common genera including *Psychrobacter*, *Macrococcus*, *Pseudomonas*, *Acinetobacter*, *Planomicrobium*, *Arthrobacter*, *Carnobacterium*, *Desemzia*, and *Corynebacterium* [21]. Bovine skin studies have mostly focused on the udder and feet, due to health issues related to the mammary gland [44] and high rates of development of pododermatitis in this species [45]. The udder is primarily colonized by high abundances of Corynebacteriaceae and Staphylococcaceae, with significant differences seen between cows and between milk samples collected from the different quarters within the same individual [44]. Even-toed and odd-toed ungulates presented congruence of their skin microbiota, which supports phylosymbiosis in skin microbial communities and their hosts [26].

Avian skin is covered with feathers, which harbors high abundances of diverse bacterial communities. Their microbiota are highly influenced by their social groups, with finches in the same family having a very similar microbiota compared to individuals in other families. Some of the most common families colonizing their skin included Planococcaceae, Carnobacteriaceae, Rhodobacteraceae, Moraxellaceae, and Bacillaceae. It is well known that bacteria can secrete volatiles that may alter odor, and in these birds, it is speculated that volatiles secreted by

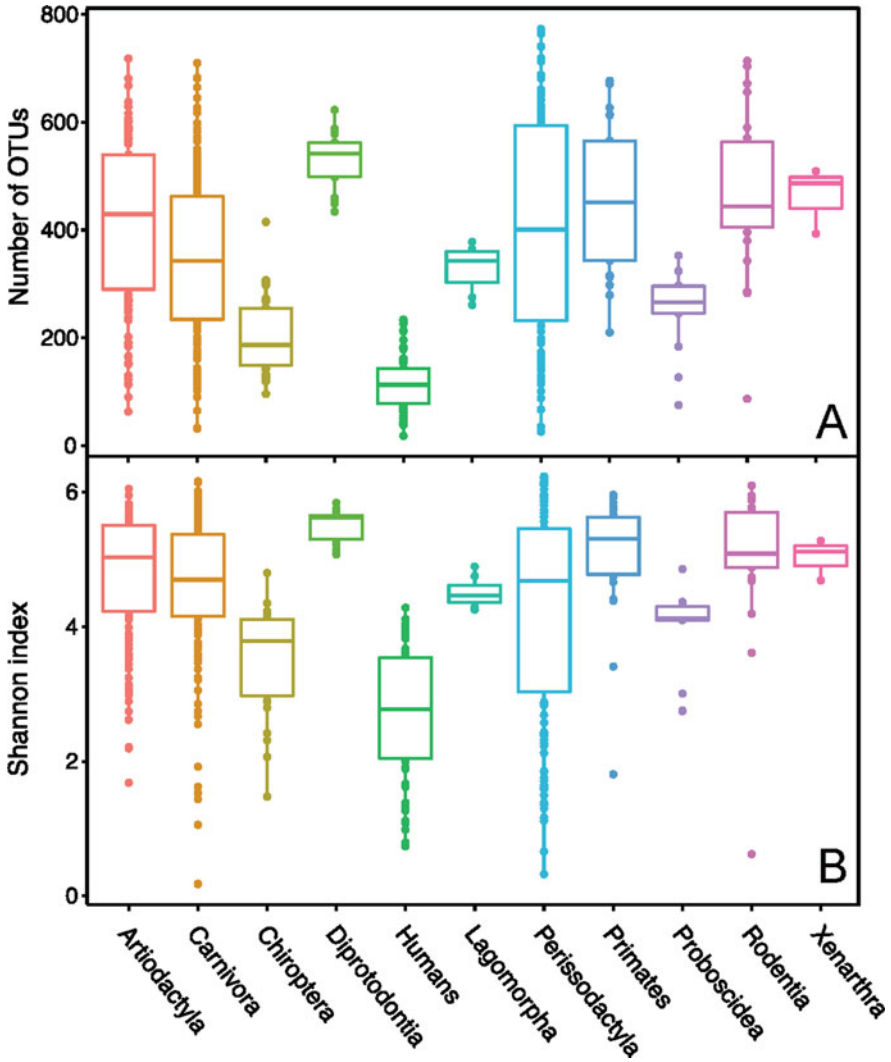

Fig. 2 Boxplots of diversity indices for 10 mammalian orders and humans, including both number of OTUs (**a**) and Shannon indices (**b**). (Reprinted with permission from Ross, A. A.; Muller, K. M.; Weese, J. S.; and Neufeld, J. D. Comprehensive skin microbiome analysis reveals the uniqueness of human skin and evidence for phylosymbiosis within the class Mammalia. *Proc Natl Acad Sci U S A* **115**, E5786-E5795, doi: 10.1073/pnas.1801302115 (2018). Copyright © 2018 the Author(s). Published by PNAS)

cutaneous bacteria may play a significant role in social communication in these birds [46].

The skin of amphibians harbors Bacteroidetes, Proteobacteria, Firmicutes, and Sphingobacteria. In one study, the host species was a strong predictor of microbial

community composition. Within the same species, wetland site is considered a significant factor related to the composition of the microbiota [47]. Since the beginning of the chytridiomycosis outbreaks, which have decimated several amphibian populations across the world, significant attention has been paid to the composition of the skin microbiota of these animals [48].

Aquatic vertebrates encompass a large number of species which inhabit incredibly diverse environments. This group includes completely aquatic mammals, which include whales and dolphins; semiaquatic mammals, such as seals and otters; and fish. Most of the skin microbiome research that has been on aquatic animals has focused on fish and cetaceans (e.g., whales and dolphins); few studies have described the skin microbiome on semiaquatic animals. Among the cetaceans that have been studied are humpback whales [18, 49, 50], killer whales [51], and bottlenose dolphins [52]. The fish species that have been studied so far are mostly those of economic importance in the aquaculture industry, including salmon [53–55] and catfish [56, 57], in addition to many wild species [17] (see Gomez et al. 2020 for a comprehensive review of fish skin microbiome) [58]. Some of the few semiaquatic animals to have their skin microbiome studied thus far are the Antarctic fur seal [59] and harbor seal [60]. Regardless of host species, Proteobacteria appears to be the most prevalent bacterial phylum found on the skin of aquatic animals, with the genus *Psychrobacter* identified on many fish species [16, 59, 60]. Besides Proteobacteria, the phyla Firmicutes, Actinobacteria, Bacteroidetes, and Fusobacteria are also typically present [15, 16, 59].

Despite the range of animals described here, there are some consistencies in the skin microbiome composition. Most of the skin microbiota on animals appears to be composed primarily of bacteria within the phyla Proteobacteria, Bacteroidetes, Actinobacteria, Firmicutes, and Fusobacteria. As mentioned previously, animals tend to harbor diverse cutaneous communities compared to humans. While humans do appear to have unique microbiomes, comparison between animals also indicates that host taxonomy is an important modulator of the skin microbiome [26].

4 Functions of Skin Microbiome

In addition to the intrinsic and extrinsic factors that have been previously described to influence the cutaneous microbial communities, the microbes present on the skin are also important determinants of the composition of communities. Resident microbes can influence the skin microbiota directly, through interspecies interactions, or indirectly through activating the host immune system to partake in community surveillance [1, 61–63].

Some microbes are able to impair the skin barrier, through the production of superantigens or exfoliative toxins [64, 65]. This method is particularly useful on the skin of a compromised individual, where they are already able to gain deeper access into the body. In certain diseases where immune dysfunction is a key characteristic,

such as atopic dermatitis, this can cause further inflammation and destruction of the skin barrier [66].

This ability of the skin microbiome to activate the immune system in a way that is harmful to host highlights the importance of training the immune system to appropriately react to microbes. Immune training is a systemic process, with some of it occurring on the skin, but with much of it occurring through the gastrointestinal tract. The critical period for training the immune system to be tolerant to commensal microbes is early in an individual's life. The importance of immune tolerance has been demonstrated through several mouse studies evaluating the influence of a germ-free environment, particularly on the gastrointestinal microbiota [67]. However, studies using murine models have demonstrated that interactions between commensal microbes and regulatory T cells in the skin are vital in the development of tolerance to commensals [68, 69]. This developmental interaction is specific to commensals; colonization of the neonatal skin by pathogenic *S. aureus*, as opposed to the commensal *S. epidermidis*, did not confer the same tolerance [70]. This study as well as evidence from other studies [71–73] supports the hypothesis that many chronic skin disorders may be due to an exaggerated immune response to commensal microbes. Perhaps, excessive cleanliness during early life may lead to augmentation of immune responses later in life and development of hypersensitivities.

The importance of the skin microbiome modulating the host immune system extends past the period of immune tolerance training. As described further below, microbes can alert the host to pathogens and induce production of antimicrobial peptides [74–76]. Commensals can also contribute to what has been termed "homeostatic immunity," which refers to the development and establishment of adaptive immune responses to the microbiota, but without inflammation [77]. In the skin, some commensals have been found to be important in recruiting Th17 cells to the epidermis; the presence of these T cells serves as a layer of protection by enhancing epidermal barrier function and inducing antimicrobial peptide production [78].

5 Host Health and Pathogen Resistance

Microbial communities have an intimate relationship with the host and have direct influences on host health. Along the evolutionary process, the microbial communities evolved with the host, building a symbiotic relationship that allowed the survival of both microbes and the host. One example of this symbiotic relationship is the microbial community on the face of vultures [79]. Vultures are scavenger animals and therefore are in contact with several microorganisms that would normally cause disease in non-scavenger species, such as tuberculosis, anthrax-like disease, pneumonia, gas gangrene, and gastroenteritis. A study of the facial skin and gut microbiome of these birds revealed a microbial core that contains *Hylemonella gracilis* and *Lactobacillus sakei*. *H. gracilis* has been shown to prevent long-term *Yersinia pestis* colonization in experiments performed in freshwater samples [80], whereas *L. sakei* has inhibitory effect against *L. monocytogenes* and certain *E. coli*

strains [81]. In addition, microbial genes involved in the biosynthesis of antibiotics, fungicides, and parasiticides were identified, indicating functional capacity of the microbiome that would benefit the host. The bacterium *Arthrobacter phenanthrenivorans* was found to be highly abundant in the skin of vultures and is capable of degrading phenanthrene, a polycyclic aromatic hydrocarbon that has skin-irritating effect, emitted from animal carcasses.

In the context of human skin, the skin commensal *Staphylococcus hominis* has shown antimicrobial activity against *Staphylococcus aureus*, an important skin pathogen in patients with atopic dermatitis [76], while *Corynebacterium accolens*, present in the nostril, inhibits the growth of *Streptococcus pneumoniae*, a pathogen of the respiratory tract [82]. Some commensal bacteria help the host by promoting wound healing, such as *S. epidermidis* which limits inflammation post-injury and whose bacterial products can prevent pathogen invasion [83]. All of these examples illustrate different pathways that the microbial population can contribute to the host health and resistance against pathogens.

Furthermore, a minor change in the microbial communities does not necessarily reflect disease to the host due to functional overlap among different taxa [79, 84]. An example of this functional redundancy is the genera *Pseudomonas*, *Acinetobacter*, and *Janthinobacterium*, all of which have shown some degree of antifungal activity against the fungus *Pseudogymnoascus destructans* [85–87], known for causing white-nose syndrome (WNS), that has caused the death of millions of bats in North America. All three genera can be highly abundant in WNS-positive bat colonies [88, 89]. A similar pattern is also observed in amphibian colonies positive for the chytrid fungus *Batrachochytrium dendrobatidis*, in which antifungal bacteria such as *Janthinobacterium lividum*, *Bacillus cereus*, *Pseudomonas fluorescens*, and *Flavobacterium* spp. are highly prevalent [90]. Additionally, in rainbow trout, *Arthrobacter* sp. and *Psychrobacter* sp. showed inhibitory activity against the aquatic fungal pathogens *Saprolegnia australis* and *Mucor hiemalis* [91]. This pattern raises the possibility of an adaptive mechanism of the microbiome to induce pathogen resistance or tolerance by the host [84].

While the primary function of the pre-disease microbial community may be altered, the post-disease microbial community may be selectively modified to respond to this new event. These changes in the microbial communities after disturbances may be temporary or permanent, depending on how resilient the microbe is and how strong the disturbance is. However, the selective pressure of adapted microbial communities that allow the coexistence with the pathogen may present as herd immunity, if enough individuals from the colony have an adapted microbiome [92]. This effect was observed in a population of frog species, *Rana muscosa*, in an area with endemic chytrid. This particular population was naïve to the chytrid fungus and thus thought to be at high risk for extinction. Two years after the initial observation of this population and despite neighboring populations being affected by chytrid outbreaks, the population survived. Researchers suspect this was likely due to a high proportion of individuals with antifungal bacteria on their skin [93].

6 Antimicrobial Peptide Production and Their Role in Maintaining a Stable Microbiome

Microbes are in constant battle with each other to maintain their position in an environment. To establish themselves as residents, rather than simply transient microbes, they need to ensure their survival at the cost of others. Some microbes will naturally be more suited to inhabit the skin than others, being able to survive even in the nutrient-poor environment that is the skin. However, oftentimes, microbes will need to take it upon themselves to adapt novel methods to thrive over their competitors, for example, through the production of metabolites that interfere with others' ability to grow and establish themselves.

Lipid metabolism by microbes can decrease the pH of the skin and thus create an even more hostile environment for many microbes; the products of this metabolism can even be directly antimicrobial [82]. Several bacteria that are known commensals of the human skin microbiome, including *C. acnes*, *S. epidermidis* [94], and *Malassezia* spp. [95], are known to perform lipid metabolism, which has likely allowed them to establish themselves as permanent residents.

Some microbes also produce molecules, including bacteriocins and antimicrobial peptides, which are likely not necessary for their own existence on the skin in the absence of competition but are produced to enhance their chance of survival. Microbes can also induce antimicrobial peptide production by the host, which often not only benefits the microbes modulating the host immune system but also the host. Many of these interspecies interactions and interactions with the host have been demonstrated on human skin with respect to staphylococcal populations.

On healthy skin, staphylococci usually represent a relatively small fraction of the bacteria that are present; several species may be present including two coagulase-negative *Staphylococcus* species (CoNS), *S. epidermidis* and *S. hominis*. One of the primary targets of healthy cutaneous staphylococcal populations is *S. aureus*; this staphylococcal species is typically present in very low abundances, if at all on healthy skin, but dramatically increases its abundance and often becomes the most abundant staphylococcal and bacterial species on the skin of patients with atopic dermatitis [24]. Both *S. epidermidis* [96] and *S. hominis* are able to produce antimicrobial compounds that target and inhibit *S. aureus* [74–76]. Some antimicrobial peptides produced by CoNS can also activate host production of AMPs and act synergistically, mounting an even more effective response [74–76].

7 Skin Disorders Affect the Structure and Composition of the Skin Microbiome

Individuals with skin disorders, such as atopic dermatitis in humans (as well as pets), acne, and psoriasis, are often presented with microbial dysbiosis, which either lead to or are a result of damage to the skin barrier. In atopic dermatitis, cutaneous dysbiosis

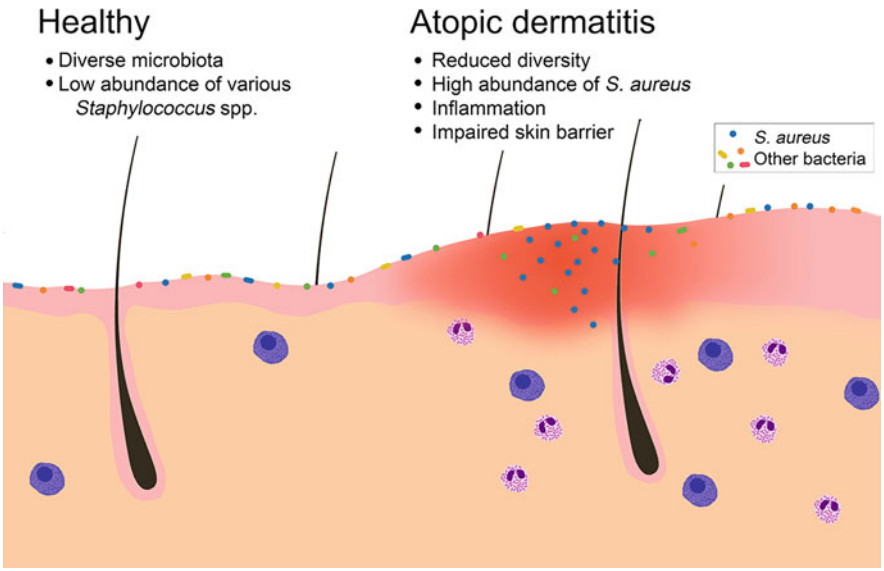

Fig. 3 The skin microbiome in human atopic dermatitis

is often characterized by increases in *Staphylococcus aureus* with loss of microbial diversity (Fig. 3). The reduction in diversity often occurs at the expense of increased relative and absolute abundances of *S. aureus*, with dysbiosis in children being described even prior to flare-up and presentation of cutaneous lesions [24]. In experimental mouse models of atopic dermatitis, it has been demonstrated that dysbiosis in the cutaneous microbiome can be responsible for the development of skin lesions [97]. High *S. aureus* abundances are also implicated in perpetuation of skin lesions [98]. Although *S. epidermidis* is often referred to as a commensal and beneficial microbe, some strains of *S. epidermidis* can have proteolytic activity on corneocytes, in a similar fashion as *S. aureus*, which can result in damage to the epidermal barrier in AD patients [99].

Loss of cutaneous microbial diversity is not only affecting the human population but also pets that often cohabit within the same household. The urbanization lifestyle of many individuals with less exposure to diverse microbial communities is leading to development of cutaneous disorders in pet populations across the world. In particular, dogs and cats are now mostly kept indoors, and in addition to their genetic susceptibility to development of allergic skin disorders, these changes in behavior and environment have been significantly associated with increases in cutaneous allergic disorders in these animal species. In some regions, development of atopic dermatitis, the most common skin disorder in dogs, can affect more than 10% of the canine population. These individuals are likely to present lower richness and/or diversity of their microbiomes, which often coincides with increases in *Staphylococcus pseudintermedius* [42].

Psoriasis, an inflammatory skin disorder, affects approximately 2% of humans worldwide. This disease is characterized by epidermal hyperplasia and hyperkeratosis and inflammatory cell infiltration. Both genetic and environmental factors are thought to play a role in the development of psoriasis lesions. The microbiome is also thought to play a role in psoriatic lesions, although its role is still not well defined and a core microbiome in these patients has not yet been identified [100]. Research studies investigating this disorder have had conflicting findings, which can either show increased or decreased microbial diversity and/or richness. Significant increases in the phylum Firmicutes, at the cost of reductions in Actinobacteria, have been found in those with higher diversity [101], whereas patients with lower richness and diversity of their bacterial microbiota were primarily colonized by four major bacterial genera: *Corynebacterium*, *Propionibacterium*, *Staphylococcus*, and *Streptococcus* [102].

Patients with acne vulgaris have inflammation of their pilosebaceous units which occurs in association with the bacterium *C. acnes*. *C. acnes* colonizes microcomedones formed within hair follicles, and the anaerobic and lipid-rich environment allows proliferation of this commensal organism. Microbiome studies have demonstrated that *C. acnes* is actually one of the most common bacteria found on human skin, especially in sebaceous microenvironments in both healthy and individuals presented with acne [100]. Different *C. acnes* phylotypes are identified in sebaceous follicles in skin biopsies, and macrocolonies are observed in approximately 37% of patients with acne versus 13% with healthy skin [103]. Similar *C. acnes*-relative abundances have been found in both healthy skin and acne lesions. However, certain strains are more common in individuals with acne lesions, with strong association with development of acne [104].

Impaired wound healing with development of chronic skin ulcers is a common chronic problem involving the skin, especially in diabetic patients. Given its severity and impaired wound healing, characterization of the core microbiomes in chronic ulcers in diabetic patients is crucial. Some studies have presented conflicting data. In a study that included almost 3000 patients with chronic ulcers, these lesions often presented high proportions of *Staphylococcus* and *Pseudomonas* species, with these bacteria accounting for approximately 63% and 25% of the composition of all wounds [105]. There were no differences in the composition of the chronic wound microbiome, regardless if a patient presented with diabetic foot ulcers, venous leg ulcers, decubitus ulcers, or nonhealing surgical wounds. Remarkably, the resident microbiota in patients that formed pustules versus those that were able to resolve skin lesions were different, with the former being composed by increased relative abundances of the phyla Proteobacteria and Bacteroidetes and the genus *Micrococcus*, *Corynebacterium*, *Paracoccus*, and *Staphylococcus*, whereas Actinobacteria and *Propionibacterium* spp. were more abundant in the latter [106].

8 Skin Microbiome Modulation

Since the discovery of the first antimicrobial drug, antibiotics have been the most available, reliable, and pragmatic choice for bacterial infections in both human and veterinary medicine. Even though still largely successful and available, the last decades were marked by an alarming increase in antimicrobial resistance, caused by the indiscriminate use of broad-spectrum antibiotics, voluntary treatment interruption, and selective pressure due to use of antibiotics as growth promoters in meat production. The surge of multidrug-resistant microbes has urged the scientific community to discover new alternatives for antibiotic use.

On healthy skin, many microbes live in a balanced interaction, where both microbe and host profit from each other. For microbes, the host provides nutrients and a stable environment. For the host, the microbes can compete against pathogens and protect the host. As discussed previously, microbes have the capacity to modulate microbial populations and the host's immune system and, therefore, the general health status of an individual. Studying the methods by which they are able to do this can provide useful insights into the development of new therapies and strategies to reduce the likelihood of developing antimicrobial resistance.

The skin microbiome has also been found to take part in skin regeneration. Bacteria using the IL1β pathway can stimulate epidermal regeneration, promoting wound healing. These findings support the need to reduce use of topical antibiotics in superficial lesions, as these products have been shown to delay wound healing by impairing the microbiota [107].

Two important ways we have exploited the microbiome to improve host health are prebiotics and probiotics, which are currently being used in the development of therapeutics and cosmetics. On the cosmetic side, several bacterial species, individually or in combination with prebiotics, are being studied for their antiaging properties [108]. On the therapeutic side, for example, the strain *Staphylococcus hominis* A9 is being tested as a new probiotic against *S. aureus* in humans with atopic dermatitis [109]. Additionally, a nasal strain of *Staphylococcus lugdunensis* has been shown to inhibit colonization of *S. aureus* by producing lugdunin, a novel thiazolidine-containing cyclic peptide antibiotic [110]. In frogs, administration of *Janthinobacterium lividum* prior to exposure to the chytrid fungus *Batrachochytrium dendrobatidis* mitigated morbidity and mortality, and the microbe persisted in the population after several months of administration [111].

Another strategy is the transplantation of a "healthy" microbiome to the skin of an individual with microbiome dysbiosis [112]. This method depends on the donor and recipient microbial composition and the load of transplant [108]. This strategy has been studied in atopic dermatitis patients who received creams with CoNS strains isolated from donors. The donor strains were capable of secreting antimicrobial peptides, properties that were lacking in the AD patients and that significantly reduced the burden of *S. aureus* [76]. A different approach to this technique is the use of autologous application of CoNS from the patient's non-lesioned skin in lesional areas [109]. Beyond its therapeutic applications, skin microbiome

transplantation can also be used as a method to mitigate the detrimental effects captivity has on the animal microbiome. Some examples are the parental contact with the offspring and the inclusion of natural subtracts, such as soil, sand, and water, to allow a more diverse microbiome [113].

Phage therapy is another method that can be used as an alternative to antibiotics, particularly for infections with antibiotic-resistant pathogens, given its high specificity against pathogenic microorganisms, while sparing nonpathogenic microbes. This therapy is based on bacterial viruses (phages), which penetrate the target bacteria, replicate, lyse the host prokaryote, and release to continue infecting and killing other bacterial cells [112, 114]. In nature, vulture skin contains the bacteriophage BPP-1, which attacks pathogenic *Bordetella* bacteria, as well as anti-*Clostridium* phages [79]. As a clinical therapy, phages have been used to treat cutaneous infections caused by several bacteria including *Propionibacterium acnes*, *Klebsiella pneumoniae*, *Staphylococcus*, *Pseudomonas*, *Proteus*, and *Escherichia* [115–117]. However, its use has been limited, given the complexity of the technique, which requires purification, characterization, and regulation. Additionally, the targeted bacterium may become resistant to the phage infection and lysis in the long term, due to evolutionary dynamics [112].

9 Conclusions

The skin represents a unique environment for microbes to live in. It is the outermost layer to the body and the first layer of protection for the host; thus it is often a harsh environment to exist on. Skin physiology is variable across vertebrates and even across the body of individuals. Despite striking anatomical and physiological differences across animal species, consistencies exist in the nature and function of the microbiome. Regardless of animal species, the skin microbiome is affected by many factors related to the skin microenvironment, host biology, environment, health status, and lifestyle. All animals have microbes that are pathogens and symbiotics living on their skin, and we now recognize the ability of skin microbes to interact with each other and with the host in many ways to keep a balanced microenvironment. Determining what interactions are occurring and how they are regulated is crucial to understand many aspects of diseases that not only affect the human and animal health but also affect the conservation of many endangered species.

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