The cutaneous ecosystem: the roles of the skin microbiome in health and its association with inflammatory skin conditions in humans and animals

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Introduction

Several studies published in the last 20 years have shown that complex communities of microbes, known as the microbiome, inhabit the different surfaces of the human and animal body. These communities often have a commensal relationship with the host and recent studies have also shown the host to be dependent on these communities. Microbes are no longer seen only as the “bad guys”; they are no longer our main enemies. Certainly, we know this is not true for all microbes, but we have now learned that the vast majority of micro-organisms inhabiting our bodies are actually beneficial. These commensal microbial communities act as our assistants, competing with pathogenic microbes for nutrients, producing numerous metabolites and modulating our immune system, allowing human and animal bodies to thrive. Due to these new concepts gathered based on research performed in the last few years, most of us no longer wish to inhabit a sterile world.

Background – Inhabiting a sterile world is no longer an acceptable or desirable concept. Recent studies developed in the microbiome field have unveiled complex microbial populations inhabiting the skin, digestive, respiratory and reproductive tracts. Microbiome studies have opened new venues to explore the human and animal second genome, its functions and its importance in maintaining health.

Skin microbiome in health – The composition of the skin microbiome varies across different body sites and across individuals, being influenced by different host habits, including for instance age, sex, diet, hygiene and lifestyle. Exposure to a diverse skin microbiome is now considered to be a key component in immune regulation, and imbalances in these microbial populations are being associated with human and animal skin inflammatory disorders.

Skin microbiome in inflammatory skin conditions – We have learned that in several skin conditions, there is a significant alteration in the diversity and composition of the microbiota colonizing the skin. For instance, in human and animal patients with atopic dermatitis, dysbiosis of the skin microbiota results in lower diversity of microbial populations. Whether these altered microbial populations are the cause or the effect of inflammatory skin conditions seen in humans and animals are still under investigation, but there is no doubt that the microbiome has an important role in maintaining skin health.

Summary – This review focuses on the most current studies describing the skin microbiome in humans and animals, its role in modulating the immune system, and its association with human and animal skin diseases.
colonize the body, but also they carry important functional genes, responsible for synthesizing numerous metabolites, which can influence host health. These diverse microbial populations inhabit the skin, digestive, respiratory and reproductive tracts within the human and animal bodies, but are variable across body sites and individuals. The vast majority of the microbiome studies to date have focused on describing the gastrointestinal microbiome, with the cutaneous microbiome gaining more attention in the past 10 years. These culture-independent studies have revealed that the skin and other body surfaces are colonized with a larger number of microbes than had been described previously based only on culture methods. Certainly, microbiome studies have some pitfalls as they account primarily for the presence of fragments from microbial genes, without considering whether these organisms are alive or dead, but they do allow us to categorize the history of the micro-organisms inhabiting these different body surfaces. It is estimated that the great majority of microbes identified with next

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**Box 1. Definition of microbiome nomenclature, diversity analysis and taxa**

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiome</td>
<td>All microbes in a habitat, their genes and metabolites</td>
</tr>
<tr>
<td>Microbiota</td>
<td>Collection of micro-organisms in a defined microenvironment Microbiota characterization is often based on conserved genes found on bacteria and fungi</td>
</tr>
<tr>
<td>Metagenome</td>
<td>Collection of genes and genomes from members of a microbiota obtained with shotgun sequencing</td>
</tr>
<tr>
<td>Operational Taxonomic Unit (OTU)</td>
<td>OTUs often correlate with microbial genus or species. The term OTU is used in microbiome diversity analysis, instead of species, as some genome sequences are not available in microbial databases</td>
</tr>
</tbody>
</table>
| Alpha diversity (within sample) | Measures used to calculate number (richness) and distribution (evenness) of taxa within a sample  
**Richness metrics**  
*Observed OTUs:* number of observed species identified within a sample  
*Chao1* – estimated OTUs that would be found if population was fully sampled  
**Diversity metrics**  
*Shannon diversity:* considers evenness and abundances of different OTUs |
| Beta diversity (between samples) | Measures used to estimate shared OTUs (microbial species) between different samples and/or subjects. Data are often presented as PCoA plots. These can be phylogenetic based, which take into account microbial evolution, or OTU based  
**Phylogenetic based**  
*Unifrac distance metric:* analysis based on relative phylogenetic distances between observed organisms in a community  
*Non phylogenetic/OTU based*  
*Bray-Curtis index:* dissimilarity between two communities based on species abundance (community structure)  
*Jaccard index:* dissimilarity based on presence or absence of species (community membership) |
| Taxonomic microbial composition | Relative abundances of different members within the microbiota. Often presented as graphs, tables or heatmaps describing different taxonomic levels for microbes of interest |

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**Box 2. Sequencing methods and targeted microbial genes used in microbiome studies**

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Next generation sequencing (NGS)</td>
<td>Amplicon sequences from targeted amplified DNA clones and nontargeted DNA (whole genome and shotgun sequencing) are obtained with NGS methods. Multiple samples can be sequenced in a single run. Most common platforms used in NGS include the Roche 454 pyrosequencing and Illumina</td>
</tr>
<tr>
<td>Whole genome shotgun sequencing</td>
<td>Shotgun sequencing-based methods randomly sequence small sheared DNA fragments from whole genomes in a sample. These small fragments are assembled into continuous longer sequences. In microbiome studies, this method is used to characterize any genes that are sequenced in a nontargeted manner from host and micro-organisms, allowing phylogenetic characterization and identification of microbial genes</td>
</tr>
<tr>
<td>Bacterial 16S rRNA</td>
<td>The transcribed form of the 16S ribosomal subunit gene (16S rRNA) gene is universal among prokaryotes. Highly conserved regions within this gene are followed by hypervariable regions. Sequences obtained from this gene allow phylogenetic characterization of bacterial communities</td>
</tr>
<tr>
<td>Fungal 18S rRNA, 28S rRNA, ITS</td>
<td>Similar to prokaryotes, eukaryotes also have conserved regions within their genome. For fungi, the 18S rRNA, 28S rRNA and the internal transcribed spacer (ITS) regions are genes of choice used in NGS studies. Although these genes allow characterization of fungal communities, fungal databases are still incomplete, offering limited characterization of obtained sequences</td>
</tr>
<tr>
<td>Virome</td>
<td>Assemblage of viral communities within a sample, including bacteriophages, single-stranded and double-stranded DNA and RNA viruses. Different from bacterial 16S rRNA, viruses lack conserved regions in their genome. Development of viral databases are challenging due to marked viral genomic variability and rapid evolution of viruses</td>
</tr>
</tbody>
</table>

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The skin microbiome is unique, it varies across different individuals and body sites. Age, sex, diet, hygiene, lifestyle and the environment influence the composition of the skin microbiome. It is estimated that the human skin is inhabited by approximately one million bacteria/cm². Using direct shotgun sequencing to analyse various complex whole genomes from different microbes and viruses, it was found that the human skin is inhabited by highly diverse communities divided between a predominantly bacterial population, and relatively lower abundances of viruses and fungi.

The human skin can be divided into dry, sebaceous and moist micro-environments based on different physiological niches. These different skin micro-environments are predominantly inhabited by the bacterial phyla Actinobacteria and Firmicutes, with lower proportions of Bacteroidetes and Proteobacteria (Table 1).

<table>
<thead>
<tr>
<th>Host</th>
<th>Skin sites and physiology</th>
<th>Alpha diversity</th>
<th>Beta diversity</th>
<th>Microbial composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry</td>
<td>High</td>
<td>Depends on skin sites, with dry areas having more interpersonal variation than moist and sebaceous</td>
<td>Dry – evenly distributed among four main phyla: Actinobacteria, Firmicutes, Proteobacteria and Bacteroidetes</td>
<td></td>
</tr>
<tr>
<td>Sebaceous</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosal surfaces/mucocutaneous junctions</td>
<td>Overall low</td>
<td>More likely to share microbiota across body sites</td>
<td>Proteobacteria, Firmicutes, Actinobacteria and Bacteroidetes</td>
<td>Moraxella spp. predominantly in the nostril Proteobacteria and Bacteroidetes predominate in the lip commissure Proteobacteria most abundant phyla, followed by Firmicutes, Actinobacteria and Bacteroidetes</td>
</tr>
<tr>
<td>Hairy skin</td>
<td>Overall high</td>
<td>High variability across individuals and body sites</td>
<td>Proteobacteria, Bacteroidetes and Propionibacterium</td>
<td>Proteobacteria, Bacteroidetes and Propionibacterium</td>
</tr>
<tr>
<td>Interdigital skin</td>
<td>High</td>
<td></td>
<td>High relative abundances of bacteria found in the oral cavity</td>
<td>Ferricutes, Spirochaetae, Bacteroidetes and Actinobacteria</td>
</tr>
<tr>
<td>Interdigital skin</td>
<td>High</td>
<td>Community membership differences between conventional and liquid-fed</td>
<td>Proteobacteria, with the genus Moraxella predominating in most samples Firmicutes, with the genera Streptococcus and Lactobacillus being the most abundant</td>
<td>Actinobacteria, Bacteroidetes, Firmicutes and Proteobacteria Dichelobacter nodosus also found in healthy skin</td>
</tr>
<tr>
<td>Nostril</td>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear pinna</td>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsal and ventral skin</td>
<td>Higher in wild than captive toads</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
The skin microbiome also extends beyond the skin surfaces and hair follicles. Using fluorescent in situ hybridization to demonstrate fragments of bacteria, and by sequencing the bacterial 16S rRNA gene, it has been demonstrated that bacteria/bacterial products are present within the deep dermis and subcutaneous tissues, skin compartments previously thought to be sterile. Although this is certainly a remarkable and intriguing finding, whether or not these actually represent viable bacteria is still unknown.

The composition of the skin microbiome seems to evolve with age.25,31 Newborn infants are colonized with relatively high abundances of Staphylococcus and the skin microbiota becomes more diverse within the first year of life.25 The composition of the skin microbiota shifts during adolescence. Within the nares, children have relatively high abundances of the phylum Proteobacteria shifting to higher relative proportions of the phylum Actinobacteria, due to increases in Corynebacteriaceae and Propionibacteriaceae in adolescents.30 It was shown that adults have a more diverse microbiota compared to children and the elderly.34

Although gender would be expected to influence the diversity and composition of the skin microbiota, most studies to date have found very little evidence demonstrating gender differences.22,27,35 Only a few studies have shown gender differences and these included the palm of the hands, where women were shown to have more diverse hand microbiota than men;36 and the glabella, which was found to have significant differences in richness, as well as composition of the microbiota.34 The gender differences observed in these two sites have been proposed to be associated with use of cosmetics and hygiene products. In fact, more and more scientific evidence supports the idea that our skin microbiota is influenced directly by our hygiene and use of cosmetics. A recent and quite impressive study describing the cartography of more than 400 skin sites of the human body under the skin: the skin virome.15,40,41 Similar to what was observed with the bacterial and fungal microbiota, marked interpersonal variation was observed in the skin virome (Box 2). Most of the skin virome was composed of bacteriophages, which are DNA viruses targeting bacteria. Of these, Propionibacterium and Staphylococcus bacteriophages were predominant in most skin sites. A few other viruses such as papillomavirus, polyomavirus and poxvirus were identified despite the fact the individuals had no clinical lesions. Even with development and improvement of these genomic studies, a large abundance of viral DNA found with shotgun sequencing could not be annotated, because viruses do not have conserved regions in their genome, as observed with RNA genes in bacteria and fungi, and viral databases are largely incomplete. Likewise, there still remains a large number of RNA

<table>
<thead>
<tr>
<th>Host</th>
<th>Micro-environment/ Skin sites</th>
<th>Alpha diversity</th>
<th>Beta diversity</th>
<th>Mycobiota composition</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most skin sites</td>
<td>Feet</td>
<td>Low</td>
<td>High sharing across body sites in the same individual</td>
<td>Composed predominantly of Malassezia spp.</td>
<td>15,30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low sharing across individuals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosal surfaces/ mucocutaneous junctions</td>
<td>Overall lower</td>
<td>High sharing across body sites in the same individual</td>
<td>Composed mainly of environmental fungi within the phylum Ascomycota, including Alternaria, Cladosporium and Epicoccum, with lower abundance of the Basidiomycota Cryptococcus and Malassezia</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Haired skin</td>
<td>Overall higher</td>
<td>High sharing across body sites in the same individual</td>
<td>Composed mainly of environmental fungi within the phylum Ascomycota, including Cladosporium and Alternaria and Epicoccum, with lower abundance of the Basidiomycota Cryptococcus</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Mucosal surfaces</td>
<td>Oral</td>
<td>Lower</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sebaceous</td>
<td>Overall high</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

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viruses to be investigated further, because current skin microbiome studies have described only DNA viruses.

**The skin microbiome is influenced by the environment and cohabitation**

Of all systems in the human and animal body, the integumentary system is the one with closest contact and direct exposure to the environment. Given its close contact with the outside world, the integumentary system and its microbiota are likely to be one of the main body systems influenced by the environment. Indeed, several studies have shown that this might be one of the reasons for such high variability and diversity one sees in the skin microbiome. For instance, urbanization of the human population has been one significant factor altering the skin microbiota.46–48 This was demonstrated in one study which found that indigenous Amerindian communities who had no contact with people from the West, have a more diverse skin microbiota than similar indigenous communities who are transitioning to a Westernized lifestyle, and an even more diverse microbiota than the skin from people in the United States.43 Similarly, the faecal microbiome was also found to be more diverse in these indigenous populations. Furthermore, their skin microbiota was more likely be similar among their group, and differed significantly from the other indigenous communities, and individuals living in the United States. Interestingly, even though these individuals have never received antimicrobial therapies, the study found antimicrobial resistance genes in the samples from their populations. Other studies also have shown similar differences in diversity between individuals that live in rural and urban areas, with individuals living in rural areas having greater diversity42 and variability in their skin microbiota compared to those living in urban areas.33

Studies looking at cohabitation have found that individuals living in the same household are more likely to share similar skin microbiota.44–45 One of these studies also found that dog ownership influenced the diversity of the microbiota and shared microbiota in adults, but not in children.45 The same study did not find any effect on microbial diversity in the skin of individuals that cohabited with cats. Another study evaluating the nares and oral cavity of humans, dogs and cats, found that humans inhabiting households with pets had a more diverse microbiota than those that did not cohabit with pets.43 Pets in households have further been shown to influence diversity and composition of the house environment microbiota.46–48 These households are particularly influenced by dog ownership, due to the dog’s resident microbiota and by bringing microbes from outdoors into the indoor environment.47,49 These studies support microbial sharing between pets and humans, and possibly increased cutaneous microbial diversity associated with pet exposure. Pet ownership also has been associated with fewer cases of allergies in children,50–53 which has been proposed to be due to exposure to diverse microbial communities brought by pets into the indoor environment. There is a certainly need for additional studies to be developed in this area to better evaluate the role of pets in prevention or development of allergies in people.

**The skin of animals is inhabited by an even more diverse microbiome than seen in humans**

Very few NGS studies have been published to date describing the skin microbiota in animals and these have included only limited numbers of animals, rendering them rather descriptive currently. Of these, a few studies have described the bacterial skin microbiota in dogs,45,54,55 the nasal cavities of cats,44 and the feet of cattle,56–58 and sheep (Table 1).59 In exotic animal species, the skin microbiota in amphibians has been characterized,60–61 given the marked concern with fungal infections decimating several amphibian species due to severe chytrid infections.

**Companion animals**

The few studies describing the canine skin microbiota have shown that canine skin is inhabited by a diverse microbiota that is even more diverse than seen in human skin.45,54,55 Based on NGS studies, the main bacterial phyla found across different body sites in dogs include Proteobacteria, Actinobacteria, Firmicutes, Bacteroidetes and Fusobacteria (Table 2). Dogs have marked variability in their microbiota and numerous bacteria colonizing their skin have been identified as environmental microbes.

In contrast to humans, the skin of dogs, and other animals, is mostly covered with dense fur. Apocrine glands are distributed throughout their bodies, whereas eccrine glands that produce sweat are found only in their feet. They also have more uniform distribution of their sebaceous glands. Given all of these physiological differences, dividing the skin of dogs between dry, moist and sebaceous microenvironments is not really feasible. A study including 12 dogs investigated microbiota differences between skin sites, and found that the mucosal surfaces (i.e. conjunctiva, lips and nostrils) were colonized with less diverse bacterial populations compared to haired skin sites (i.e. axilla, groin, dorsum, ear pinna, dorsal aspect of the nose).54 Of all these sites, the dorsal aspect of the nose was more diverse, on average. This is an interesting finding, which fits well with dog behaviour and their habits of having their nose in close contact with different surfaces. Their nostrils are colonized primarily with the bacterial genus *Moraxella*. Significant variability was found across different body sites in dogs and, similar to humans, some skin regions were more similar across different dogs, than across different body sites from the same dog. Dogs also share their microbiota and, similar to humans, dogs that cohabit the same household are more likely to share their microbiota than dogs inhabiting different households.45 Although their skin bacterial microbiota was highly variable across different body sites, predicted metabolic profiles produced by their cutaneous microbiota was fairly similar across different body sites (A. Rodrigues Hoffmann, unpublished data), a characteristic that has been demonstrated previously in humans.1

Based on preliminary studies describing the skin microbiota in 11 healthy cats, the feline skin microbiota is highly diverse, as observed in the skin of dogs, and some of the most common bacterial phyla observed on feline skin were Proteobacteria, Bacteroidetes, Firmicutes and
Actinobacteria (Table 1). Interestingly, their skin had relatively more abundant Bacteroidetes across different body sites than seen in the skin of dogs, and the main families seen in this phylum were Porphyromonadaceae and Paraprevotellaceae, some of the most common bacterial families found in the oral cavity. These findings are likely related to their grooming habits.

A recent study also has characterized the fungal microbiota (mycobiota) inhabiting the skin of 10 healthy dogs across different body sites (Table 2). The study described the mycobiota of dogs as being highly diverse and, similar to the bacterial microbiota, was more diverse than observed in human skin. The canine mycobiota was more likely to be similar across different body sites within the same dog, than at the same body site between different dogs. Based on NGS studies, the skin of dogs was colonized predominantly with fungi within the phyla Ascomycota and Basidiomycota. Within the phylum Ascomycota, Alternaria, Cladosporium and Epicoccum were the most abundant genera found on the skin of dogs. Although Malassezia is one of the most common fungal genera cultured from the skin of dogs, overall low abundances were identified in this dog study population. However, a few dogs in the study also presented relatively higher abundances of Malassezia spp. in some skin sites. The feline mycobiota evaluated in 11 healthy cats also was highly diverse and, similar to dogs, the main fungi found on the skin of these cats were within the phyla Ascomycota, including the genera Cladosporium and Alternaria, and the phyla Basidiomycota (Table 2).

The fungi found in the skin of companion animals are ubiquitous fungi likely acquired from their environment and additional studies including larger number of animals should further investigate whether these are transient microbes, or are truly indigenous mycobiota. In both cases, carriage of different microbes in the skin of companion animals could possibly impact exposure and sensitization of humans in early life, which may explain the association of lower cases of allergies in individuals cohabiting with pets.

Large animals

Fewer studies have described the skin microbiome using NGS in large animals, and no studies to date have characterized the skin microbiome inhabiting different skin surfaces in large animals. In ruminants, most attention has been given to describing the microbiome of digits (Table 1), due to the high prevalence of digital dermatitis. The digits of bovine are highly diverse and Firmicutes, Spirochaetes, Bacteroidetes and Actinobacteria are the most predominant phyla. The digits of sheep have high abundances of Actinobacteria, Bacteroidetes, Firmicutes and Proteobacteria, with high abundances of the genus Peptostreptococcus. Furthermore, Dichlobacter nodosus, a common cause of ovine footrot was amplified from healthy skin; however, it required the use of real-time PCR targeting and amplifying specific regions in this bacterium, due to mismatches in the 16S rRNA gene.

The skin microbiota in ear and nostril regions in pigs have been described previously. In the study that evaluated the ear, pigs were followed over time, and neonatal pigs had higher diversity of their microbiota compared to 21-week-old pigs. The most common bacterial genera colonizing the ear were Streptococcus and Lactobacillus. Within the nasal cavity, the predominant phylum was Proteobacteria, with the genus Moraxella accounting for more than one third of all sequences. The community membership in the nasal microbiota was different between pigs from conventional antibiotic-free farms and pigs from liquid-fed farms routinely treated with tyllosin; however, no differences were observed between MRSA carriage.

Exotic species

In exotic species, most NGS studies have focused on characterizing the skin microbiota of amphibians. The most common phylotypes colonizing their skin include Bacteroidetes, Proteobacteria, Firmicutes and Sphingobacteria (Table 1). One study found that different amphibian species were strong predictors of microbial community composition and wetland sites explained significant variations across the same species of amphibians. Furthermore, another study found wild toads had greater bacterial richness and diversity than captive toads.

A study from Australia evaluated the skin, oral cavity and faecal microbiota of the Tasmanian devil, and found that the faecal microbiota was more diverse compared to the skin and oral cavities. Their skin was colonized mainly with bacteria in the phyla Firmicutes followed by Proteobacteria.

Microbial dysbiosis is associated with inflammatory skin conditions

Most focus in the microbiome field has been given to gastrointestinal inflammatory conditions and there are sufficient data to support the gastrointestinal microbiome being responsible for causing certain gastroenteritis in humans and animals. Studies evaluating the skin microbiome in inflammatory skin conditions have been limited and rather descriptive, and it is still unclear whether microbial dysbiosis is the cause or the result of inflammatory skin conditions in humans and animals. Despite the limited number of studies published to date, exposure to a diverse skin microbiome is now considered to be a key component in immune regulation; cutaneous dysbiosis, which is defined as imbalances in the composition of microbial populations, are associated with human and animal inflammatory skin disorders.

It has been demonstrated that the commensal skin microbiota directly influences skin immunity. In this study, Staphylococcus epidermidis enhanced innate immunity and limited pathogen invasion, by inducing specialized T cells to move to the epidemis, which occurs in coordination with dendritic cells residing in the skin. In this experimental model, no inflammatory skin responses were associated with S. epidermidis exposure. However, when the skin encountered a new commensal, there were increases in IL17A+ T cells and induction of the cytokine IL-17A. This mechanism was mediated by the skin commensal S. epidermidis. The study showed that the skin is a dynamic environment, with its immune system responding to alterations in its commensal microbiota. It appears...
that even Staphylococcus aureus might be capable of modulating the immune system, given that S. aureus carriers tend to have better outcomes when developing bacteremia, when compared to noncarriers.76 This suggests that S. aureus colonization might also be able to “prime” the immune system of carrier individuals.

A recent study has shown that neonatal exposure to commensal bacteria is required to establish immune tolerance to these commensal microbes. Using a murine model, it has been demonstrated that S. epidemidis colonization in neonatal life was responsible for activating a wave of regulatory T cells, which resulted in tolerance to commensal microbes.77 This study as well as evidence from other published studies,72,78,79 suggest that some chronic skin disorders could be a result of exaggerated skin response to the commensal skin microbiota. Furthermore, given the rise of autoimmune diseases in urbanized populations, it is been proposed that reduced exposure to commensal microbes, due to increased cleanliness in urban areas, has resulted in augmentation of immune responses later in life, further leading to development of hypersensitivities. We have now learned that in several skin conditions, there is a significant alteration in the diversity and composition of the microbiota colonizing the skin.

Human atopic dermatitis

Atopic dermatitis (AD) is the most common chronic inflammatory skin disorder diagnosed in humans, being especially common in children. AD incidence has increased worldwide over the last decades.80 Patients with AD have intermittent lesions characterized by dry, erythematous, and pruritic skin. A population of patients with AD have altered skin barrier function, due to mutations in the flaggrin genes, which result in disruption of stratum corneum, allowing penetration of foreign antigens and hypersensitization to occur.81 In a longitudinal study, it was shown that lesional skin of children during AD flares has lower microbiota diversity, which corresponded to significant increases in the relative proportions of S. aureus.82 In that study, relative increases in the proportions of S. aureus were seen before development of lesions and the diversity of the microbiota was restored even before recovery of skin lesions. In children that received intermittent treatment, the diversity of the microbiota and relative proportions of S. aureus were maintained similar to nonaffected skin. It is possible that these increases in S. aureus abundances are related to permissiveness of an altered skin barrier to colonization by S. aureus. This hypothesis is supported, at least in part, by a study describing that after tape stripping and following removal of the superficial skin layers, fewer bacterial genera than seen in intact stratum corneum, primarily Staphylococcus and Propionibacterium, recolonized the deeper stratum corneum.83

Certain human primary immunodeficiencies (PID) are characterized by AD-like skin disease. These individuals have increased skin permssiveness and dysbiosis of their skin microbiota, characterized by lower specificity and temporal stability. In these PID conditions, disease severity has been correlated with increases in Staphylococcus spp. and Corynebacterium spp., as well as other less abundant taxa.82

More and more scientific evidence, based on natural and experimental studies, demonstrates that S. aureus is a key player in the development and increased severity of skin lesions in AD. A mouse model was developed with ADAM17-deficiency which developed eczema and microbial dysbiosis, similar to AD in humans.83 In this experimental study, it was not only demonstrated that S. aureus lead to eczema formation, but also showed subsequent Corynebacterium bovis colonization induced T helper 2 cell responses. The findings in this experimental mouse study are the first to suggest microbial dysbiosis might be capable of driving eczematous lesions and show evidence to support that the skin microbiota is capable of causing skin lesions.

In AD and PID patients with AD-like lesions, it has been described that the diversity of the mycobacteria increases with development of skin lesions.82,84 This is in contrast to what is observed in the bacterial microbiota, wherein diversity tends to decrease with development of skin lesions.85 Relative increases in opportunistic fungi, including those in the genera Candida and Aspergillus, were observed in AD patients.86 Another study found that Candida albicans, Cryptococcus diffluens, Cryptococcus liquefaciens, Cladosporium spp. and Toxicocladosporum irrigans were the predominant fungal taxa in AD patients.86

In both healthy and AD individuals, Malassezia spp. predominate in the skin. Some studies have reported that AD individuals have higher abundances of M. sympodialis than observed in healthy individuals.87 Other studies have found different Malassezia spp. to be increased in AD patients. These findings highlight some of the problems of skin microbiome research, and although it still not well defined whether certain Malassezia species are associated with skin lesions, it is a consensus that Malassezia exacerbate AD skin lesions.86

Dysbiosis of the skin microbiome is associated with skin diseases in animals

Atopic dermatitis and allergic skin diseases in companion animals

Similar to humans, dogs naturally develop AD with chronic skin lesions, being characterized by erythematous macules and patches with intense pruritus primarily involving the face, axilla, inguinal region and feet.87 Canine AD is characterized by a hypersensitivity reaction with production of IgE antibodies against environmental allergens, such as house dust mites (HDM), pollens and moulds. Occasionally, dogs also may develop hypersensitivity against S. pseudintermedius or M. pachydermatis.88 The skin lesions can be exacerbated by bacterial and/or fungal infections (most commonly S. pseudintermedius infection),89 which result in development of papules, pustules and crusts.88 Only a limited number of studies including very few animals have been reported to date to investigate the role of the microbiota in skin diseases in companion animals and these have been mostly descriptive (Table 3). In a preliminary study including six allergic/atopic dogs during remission of skin lesions, the skin microbiota of these dogs was evaluated and compared with healthy dogs.54 The allergic dogs had lower richness of their skin microbiota and were colonized with...
different abundances of bacterial populations than the healthy dogs. A longitudinal study including 14 dogs showed that the skin of AD dogs had increased relative abundances of *S. pseudintermedius* during development of skin lesions, which resulted in reduced diversity of the microbiota, similar to that described previously in humans.90 Bacterial diversity also correlated with transepidermal water loss and pH changes. Following treatment, remission of lesions correlated with increases and restored microbial diversity and lower *Staphylococcus* spp. relative abundances, similar to nonlesional skin. 

The skin microbiota also was longitudinally evaluated in a canine model of AD using HDM challenges.91 This experimental study included eight dogs that were hyper-sensitized with HDM and when challenged on the right side, whereas the skin of healthy dogs is characterized by more diverse fungal populations.63 It was hypothesized that the canine mycobiota shifts in disease states, lowering fungal diversity and allowing certain fungal populations to predominate in skin lesions. Furthermore, the skin of atopic dogs also is described to be associated with altered skin barrier, such as caused by filagrin mutations, whereas similar alterations in skin barriers have not been described or confirmed in allergic cats, which might explain why no alterations were seen in diversity in the feline allergic skin disease.64

**Pododermatitis in ruminants**

A significant proportion of cases of lameness observed in cattle are due to skin lesions involving the digits and resulting in digital dermatitis (DD). DD is seen most often in dairy cattle although less frequently it also occurs in beef cattle. DD is a polymicrobial disease and the most common bacteria associated with DD include multiple *Treponema* species.92 Bacterial 16S rRNA gene studies reveal that these lesions have remarkable diversity (Table 3). In DD lesions, Firmicutes predominated in superficial and intermediate lesions, whereas *Treponema* dominated the deeper layers of the DD lesions.56 Another study based on 16S rRNA gene and fluorescent in situ hybridization (FISH), showed approximately that 50% of the sequences were *Treponema*-like, 25% were of

<table>
<thead>
<tr>
<th>Host</th>
<th>Skin condition</th>
<th>Bacterial diversity</th>
<th>Bacterial composition</th>
<th>Fungal diversity</th>
<th>Fungal composition</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopic dermatitis (AD)</td>
<td>Low in lesional skin and AD versus healthy</td>
<td>Lesional skin has abundant <em>Staphylococcus aureus</em></td>
<td>Low, with shared mycobiota among AD</td>
<td>Different proportions of fungal taxa predominate in AD versus healthy dogs</td>
<td>54, 63, 90</td>
<td></td>
</tr>
<tr>
<td>Allergic skin disease</td>
<td>Not altered</td>
<td>Different proportions of fungal taxa predominate in allergic versus healthy cats</td>
<td>Not altered</td>
<td>Increased Agaricomycetes and Sordariomycetes, lower Epicoccum proportions compared to healthy</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Digital dermatitis (DD)</td>
<td>High</td>
<td>Increased Spirochaetes, Bacteroidetes and Proteobacteria in DD <em>Treponema</em> spp. and <em>Fusobacterium necrophorum</em> predominate, especially in deeper lesions</td>
<td></td>
<td></td>
<td>55–58, 92, 93</td>
<td></td>
</tr>
<tr>
<td>Footrot</td>
<td>Increased richness and diversity in acute footrot</td>
<td>Increased <em>Corynebacterium</em> spp. and <em>Staphylococcus</em> spp. in footrot</td>
<td>Higher abundances of <em>Dichelobacter nodosus</em> in footrot</td>
<td></td>
<td>59, 94</td>
<td></td>
</tr>
<tr>
<td>Chytrid infection</td>
<td>High</td>
<td>Composition is driven by chytrid infections</td>
<td></td>
<td></td>
<td>60, 61, 95</td>
<td></td>
</tr>
</tbody>
</table>
Fusobacterium necrophorum and the remaining were composed of other bacterial species.\textsuperscript{93}

In a metagenomic study, using shotgun sequencing, it was reported that cattle with DD had increased relative abundances of Spirochaetes, Bacteroidetes and Proteobacteria, in contrast to healthy feet which were colonized predominantly by Firmicutes and Actinobacteria.\textsuperscript{57} Treponema denticola and T. vincentii were the predominant bacterial species identified in both active and inactive DD. They further described the functional composition of the microbiome and higher abundance of genes associated with resistance to copper and zinc, products commonly used in footbaths to prevent DD, and genes associated with antibiotic resistance, were observed in cattle with DD. In another study it was shown that distinct Treponema phylotypes colonized the skin of active (ulcerative) versus inactive (healing) DD.\textsuperscript{58} It was suggested that the gut might be an important reservoir for these Treponema species, as these were found ubiquitously in the ruminal and faecal microbiomes; however, other studies have failed to identify similar Treponema species in the gut and feet of cattle with DD.\textsuperscript{92} These studies have now shown that bovine DD is a polymicrobial disease, making this an excellent model to investigate the role of the microbiome and the immune system.

Another example of a polymicrobial disease is footrot in sheep and goats. The causative agents for this disease are Dichelobacter nodosus and Fusobacterium necrophorum.\textsuperscript{94} Several bacterial taxa have been associated with this disease and, based on a 16S rRNA gene study,\textsuperscript{59} microbial diversity and richness was greater in tissues from sheep with interdigital dermatitis, the first clinical sign in footrot lesions, than in healthy interdigital areas, or those with a chronic form of footrot (Table 3). This chronic form is known as virulent footrot and results in separation of the hoof horn from sensitive tissue. The study demonstrated that the genus Corynebacterium was associated with interdigital dermatitis and the genus Staphylococcus with virulent footrot. Additionally, a specific real-time PCR assay for D. nodosus demonstrated sheep with interdigital dermatitis had significantly higher numbers of D. nodosus than sheep with healthy digits or virulent footrot.

Skin infections in amphibians
The chytrid fungus Batrachochytrium dendrobatidis (Bd) has been studied extensively due to severe cutaneous infections resulting in marked mortality in several amphibian species and raising serious concerns especially to endangered amphibian species. Due to its severity, a few studies were developed to better understand the interactions between this fungus with the skin microbiota.\textsuperscript{60,95} One study\textsuperscript{95} demonstrated that Bd infection caused significant changes to the bacterial microbiota inhabiting the skin (Table 3). The fungus Bd was capable of driving changes in the cutaneous bacterial communities, with strong correlation between chytrid infection load and bacterial community composition. Despite this strong correlation, 100% mortality was observed in postmetamorphic frogs, and there was no association between survival and bacterial microbiota. The findings of that study indicated a significant and relatively predictable interaction between the skin microbiota and Bd infections.

Conclusions
The studies described above are some examples supporting the hypothesis that the skin microbiome of humans and animals play a significant role in maintaining skin health. The skin microbiome is vastly diverse, and remarkable variation between and across individuals are observed in humans and the different animal species studied to date. Despite these variations, such studies have demonstrated that imbalances in these microbial populations can contribute to development and/or severity of skin lesions. Moreover, recent studies have demonstrated that interactions between the skin microbiome and the immune system can maintain a healthy skin versus the establishment of a disease status. New mechanisms used by these commensal microbes are now being described, explaining the interplay between the microbiome and the immune system.

The microbiome is certainly an exciting area and there is still much more to be done in this field, as we are only starting to unveil the cutaneous ecosystem. Additional studies including larger number of animals investigating the skin microbiome composition in different skin diseases are needed. Future studies should focus on functional aspects of the microbiota, including evaluation of metabolomics, transcriptomics and proteomics. There is a need to better understand the relationships between microbes and the host immune system, and to determine if and how the microbiome can cause skin lesions, or alter its severity. Furthermore, studies looking at development of new drugs to treat different skin conditions should include evaluation of the microbiome as an additional resource to monitor treatment outcomes. We foresee that in the future NGS and microbiome studies could be further used in assisting in diagnostic tests for skin infections and identification of novel pathogens. It is also highly possible that the understanding of these mechanisms and with advancement of these technologies, we will be able to modulate the microbiome in favour of its host by augmenting beneficial microbes. Together with other disciplines, microbiome studies will allow us to better understand the complexity of the human and animal body functions, how the skin and other organs respond to exposure to different microbes, as well as pathogenesis of infectious and inflammatory diseases.

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Resumé
Contexte – Vivre dans un monde stérile n’est plus un concept acceptable ou désirable. Des études récentes portant sur le microbiome ont dévoilé des populations microbiennes complexes vivant sur la peau, le tube digestif, les tractus respiratoire et reproducteur. Les études du microbiome ont ouvert de nouvelles voies pour explorer le génome humain et animal, ses rôles et son importance dans le maintien de la santé.

Microbiome de la peau saine – La composition du microbiome cutané varie entre les différents sites corporels et entre les individus, est influencée par des caractéristiques de l’hôte comme l’âge, le genre, l’alimentation, l’hygiène et le mode de vie. L’exposition à un microbiome cutané varié est maintenant considéré comme étant un facteur clé de la régulation immunitaire, et des variations de ces populations microbienne sont associées à des désordres inflammatoires dans la peau de l’homme et de l’animal.

Microbiome cutané de la peau inflammatoire – Nous avons appris que dans plusieurs atteintes cutanées, il y a une altération significative dans la diversité et la composition du microbiote colonisant la peau. Par exemple, chez l’homme et l’animal atteint de dermatite atopique, la dysbiose cutanée résulte en une plus faible diversité des populations microbienne. Nous ne savons toujours pas si ces altérations de populations microbienne sont une cause ou un effet de l’inflammation cutanée chez l’homme et l’animal, mais il n’y a pas de doute quant à l’importance du microbiome dans le maintien de la peau saine.


Resumen
Introduccion – Habitar un mundo estéril ya no es un concepto aceptable o deseable. Estudios recientes desarrollados en el campo del microbioma han revelado poblaciones microbianas complejas que habitan la piel, el aparato digestivo, respiratorio y reproductivo. Los estudios sobre microbiomas han abierto nuevos lugares para explorar el segundo genoma humano y animal, sus funciones y su importancia en el mantenimiento de la salud.

El microbioma de la piel en la salud – La composición del microbioma de la piel varía entre los diferentes sitios del cuerpo y entre los individuos, estando influenciado por diferentes hábitos del hospedador, incluyendo por ejemplo edad, sexo, dieta, higiene y estilo de vida. La exposición a un microbioma cutáneo diverso se considera ahora un componente clave en la regulación inmune, y los desequilibrios en estas poblaciones microbianas están siendo asociados con trastornos inflamatorios de la piel humana y animal.

El microbioma de la piel en condiciones inflamatorias de la piel – Hemos aprendido que en varias afecciones cutáneas hay una alteración significativa en la diversidad y composición de la microbiota que coloniza la piel. Por ejemplo, en pacientes humanos y animales con dermatitis atópica, la disbiosis de la microbiota cutánea da lugar a una menor diversidad de poblaciones microbianas. Si estas alteraciones de las poblaciones microbianas son la causa o el efecto de las condiciones inflamatorias de la piel visto en los seres humanos y los animales es algo todavía bajo investigación, pero no hay duda de que el microbioma tiene un papel importante en el mantenimiento de la salud de la piel.

Resumen – Esta revisión se centra en los estudios más actuales que describen el microbioma de la piel en humanos y animales, su papel en la modulación del sistema inmunológico y su asociación con las enfermedades de la piel humana y animal.

Zusammenfassung


Mikrobiome der Haut und entzündliche Hauterkrankungen – Mittlerweile wissen wir, dass bei einigen Hauterkrankungen eine signifikante Veränderung der Diversität und der Zusammensetzung der Mikrobiota, die die Haut besiedeln, erfolgt. So resultiert zum Beispiel die Dysbiose der Mikrobiome der Haut bei Menschen und Tieren mit atopischer Dermatitis, in einer geringeren Diversität der mikrobiellen Populationen. Ob diese geänderten mikrobiellen Populationen die Ursache oder die Auswirkung der entzündlichen Hautveränderungen, die beim Menschen und bei Tieren gesehen werden, darstellt, wird noch immer...
Hoffmann

untersucht. Es besteht jedoch kein Zweifel, dass die Mikrobiome eine wichtige Rolle bei der Aufrechterhal-
tung der Gesundheit der Haut spielen.

Zusammenfassung – Diese Review konzentriert sich auf die jüngsten Studien, die die Mikrobiome der
Haut beim Menschen und bei Tieren beschreiben, sowie die Rolle, die sie bei der Modulierung des Immun-
systems spielen und ihren Zusammenhang mit Hauterkrankungen bei Mensch und Tier.

要約
背景 — 無菌的な環境に住むという考え方は、もはや受け入れられておらず、望ましいと考えられてい
ない。近年の微生物学に関する研究によって、皮膚、消化器、呼吸器および生殖器に息する複雑な微
生物叢の構成が明らかになってきた。微生物叢の研究は、人や動物の第二のゲノム、その機能や健康維
持における重要性を追求する新たな研究分野を切り開いてきた。

健康な皮膚微生物叢 — 皮膚の微生物叢の構成は、異なる体部位や個休体によって変化し、また、年齢、
性別、食事、衛生環境や生活習慣などのそれぞれに異なる宿主の習慣によっても影響される。いまや多
様な皮膚の微生物叢に暴露されることは、免疫調節の鍵になると考えられており、これら微生物叢構成
の不均衡は、人や動物の皮膚の炎症性疾患に関与すると考えられている。

炎症性皮膚疾患の皮膚微生物叢 — 様々な皮膚疾患において、皮膚に定着する微生物叢の多様性や構成が
有意に変化することが分かってきた。例えば、アトピー性皮膚炎の人や動物では、皮膚の微生物叢のバ
ランス失調が、微生物叢構成の多様性の減少につながる。人や動物で認められるこれら微生物叢の構成
の変化が原因なのかそれとも炎症性皮膚疾患の結果なのかについては、まだ研究中であるが、micro-
biomeが皮膚健康の維持に重要な役割を果たしていることは疑いない。

まとめ — 本書は、人と動物の皮膚微生物叢、その免疫調節性、そして人および動物の皮膚疾患への関
与についての最新の研究に焦点を当てた。

摘要
背景 — 在无菌环境中生活，不再是一个可接受或可取的概念，微生物领域的最新研究表明，在皮肤、消化道、呼
吸道和生殖道内都有复杂的微生物群。微生物群已经打开了新领域，去探索人类和动物的次基因组，其在维护
健康方面的重要性和功能性。

皮肤微生物对健康的影响 — 不同身体部位和不同个体，其皮肤微生物组成不尽相同，受到不同宿主习性的影
响，包括年龄、性别、饮食、卫生和生活方式。不同的皮肤微生物现在被认为是免疫调节的关键组
成，而人和动物的皮肤疾患疾病可造成微生物群的失衡。

炎症性皮肤病的皮肤微生物 — 我们已经得知，在几种皮肤病中，定植于皮肤的微生物，其多样性组成均发生了
明显变化。例如，患有异位性皮炎的人和动物，皮肤微生物的失调导致其多样性下降。这些转变的微生物
群，是否会引起或影响人和动物性疾病皮肤病，仍在调查研究中。但可以肯定的是，微生物在维护皮肤健康中起着
重要作用。

总结 — 关于人和动物皮肤微生物的最新研究表明，其可以调节免疫系统，并且会引发人和动物的皮肤疾病。

Resumo
Contexto – Habitar um mundo estéril é um conceito não mais aceito ou desejável. Estudos recentes
desenvolvidos na área de microbioma tem revelado populações microbianas complexas habitando a pele e
os tratos digestivo, respiratório e reprodutivo. Estudos de microbioma tem aberto novos caminhos para
explorar o segundo genoma humano e animal, suas funções e sua importância na manutenção da saúde.

Microbioma cutâneo na saúde – A composição do microbioma cutâneo varia de acordo com as regiões
cutâneas e entre indivíduos, sendo influenciada por diferentes hábitos do hospedeiro, incluindo idade,
gênero, dieta, higiene e estilo de vida. Exposição a um microbioma cutâneo diverso é considerada atual-
mente um fator chave na regulação imune, e o desequilíbrio destas populações microbianas tem sido asso-
ciado a dermatopatias inflamatórias em humanos e animais.

Microbioma cutâneo em dermatopatias inflamatórias – Sabemos que em diversas doenças cutâneas,
há uma alteração significativa na diversidade e composição da microbiota que coloniza a pele. Em pacien-
tes humanos e animais com dermatite atópica, a disbiose do microbiota cutâneo resulta em diversidade
reduzida de populações microbianas. Se estas alterações na população microbiana são a causa ou o efeito
das dermatopatias inflamatórias ainda permanece sob investigação, entretanto, indubitavelmente, o micro-
bioma exerce função importante na manutenção da saúde cutânea.

Sumário – Esta revisão foca nos estudos mais recentes descrevendo o microbioma cutâneo em humanos
e animais, sua função na modulação do sistema imune e a sua associação com dermatopatias em huma-
nos e animais.