REVIEW ARTICLE

Microbiome in healthy skin, update for dermatologists

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Abstract

The skin is a complex barrier organ made of a symbiotic relationship between microbial communities and host tissue via complex signals provided by the innate and the adaptive immune systems. It is constantly exposed to various endogenous and exogenous factors which impact this balanced system potentially leading to inflammatory skin conditions comprising infections, allergies or autoimmune diseases. Unlike the gut and stool microbiome which has been studied and described for many years, investigations on the skin or scalp microbiome only started recently. Researchers in microbiology and dermatology started using modern methods such as pyrosequencing assays of bacterial 16S rRNA genes to identify and characterize the different microorganisms present on the skin, to evaluate the bacterial diversity and their relative abundance and to understand how microbial diversity may contribute to skin health and dermatological conditions. This article aims to provide an overview on the knowledge about the skin microbiota, the microbiome and their importance in dermatology.

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Conflicts of interest

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Introduction

Human skin is a complex barrier organ made of a symbiotic relationship between microbial communities in constant dialogue with the host by the virtue of complex signals provided by the innate and the adaptive immune systems. This mutualistic relationship leads to a well-controlled but delicate equilibrium, the microbiota, which is mandatory for a healthy skin. However, the skin is constantly exposed to various endogenous and exogenous factors which potentially impact this balanced system, thereby creating pathophysiologically relevant situations. The lack of effective compensatory mechanisms could thereby ultimately lead to inflammatory skin conditions such as infections, allergies or autoimmune diseases.

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The objective of this article is to provide an overview on current knowledge about the formation, character of the human skin microbiome, its assessment and its role in skin health and skin disease.

History and definitions

Scientists have been interested in microorganisms that colonize the skin since Antoni van Leuwenhoek's first microscopic observation in 1683. But, the field of human microbiota in dermatology research really began with Kligman in the 1950's using improved cell culture methods.[1] In 2000, the Nobel laureate Joshua Lederberg suggested using the term 'human microbiome' to describe the collective genome of our indigenous microorganisms (microflora) colonizing the whole body.[2,3]

Unlike the gut and stool microbiome which has been studied and described for many years,[4,5] investigations on the skin or

scalp microbiome only started recently. Researchers in microbiology and dermatology have joined forces to identify and characterize the different microorganisms present on the skin, to evaluate the abundance of each population and to understand how microbial diversity may contribute to dermatological conditions.[6–8]

The microbiota refers to any microorganism present in and on the body, such as gut, nose, oral mucosa, pulmonary mucosa, scalp and the skin.[9] It should be noticed that overall, only about 200 truly pathogenic microorganisms have been characterized. The remaining part of the microbiotic world is to be considered either commensal or facultative pathogenic. Recent experiments have shown that the microbiome may be permissive for the establishment of infections.[10] These observations support the concept of the so-called 'hologenome'.[11]

The microbiome is defined as the collective genome of the microorganisms.[2] Consequently, the skin microbiome is the genome of the microorganisms present on the skin to which microorganisms maintain a complex relationship.[8,12]

The metagenome refers to the genetic information of the microbiota while the meta-transcriptome corresponds to the transcriptome (mRNA) generated by the microbiota.[9]

Probiotics are 'live microorganisms which when administered in adequate amounts confer a health benefit on the host,' whereas prebiotics are 'non-viable food components that confer a health benefit on the host associated with modulation of the microbiota'.[13]

An antibiotic is a substance produced by various microorganisms and fungi, inhibiting the growth or destroying bacteria and other microorganisms.

Table 1 provides an overview of these definitions.

How is the skin microbiome studied?

Three main sampling methods are currently used to harvest the resident skin microbiota. (i) Skin swabbing using a sterile cotton swab is the most practical method for large-scale skin sampling. It is quick and simple but can accurately collect only resident microbiota from the stratum corneum. (ii) Skin scraping or skin stripping (D-squame) with adhesive tape collects both superficial skin cells stratum corneum, granular layers and the upper part of follicles.[14,15] Both techniques are non-invasive but do not provide a picture of the full spectrum of skin microbiota, particularly in some specific subniches, such as the dermis.[8,15] (iii) Punch biopsies are invasive but offer the best representation of skin microbiota in deep epidermis, dermis and glands such as the sebaceous gland.[15] Due to its invasive character, the latter is only little used for qualitative analyses.[14]

Combining these different sampling techniques allows for a complete evaluation.

(i) Traditional cell culture methods breed live colonies on gel plates. The bacteria are then isolated, counted and characterized. Unfortunately, these techniques are limited by the preferred lifestyle of each bacterial species. Only a restricted number of species flourish in a laboratory environment, overpopulating the culture media and outnumbering the other more fussy bacteria, which makes it difficult for researchers to correctly isolate and identify those more discrete bacterial species and evaluate the relative abundance *in situ* from each sample. Culture-dependent assays are only able to estimate less than 1% of inhabitant bacterial species.[16] (ii) New culture-independent methods arising from advances in genomic technology. These modern techniques recognize either the specific DNA or RNA (16S ribosomal RNA) fingerprint sequences that each organism contains. This allows researchers to identify, characterize and measure the true relative abundance of each bacterial operational taxonomic units, a new genetic tool in a given clinical sample.[15,17–19] Although genomic techniques allow researchers to identify resident species and characterize their dynamics, they only provide limited or no information about the gene composition, cell function and dynamics, or on microbe–microbe or microbe–host interactions and do not differentiate between dead and alive microorganisms. But with this technology we can compare the global bacterial landscape of two different biotopes of the skin, e.g. affected and the closest non-affected area or before and after a treatment.

Treatment and handling of samples after collection is a critical aspect when using DNA-based methods. Samples were not significantly influenced by the storage temperature or the duration of storage as shown by results from pyrosequencing assays of bacterial 16S rRNA genes. Likewise, the relative abundances of most taxa were largely unaffected by temperature even after 14 days of storage.[20]

Table 1 Glossary

Microbiota	Total of microorganisms in/on our body
Cutaneous microbiota	Total of microorganisms in/on our skin
Microbiome	Collective genome of microorganisms
Microbiotic diversity	Degree of heterogeneity of the microbiota (the more, the healthiest)
Dysbiosis of the microbiota	Unbalanced diversity of the microbiota
Metagenome	Total of genomic information from the microbiota
Metatranscriptome	Transcriptome generated by the microbiota
Pre- and probiotics	Probiotics are live microorganisms which when administered in adequate amounts confer a health benefit on the host Prebiotics are non-viable food component that confers a health benefit on the host associated with modulation of the microbiota
Antibiotics	Antibiotics have the capacity in dilute solutions to inhibit the growth of or to destroy bacteria and other microorganisms

When does the human skin microbiota get established?

Fetal skin will be colonized by microorganisms from the mother as early as birth.[21] This very initial flora is low in diversity and resembles that of the delivery site, i.e. a vaginal birth will

colonize a new-born with vaginal flora and a caesarean section birth with flora typical of tummy skin.[3,22,23] This process of skin colonization during early neonatal life is required to establish immune tolerance to commensal microorganisms.[24] During this very short time span, an abrupt inflow of highly activated regulatory T cells into neonatal skin is observed. T-cells inhibition results in abrogation of tolerance to these commensals, suggesting that the skin microbiome composition is crucial to develop adapted immune responses.[24] As vaginal delivery and the above-mentioned mechanisms have been recognized as a crucial step in the education of the immune system, new strategies aimed to allow the contact of the skin of new borns delivered by caesarean section with vaginal microbiota have been developed to promote a healthy skin microbiome.[25]

Skin colonization by commensal skin microorganisms continues during breastfeeding.[26] In parallel, microorganisms from the environment attempt to colonize the skin and scalp as well as specific areas such as the perigenital and perioral areas and some succeed in building a healthy relationship with host skin cells. Thus, by adulthood a final state of equilibrium is acquired with an astoundingly diverse commensal/mutualistic skin and scalp microbiota that is unique, at genus level for each individual.[6] Conversely, disruption of T cells during the very first age may result in health consequences.[24]

What is a healthy skin microbiota?

The skin microbiota includes two groups: (i) Resident microorganisms, which are a relatively fixed group of microorganisms (the core microbiota) that are routinely found in the skin and that re-establish themselves after perturbation. The core skin microbiota is considered to be commensal, meaning that these microorganisms are usually harmless and most probably provide some benefit to the host. (ii) Transient microorganisms (the 'tourists') do not establish permanent residency, but rather arise from the environment and persist for hours to days before disappearing. Under normal conditions both groups are non-pathogenic.[17,27] Recent research showed that the healthy human skin microbiome is stable over time despite external exposures.[28]

Grice *et al.* characterized four main phyla: Actinobacteria, Firmicutes, Proteobacteria and Bacteroides. The three most common genera were as follows: Corynebacteria, Propionibacteria and Staphylococci.[7]

Findings also suggest that the skin is inhabited with a more diverse number of bacterial colonies than any other epithelial surface.[29] Both the composition and abundance vary considerably between individuals and over time, resulting in an extremely dynamic and greatly fluctuating microbiota.[15,30] Although microbiota research up until now has largely focused on identifying bacteria, it is important to remember the many other types of organisms that also reside on the skin. Some techniques have begun to identify some of these such as *Malassezia*, a polymorphic yeast, sometimes classified as a fungus present on most parts of the body, especially on the scalp and accounting for 80% of cutaneous fungi.[31] Demodex, a parasitic arthropod has also been identified in normal skin, although its role as a commensal organism remains elusive.[32] To date, viruses are the least well-known members of the skin microbiota.

From a bacteriological point of view, our skin can be considered a culture medium. Its composition is mainly the consequence of our genetics, diet, life style and the area we are living in. As a result each human skin is unique and at a genus level each microbiota present in the different areas of our skin is unique.

From a macroscopic point of view, the skin is a complex terrain with many invaginations, pockets and niches. Each anatomical niche provides an ecologically distinct microenvironment to which their resident microbial communities adapt. There are four main types of environments on the human skin (Fig. 1): moist, sebaceous, dry and others.[7,8] Moist areas include the axilla, inner elbow or inguinal fold. Sebaceous areas include the forehead, the alar crease (side of the nostril), the retro auricular crease (behind the ear) and the back,[29] whereas the drier sites include the upper buttock area.[33] Further microenvironments include the sweat glands, the hair follicles and the dermal layers.[34]

Each microbial community has its preferred habitat within the various microenvironments on the skin. The moist regions such as the navel or axilla harbour mostly *Staphylococcus* and Corynebacteria species.[7] Sebaceous sites have higher density of particularly lipophilic species such as Propionibacteria which has adapted to this lipid-rich, anaerobic environment.[19,35–37] The drier sites host predominantly *Staphylococcus*, *Propionibacterium*, *Micrococcus*, *Corynebacterium*, *Enhydrobacter* and *Streptococcus* species.[38]

At a microscopic level, even smaller more distinct habitats such as eccrine and apocrine glands, sebaceous glands and hair follicles are likely to be associated with their own unique microbiota.[17,39] Sebaceous follicles, e.g. an anaerobic, lipid-rich environment to which *Propionibacterium* is particularly adapted.[40,41] The axillar area consists mainly of Gram-positive bacteria of the genera *Staphylococcus*, *Micrococcus*, *Corynebacterium* as well as of *Propionibacterium*.[39,42]

Figure 2 provides information about phyla and genera of skin microorganisms throughout the interpersonal skin microbiome of four healthy volunteers.[8]

Multiple independent detection techniques showed that bacteria are not only present on the skin surface, but are also found in deeper layers of the epidermis and even in the dermis and dermal adipose tissue.[34] These layers have specific microbiome profiles and also contain many specialized cell types such as dendritic cells, melanocytes and Langerhans cells that each express unique repertoire of functional pattern recognition receptors (PRRs) which respond actively when exposed to components of microorganisms.[34,43–45] It is hypothesized that the

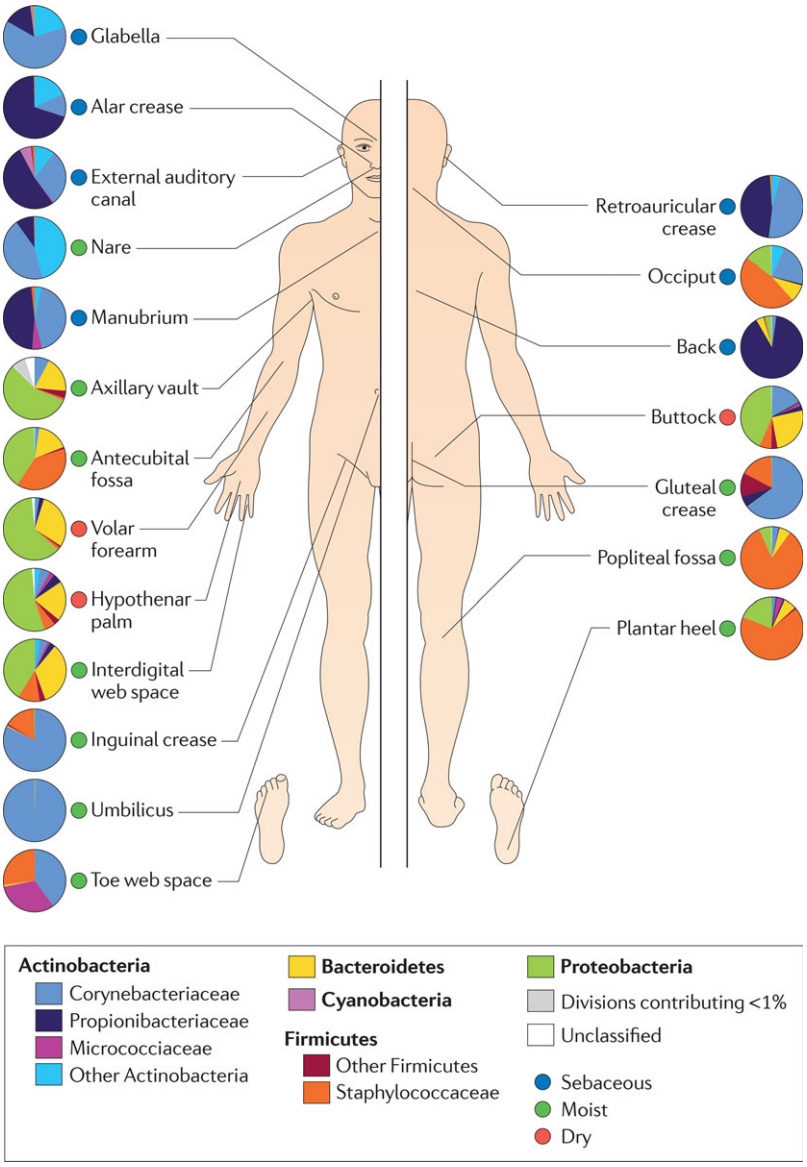

Figure 1 Topographical distribution of bacteria on skin sites.[8] Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Microbiology, 'The skin microbiome', Grice EA, Segre JA., Nat Rev Microbiol. 2011 Apr; 9(4): 244–253.

microbiota residing in superficial layers or appendage structures might be translocated into the subepidermal compartments by phagocytic cells. Yet the route of entry of such microbes remains to be determined.[34]

Why is the skin microbiome so important?

The skin barrier and the microbiota act like a shield that protects the body against external aggressions. There is a balanced interplay between the host and resident and/or transient bacterial populations. This balance is continuously affected by intrinsic (host) and extrinsic (environmental) factors that alter the composition of skin microorganism communities and the host skin barrier function. Altering this equilibrium is called dysbiosis.

Underlying pathobiology or genetically determined variations in stratum corneum properties might result in a dysbiosis that changes the abundance and diversity of commensal species, which disturbs skin barrier function and aggravates chronic skin diseases such as atopic dermatitis and psoriasis[46–50] or acne.[33,34,51–53] For example, *Staphylococcus epidermidis* is a skin commensal but can be an opportunistic pathogen in immunocompromised hosts.[54] *Staphylococcus aureus* has been identified

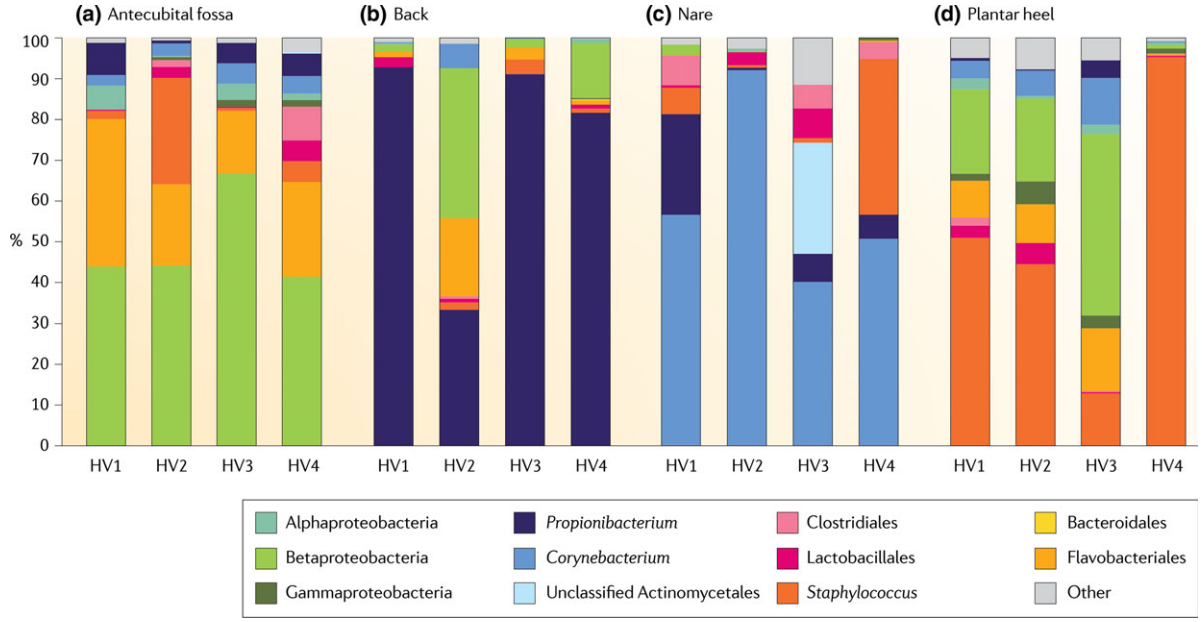

Figure 2 Interpersonal variation in the skin microbiome.[8] The microbial distribution of four sites on four healthy volunteers (HV1, HV2, HV3 and HV4) is depicted at the antecubital fold (inner elbow; part a); the back (part b); the nare (inside the nostril; part c) and the plantar heel (bottom of the heel of the foot; part d). Skin microbial variation is more dependent on the site than on the individual. Bars represent the relative abundance of bacterial taxa as determined by 16S ribosomal RNA sequencing. Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Microbiology, 'The skin microbiome', Grice EA, Segre JA., Nat Rev Microbiol. 2011 Apr; 9(4): 244–253.

as a resident microbe,[55] yet it is also an important pathogen[17] when over-colonizing the skin. As another example, *Propionibacterium acnes* contributes to making the skin inhospitable for pathogens such as *S. aureus* and *Streptococcus pyogenes* but also allows less virulent Staphylococci strains such as *S. epidermis* and Corynebacteria to grow.[3,8]

But, dysbiosis does not only occur between bacteria, disequilibrium between bacteria and commensal fungi strains on the scalp has been observed in subjects prone to dandruff.[56,57]

Host skin cells constantly sample the microorganisms inhabiting the epidermis and dermis via pattern recognition receptors (PRRs). The portion of the activated immune system and how changes are regulated differentiate a commensal organism from a potential pathogen.[29,58] Some examples of usually commensal species that prevent pathogen growth and maintain the stability of the resident cutaneous community include *P. acnes* and *S. epidermis*. Both play a role in controlling growth of pathogens such as *S. pyogenes* or *S. aureus*. *P. acnes* has also been shown to reduce Methicillin-resistant *S. aureus* (MRSA) growth.[59] Both produce various antimicrobial molecules: *P. acnes* liberates fatty acids from sebum lipids that retard bacterial growth on the skin surface and promote the growth of lipophilic yeasts including *Malassezia* species,[3,59,60] while *S. epidermidis* causes microbial lipid membrane leakage and further cooperates with human host antimicrobial peptide (AMPs) production to reduce the quantity of these bacteria. These AMPs are important communication signals between the host innate immune system and the microbiota. Approximately 30% of the transcriptome of typical epithelial cells are dedicated to this communication.[61]

Skin microorganisms are capable of influencing their host cells, thus contributing to the host immunity. *S. epidermis* has been shown (i) to induce AMPs such as β defensins 2 and 3 boosting the host immunity to *S. aureus*, (ii) to activate mast cell-mediated antiviral immunity, (iii) to suppress uncontrolled inflammatory reactions during wound healing, inducing skin's AMP production and (iv) stimulating cutaneous T-cell maturation.[62,63] They thus work in cooperation with the host defence system and endogenous AMPs to protect the skin.[64–66] Moreover, the microbiome may represent a kind of filter for the environment as most agents in contact with and/or penetrating through the skin are also in contact with the microbiota. It should be noted that there is evidence for a strong influence of the (genetically determined) immune system on the composition of the microbiota.

On the other hand, after sensing the presence of microbiota through their Toll-like receptors (TLRs), epidermal Langerhans cells are able to instruct naïve T cells to mount a Th17 response which in turn will control the AMP secretion by keratinocytes. Thus, beside the innate immune response, epidermal dendritic cells seem to educate the adaptive immune system and thereby contribute to the complex dialogue that controls microbial growth in the skin (T. Bieber, personal communication).

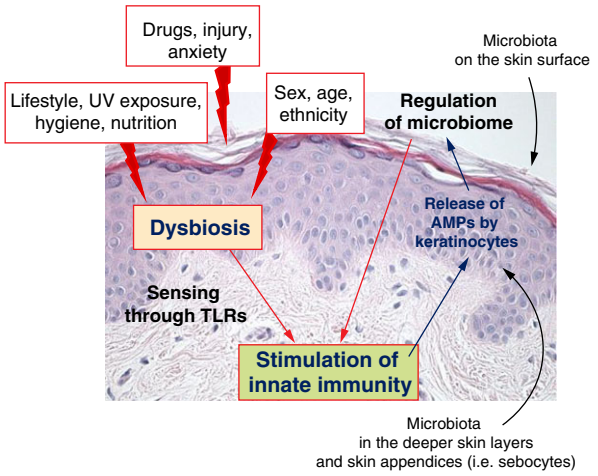

Figure 3 Factors leading to dysbiosis and innate immunity response of the skin.

Figure 3 provides a list of the factors that may lead to dysbiosis and to the innate immunity response of the skin.

What impacts the healthy skin microbiota?

In addition to intrapersonal anatomical variations in the skin microbiota, the diversity and abundance of the cutaneous microbial flora varies between gender, age, seasons, ethnicity as well as various stressors, including physiological injury and psychological anxiety, promoting endocrine and metabolic changes within the cutaneous microenvironments that directly impact the metabolic requirements and pathogenicity of various microorganisms.[19,58,67–73]

Even in a very recent publication Oh *et al.* reported that the skin microbiome is not affected by external factors and remains largely stable in 12 healthy adults followed up for 2 years,[28] the impact of environmental factors such as climate, including temperature and UV exposure but also of lifestyle, including alcoholism or nutrition on microbial communities remains to be elucidated. Indeed, ultraviolet B and C light have been reported to be bactericidal,[74–76] while excessive alcohol consumption has been shown to diminish host resistance and nutrient and vitamin deficiency has been shown to impact on the skin microbiota balance, resulting in infection and skin barrier disturbance.[37,77,78]

But there are not only external factors that impact on the microbial community, the pH and temperature of the different

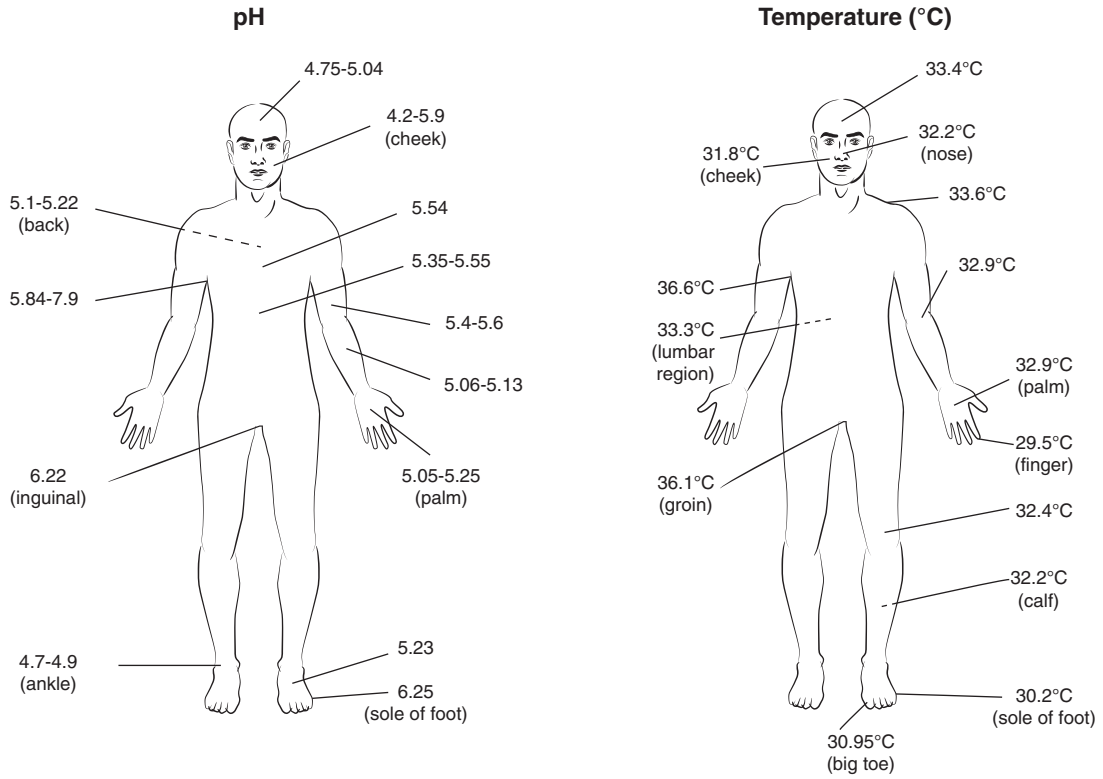

Figure 4 Distribution of pH and temperature of a healthy human skin.[79] Adapted by permission from Cambridge Edition: Cambride University press, 'Inhabitants of Humans: Their Ecology And Role in Health And Disease.' Wilson M. 2005 Apr; 9(4): 244–253.

areas of the human body may play a role in the growth or inhibition of microorganisms as shown in Fig. 4. Indeed, pH of the human body ranges from 4.2 to 7.9 and the temperature from 29.5 to 36.6°C.[79]

Anti-inflammatory therapies currently used in the treatment of atopic dermatitis and psoriasis impact the bacterial microbiome by manipulating local and systemic host stress molecules, promoting pathological wound healing and infections via antagonistic effects on growth factors and collagen deposition in wound healing.[77] The production of hypoxia-inducible factor-1 (HIF-1), a key transcriptional factor in wound healing and interactions between catecholamines such as transferrin and lactoferrin, reduces the bacteriostatic nature of blood, serum and mucosal secretions to the extent that they become a highly supportive bacterial culture medium taking part in the dysbiosis of the microbiome.[80–84]

Frequent washing has been reported to disturb the skin barrier resulting in skin irritation and in changes in the microbiome on hand skin.[85] Cosmetics, hygiene products, makeup and moisturizers have also been implicated in modifying the skin microbiome.[7,8,19,27,35,86–88]

The overuse of antibiotics, which were initially and still are an important milestone in the treatment of all kind of bacterial infections, has become a general health issue leading to a certain number of antibiotic-resistant strains of pathogenic microorganisms making the treatment of infections almost impossible and hence permanently unbalance the gut and skin microbiota.[89,90] For these reasons, overuse of antibiotics should be avoided.

Radiotherapy and chemotherapy used to treat cancer may also impact the microbiota.[91]

But, there are not only extrinsic factors that imbalance the healthy skin microbiota. Intrinsic factors such as a sebum overproduction, e.g. during puberty, enhance the over-colonization by *P. acnes* potentially leading to acne and to an imbalanced skin microbiota.

Even though much investigational work has been done in the past to determine if skin diseases such as atopic dermatitis, acne, dandruff, psoriasis, perioral and seborrhoeic dermatitis and rosacea are the result or the triggering factors for impacting the skin microbiota, still much needs to be learned and the mode of onset of the diseases and action of the triggering factors on the skin microbiota remain elusive.[8,77]

What are the perspectives?

Recent research confirmed the importance of a healthy gut microbiome.[92] The composition of its microbiota may have a substantial impact on the clinical response to specific immunotherapies in cancer exerting procarcinogenic or anticarcinogenic activities depending on the microenvironment.[93] Therefore, the maintenance of a healthy gut microbiome by preserving a balanced resident population is mandatory.

In the close future, the gut model will be adapted to the skin. Indeed, the role of the skin microbiome preventing other, unwanted pathogens from colonizing, thus maintaining an ecological balance in each skin niche has now been confirmed.[6,22] The gut–skin axis hypothesis raised by Arck *et al.* in 2010 who referred to a potential gut–brain–skin axis allowed for investigating the benefit of oral pre- and probiotics for the skin. In addition to oral probiotics formulations developed for the skin, a new generation of emollients and moisturizers has now been developed including lysates of bacteria, such as *Vitreoscilla filiformis* or *Lactobacillus*.[94–97] These topical probiotic formulations have been designed to support the management of skin diseases such as atopic dermatitis or acne by helping restoring the skin barrier and the skin microbiome and by controlling the activation of innate immunity.[98–104]

The development of these 'topical probiotics' has been supported by new technologies such as 3D mapping of mass spectrometry data and microbial 16S-rRNA, allowing studying in more details the spatial relationship of the skin and its microbiota with the aim to develop more tailored products.[105]

In conclusion, much is already known about the stool microbiome and intensive research has been done on the gut microbiome, and even though it seems today as if a parallel can be drawn between the gut and the skin microbiome much still needs to be learned about the latter. Therefore, improving the knowledge about the skin microbiome may open new perspectives in the management of the healthy and diseased skin and of its microbiome in, e.g. increasing selectively the activity and growth of beneficial healthy skin microbiota.[101,104]

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