Microbiome in healthy skin, update for dermatologists

B. Dréno,1,4* E. Araviiskaia,2 E. Berardesca,3 G. Gontijo,4 M. Sanchez Viera,5 L.F. Xiang,6 R. Martin,7 T. Bieber8

1Department of Dermato-cancerology, Nantes University, Nantes, France
2Department of Dermatology, First Pavlov State Medical University of St. Petersburg, St. Petersburg, Russia
3San Gallicano Dermatological Institute, Rome, Italy
4Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil
5Institute for Dermatology, Skin Health, Aging and Cancer, Madrid, Spain
6Department of Dermatology, Huashan Hospital, Fudan University, Shanghai, China
7L’Oréal Research and Innovation, Tours, France
8Department of Dermatology and Allergy, University Medical Center, Bonn, Germany
*Correspondence: B. Dréno. E-mail: brigitte.dreno@wanadoo.fr

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.

Received: 16 March 2016; Accepted: 4 August 2016

Conflicts of interest
None declared.

Funding sources
This review board was supported by Active Cosmetics International, Asnières sur Seine, France.

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.

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 Leeuwenhoek’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.
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 microbiorganisms 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

**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.\textsuperscript{3,22,23} This process of skin colonization during early neonatal life is required to establish immune tolerance to commensal microorganisms.\textsuperscript{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.\textsuperscript{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.\textsuperscript{25}

Skin colonization by commensal skin microorganisms continues during breastfeeding.\textsuperscript{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 astonishingly diverse commensal/mutualistic skin and scalp microbiota that is unique, at genus level for each individual.\textsuperscript{6} Conversely, disruption of T cells during the very first age may result in health consequences.\textsuperscript{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.\textsuperscript{17,27} Recent research showed that the healthy human skin microbiome is stable over time despite external exposures.\textsuperscript{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.\textsuperscript{7}

Findings also suggest that the skin is inhabited with a more diverse number of bacterial colonies than any other epidermal surface.\textsuperscript{29} Both the composition and abundance vary considerably between individuals and over time, resulting in an extremely dynamic and greatly fluctuating microbiota.\textsuperscript{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.\textsuperscript{31} Demodex, a parasitic arthropod has also been identified in normal skin, although its role as a commensal organism remains elusive.\textsuperscript{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.\textsuperscript{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,\textsuperscript{29} whereas the drier sites include the upper buttoc area.\textsuperscript{33} Further microenvironments include the sweat glands, the hair follicles and the dermal layers.\textsuperscript{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.\textsuperscript{2} Sebaceous sites have higher density of particularly lipophilic species such as Propionibacteria which has adapted to this lipid-rich, anaerobic environment.\textsuperscript{19,35–37} The drier sites host predominantly *Staphylococcus*, *Propionibacterium*, *Micrococcus*, *Corynebacterium*, *Enhydrobacter* and *Streptococcus* species.\textsuperscript{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.\textsuperscript{17,39} Sebaceous follicles, e.g. an anaerobic, lipid-rich environment to which *Propionibacterium* is particularly adapted.\textsuperscript{40,41} The axillar area consists mainly of Gram-positive bacteria of the genera *Staphylococcus*, *Micrococcus*, *Corynebacterium* as well as of *Propionibacterium*.\textsuperscript{39,42}

Figure 2 provides information about phyla and genera of skin microorganisms throughout the interpersonal skin microbiome of four healthy volunteers.\textsuperscript{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.\textsuperscript{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.\textsuperscript{34,43–45} It is hypothesized that the
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. 51–53 For example, Staphylococcus epidermidis is a skin commensal but can be an opportunistic pathogen in immuno-compromised hosts. 54 Staphylococcus aureus has been identified.
as a resident microbe, yet it is also an important pathogen 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.

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. 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.

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. 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, while *S. epidermis* 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.

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. They thus work in cooperation with the host defence system and endogenous AMPs to protect the skin. 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 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.19,58–73

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
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 seborrheic 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

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.8,88 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 Vitroscilla 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

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 ant carcino genetic activities depending on the microenvironment.93 Therefore, the maintenance of a healthy gut microbiome by preserving a balanced resident population is mandatory.

Acknowledgment

The authors acknowledge the writing support of Patrick Göritz, SMWS-Scientific and Medical Writing Services, France.

References

1. Pillsbury DM, Shelley WB. Dermatology. Ann Rev Med 1954; 5: 363–388.
2. Lederberg J. Infectious history. Science 2000; 288: 287–293.
3. Ladizinski B, McLean R, Lee KC, Elpern DJ, Eron L. The human skin microbiome. Int J Dermatol 2014; 53: 1177–1179.
4. Ianiro G, Bibbo S, Gasbarrini A, Cammarota G. Therapeutic modulation of gut microbiota: current clinical applications and future perspectives. Curr Drug Targets 2014; 15: 762–770.
5. Cammarota G, Ianiro G, Bibbo S, Gasbarrini A. Gut microbiota modulation: probiotics, antibiotics or fecal microbiota transplantation? Intern Emerg Med 2014; 9: 365–373.
6. Peterson J, Garges S, Giovanni M, McInnes P, Wang L, Schloss JA, et al. The NIH human microbiome project. Genome Res 2009; 19: 2317–2323.
7. Grice EA, Kong HH, Conlan S, Deming CB, Davis J, Young AC, et al. Topographical and temporal diversity of the human skin microbiome. Science 2009; 324: 1190–1192.
8. Grice EA, Segre JA. The skin microbiome. Nat Rev Microbiol 2011; 9: 244–253.
9. Consortium HMP. Structure, function and diversity of the healthy human microbiome. Nature 2012; 486: 207–214.
10 Singh P, Teal TK, Marsh TL, Tiedje JM, Mosci R, Jernigan K, et al. Intestinal microbial communities associated with acute enteric infections and disease recovery. Microbiome 2015; 3: 45.

11 Ziller-Rosenberg I, Rosenberg E. Role of microorganisms in the evolution of animals and plants: the hologenome theory of evolution. FEMS Microbiol Rev 2008; 32: 723–735.

12 Gill SR, Pop M, Deboy RT, Eckburg PB, Turnbaugh PJ, Samuel BS, et al. Metagenomic analysis of the human distal gut microbiome. Science 2006; 312: 1355–1359.

13 FAO. FAO Technical Meeting Report on PREBIOTICS: Food Quality and Standards Service (AGNS) Food and Agriculture Organization of the United Nations (FAO), 2008.

14 Updegroff DM. Methods for determining the distribution of bacteria in the skin. J Am Oil Chem Soc 1967; 44: 481–483.

15 Grice EA, Kong HH, Renaud G, Young AC, Bouffard GG, Blakesley RW, et al. Molecular analysis of human forearms: a meta-analysis. Proc Natl Acad Sci USA 2008; 105: 1043–1050.

16 Staley JT, Konopka A. Measurement of in situ activities of nonphotosynthetic microorganisms in aquatic and terrestrial habitats. Annu Rev Microbiol 1985; 39: 321–346.

17 Kong HH, Segre JA. Skin microbiome: looking back to move forward. J Invest Dermatol 2012; 132(3 Pt 2): 933–939.

18 Gao Z, Tseng CH, Pei Z, Blaser MJ. Molecular analysis of human forearm superficial skin bacterial. Proc Natl Acad Sci USA 2007; 104: 2927–2932.

19 Costello EK, Lauber CL, Hamady M, Fierer N, Gordon JI, Knight R. Bacterial community variation in human body habitats across space and time. Science 2009; 326: 1694–1697.

20 Lauber CL, Zhou N, Gordon JI, Knight R, Fierer N. Effect of storage conditions on the assessment of bacterial community structure in soil and human-associated samples. FEMS Microbiol Lett 2010; 307: 80–86.

21 Capone KA, Dowd SE, Stamatas GN, Nikolovski J. Diversity of the human skin microbiome early in life. J Invest Dermatol 2011; 131: 2026–2032.

22 Biviera G, Leoni MC, Capra L, Cipriani F, Longo G, Maiello N, et al. Microbiota in healthy skin and in atopic eczema. Biomed Res Int 2014; 2014: 436921.

23 Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci USA 2010; 107: 11971–11975.

24 Scharschmidt TC, Vasquez KS, Truong HA, Gearty SV, Pauli ML, Nosbaum A, et al. A wave of regulatory T cells into neonatal skin mediates tolerance to commensal microbes. Immunity 2015; 43: 1011–1021.

25 Dominguez-Bello MG, De Jesus-Labyo KM, Shen N, Cox LM, Amir A, Gonzalez A, et al. Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. Nat Med 2016; 22: 250–253.

26 Latuga MS, Stuebe A, Seed PC. A review of the source and function of microbiota in breast milk. Semin Reprod Med 2014; 32: 68–73.

27 Cogen AL, Nizet V, Gallo RL. Skin microbiota: a source of disease or defence? Br J Dermatol 2008; 158: 442–455.

28 Oh J, Byrd AL, Park M, Kong HH, Segre JA. Temporal stability of the human skin microbiome. Cell 2016; 165: 854–866.

29 Sanford JA, Gallo RL. Functions of the skin microbiota in health and disease. Semin Immunol 2013; 25: 370–377.

30 Zhou R, Jiang X. Effects of adipalene-benzoyl peroxide combination gel in treatment or maintenance therapy of moderate or severe acne vulgaris: a meta-analysis. Ann Dermatol 2014; 26: 43–52.

31 Gao Z, Perez-Perez GI, Chen Y, Blaser MJ. Quantitation of major human cutaneous bacterial and fungal populations. J Clin Microbiol 2010; 48: 3575–3581.

32 Lacey N, Ni Raghallaigh S, Powell FC. Demodecites- commensals, parasites or mutualistic organism? Nat Med 2016; 22: 250–253.

33 Zeeuwen PL, Kleerebezem M, Timmerman HM, Schalkwijk J. Microbiome and skin diseases. Curr Opin Allergy Clin Immunol 2013; 13: 514–520.

34 Nakatsuji T, Chiang HI, Jiang SB, Nagarajan H, Zengler K, Gallo RL. The microbiome extends to subepidermal compartments of normal skin. Nat Commun 2013; 4: 1431.

35 Belkaid Y, Segre JA. Dialogue between skin microbiota and immunity. Science 2014; 346: 954–959.

36 Finley K, Oh J, Yang J, Conlan S, Deming C, Meyer JA, et al. Topographic diversity of fungal and bacterial communities in human skin. Nature 2013; 498: 367–370.

37 Rosenthal M, Goldberg D, Aiello A, Larson E, Foxman B. Skin microbiota: microbial community structure and its potential association with health and disease. Infect Genet Evol 2011; 11: 839–848.

38 Zeeuwen PL, Boekhorst J, van den Bogaard EH, de Kerkhof PM, Saulnier DM, et al. Microbiome dynamics of human epidermis following skin barrier disruption. Genome Biol 2012; 13: R101.

39 James AG, Austin CJ, Cox DS, Taylor D, Calvert R. Microbiological and biochemical origins of human axillary odour. FEMS Microbiol Ecol 2013; 83: 527–540.

40 Bek-Thomsen M, Lombolt HB, Kilian M. Acne is not associated with yet-uncultured bacteria. J Clin Microbiol 2008; 46: 3355–3360.

41 Zouboulis CC. Acne and sebaceous gland function. Clin Dermatol 2004; 22: 360–366.

42 Leyden JJ, McGinley KJ, Holzle E, Labows JK, Kligman AM. The microbiology of the human axilla and its relationship to axillary odor. J Invest Dermatol 1981; 77: 413–416.

43 Yu N, Zhang S, Zuo F, Kang K, Guan M, Xiang L. Cultured human melanocytes express functional toll-like receptors 2-4, 7 and 9. J Dermatol Sci 2009; 56: 113–120.

44 Miller LS, Modlin RL. Toll-like receptors in the skin. Semin Immunopathol 2007; 29: 15–26.

45 Zouboulis CC. Sebaceous gland receptors. Dermatolendocrinol 2009; 1: 77–80.

46 Tomi NS, Kräne B, Aberer E. Staphylococcal toxins in patients with psoriasis, atopic dermatitis, and erythroderma, and in healthy control subjects. J Am Acad Dermatol 2005; 53: 67–72.

47 Salava A, Lauerma A. Role of the skin microbiome in atopic dermatitis. Clin Transl Allergy 2014; 4: 33.

48 Sanchez DA, Nosenchuk JD, Friedman AJ. The skin microbiome: is there a role in the pathogenesis of atopic dermatitis and psoriasis? J Drug Dermatol 2015; 14: 127–130.

49 Seife S, Bieber T. Barrier function and microbiotic dysbiosis in atopic dermatitis. Clin Cosmet Investig Dermatol 2015; 8: 479–483.

50 Williams MR, Gallo RL. The role of the skin microbiome in atopic dermatitis. Curr Allergy Asthma Rep 2015; 15: 65.

51 Wanke I, Steffen H, Christ C, Krismer B, Gotz F, Peschel A, et al. Skin commensals amplify the innate immune response to pathogens by activation of distinct signaling pathways. J Invest Dermatol 2011; 131: 382–390.

52 Fitz-Gibbon S, Tomida S, Chiu BH, Nguyen L, Du C, Liu M, et al. Propionibacterium acnes strain populations in the human skin microbiome associated with acne. J Invest Dermatol 2013; 133: 2152–2160.

53 Weyrich LS, Dixit S, Farrer AG, Cooper AJ. The skin microbiome: associations between altered microbial communities and disease. Australas J Dermatol 2015; 56: 268–274.

54 Otto M. Staphylococcus epidermidis-the ‘accidental’ pathogen. Nat Rev Microbiol 2009; 7: 555–567.

55 Wang Y, Kuo S, Shu M, Yu J, Huang S, Dai A, et al. Staphylococcus epidermidis in the human skin microbiome mediates fermentation to inhibit the growth of Propionibacterium acnes: implications of probiotics in acne vulgaris. Appl Microbiol Biotechnol 2014; 98: 411–424.

56 Clavaud C, Jourdain R, Bar-Hen A, Tichit M, Bouchier C, Pouradier F, et al. Dendruff is associated with disequilibrium in the proportion of the major bacterial and fungal populations colonizing the scalp. PLoS ONE 2013; 8: e58203.
Christensen GJ, Bruggemann H. Bacterial skin commensals and their role as host guardians. Benef Microbes 2014; 5: 201–215.

Kostic AD, Howitt MR, Garrett WS. Exploring host-microbiota interactions in animal models and humans. Genes Dev 2013; 27: 701–718.

Lai Y, Cogen AL, Radek KA, Park HJ, Macleod DT, Leichtle A, et al. Activation of TLR2 by a small molecule produced by Staphylococcus epidermidis increases antimicrobial defense against bacterial skin infections. J Invest Dermatol 2010; 130: 2211–2221.

Wang Z, MacLeod DT, Di Nardo A. Commensal bacteria lipoteichoic acid increases skin mast cell antimicrobial activity against vaccinia viruses. J Immunol 2012; 189: 1551–1558.

Gallo RL, Nakatsuji T. Microbial symbiosis with the innate immune defense system of the skin. J Invest Dermatol 2011; 131: 1974–1980.

Lai Y, Di Nardo A, Nakatsuji T, Leichtle A, Yang Y, Cogen AL, et al. Commensal bacteria regulate Toll-like receptor 3-dependent inflammation after skin injury. Nat Med 2009; 15: 1377–1382.

Cogen AL, Yamasaki K, Sanchez KM, Dorschner RA, Lai Y, MacLeod DT, et al. Selective antimicrobial action is provided by phenol-soluble modulins derived from Staphylococcus epidermidis, a normal resident of the skin. J Invest Dermatol 2010; 130: 192–200.

Leyden JJ, McGinley KJ, Mills OH, Kligman AM. Age-related changes in the resident bacterial flora of the human face. J Invest Dermatol 1975; 65: 379–381.

Giacomoni PU, Mammente T, Teri M. Gender-linked differences in human skin. J Dermatol Sci 2009; 55: 144–149.

Akaza N, Akamatsu H, Sasaki Y, Takeoka S, Kishi M, Mizutani H, et al. Cutaneous Malassezia microbiota of healthy subjects differ by sex, body part and season. J Dermatol 2010; 37: 786–792.

Staudinger T, Pipal A, Redl B. Molecular analysis of the prevalent microbiota of human male and female forehead skin compared to forearm skin and the influence of make-up. J Appl Microbiol 2011; 110: 1381–1389.

Zapata HI, Quagliarello VJ. The microbiota and microbiome in aging: potential implications in health and age-related diseases. J Am Geriatr Soc 2015; 63: 776–781.

Pochi PE, Strauss JS, Downing DT. Age-related changes in sebaceous gland activity. J Invest Dermatol 1979; 73: 108–111.

Holmes CJ, Plichta JK, Gamelli RL, Radek KA. Dynamic role of host stress responses in modulating the cutaneous microbiome: implications for wound healing and infection. Adv Wound Care (New Rochelle) 2015; 4: 24–37.

Faergemann J, Larko O. The effect of UV-light on human skin microorganisms. Acta Derm Venereol 1987; 67: 69–72.

Napolitano NA, Mahapatra T, Tang W. The effectiveness of UV-C radiation for facility-wide environmental disinfection to reduce health care-acquired infections. Am J Infect Control 2015; 43: 1342–1346.

MacLean M, McKenzie K, Anderson JG, Gettinby G, MacGregor SJ. 405 nm light technology for the inactivation of pathogens and its potential role for environmental disinfection and infection control. J Hosp Infect 2014; 88: 1–11.

Guo S, Dipietro LA. Factors affecting wound healing. J Dent Res 2010; 89: 219–229.

Choudhry MA, Chaudhry IH. Alcohol intoxication and post-burn complications. Front Biosci 2006; 11: 998–1005.

Microbial Wilson M. Inhabitants of Humans: Their Ecology and Role In Health And Disease. Cambridge University Press, Cambridge, UK, 2005.

Sandrini SM, Shergill R, Woodward J, Muralikuttan R, Haigh RD, Lyte M, et al. Elucidation of the mechanism by which catecholamine stress hormones liberate iron from the innate immune defense proteins transferrin and lactoferrin. J Bacteriol 2010; 192: 587–594.

Choi EH, Demerjian M, Crumrine D, Brown BE, Mauro T, Elias PM, et al. Glucocorticoid blockade reverses psychological stress-induced abnormalities in epidermal structure and function. Am J Physiol Regul Integr Comp Physiol 2006; 291: R1657–R1662.

Kraukauer T, Buckley M. Dexamethasone attenuates staphylococcal enterotoxin B-induced hypothermic response and protects mice from superantigen-induced toxic shock. Antimicrob Agents Chemother 2006; 50: 391–395.

Wicke C, Halliday B, Allen D, Roche NS, Scheuenstuhl H, Spencer MM, et al. Effects of steroids and retinoids on wound healing. Arch Surg 2000; 135: 1265–1270.

Wagner AE, Huck G, Stiehl DP, Jelkmann W, Hellwig-Burgel T. Dexamethasone impairs hypoxia-inducible factor-1 function. Biochem Biophys Res Commun 2008; 372: 336–340.

Rocha LA, Ferreira de Almeida EBL, Gontijo Filho PP. Changes in hands microbiota associated with skin damage because of hand hygiene procedures on the health care workers. Am J Infect Control 2009; 37: 135–139.

Stingley RL, Zou W, Heinz TM, Chen H, Cerniglia CE. Metabolism of azo dyes by human skin microbiota. J Med Microbiol 2010; 59(Pt 1): 108–114.

Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JJ. The human microbiome project. Nature 2007; 449: 804–810.

Holland KT, Bojar RA. Cosmetics: what is their influence on the skin microbiota? Am J Clin Dermatol 2002; 3: 445–449.

Leccia MT, Auffret N, Poli F, Claudel JP, Corvec S, Dreno B. Topical acne treatments in Europe and the issue of antimicrobial resistance. J Eur Acad Dermatol Venereol 2015; 29: 1485–1492.

Langdon A, Crook N, Dantas G. The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. Genome Med 2016; 8: 39.

Bensadoun RJ, Humbert P, Krutman J, Luger T, Triller R, Rougier A, et al. Daily baseline skin care in the prevention, treatment, and supportive care of skin toxicity in oncology patients: recommendations from a multinational expert panel. Cancer Manag Res 2013; 5: 401–408.

Nishijima S, Suda W, Oshima K, Kim SW, Hirose Y, Morita H, et al. The gut microbiome of healthy Japanese and its microbial and functional uniqueness. DNA Res 2016; 23: 125–133.

Vetizou M, Pitt JM, Daillere R, Lepage P, Waldschmitt N, Flament C, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science 2015; 350: 1079–1084.

Lacour JP. Skin microbiota and atopic dermatitis: toward new therapeutic options? Adv Dermatol Venereol 2015; 142(Suppl 1): S18–S22.

Mahe YF, Perez MJ, Tachue C, Fanchon C, Martin R, Rousset F, et al. A new Vitreoscilla filiformis extract grown on spa water-enriched medium activates endogenous cutaneous antioxidant and antimicrobial defenses through a potential Toll-like receptor 2/protein kinase C, zeta transduction pathway. Clin Cosmet Investig Dermatol 2015; 8: 191–196.

La Colla L, Mangano A, Albertin A. Effects of nonpathogenic gram-negative bacterium Vitreoscilla filiformis lysozyme on atopic dermatitis: a prospective, randomized, double-blind, placebo-controlled clinical study. Does this make a real difference?. Br J Dermatol 2009; 161: 477–478; author reply 8–9.
97 Kwon HH, Yoon JY, Park SY, Min S, Suh DH. Comparison of clinical and histological effects between *Lactobacillus*-fermented *Chamaecyparis obtusa* and tea tree oil for the treatment of acne: an eight-week double-blind randomized controlled split-face study. *Dermatology* 2014; **229**: 102–109.

98 Lane ME, Hadgraft J, Oliveira G, Vieira R, Mohammed D, Hirata K. Rational formulation design. *Int J Cosmet Sci* 2012; **34**: 496–501.

99 Gayraud F, Sayag M, Jourdan E. Efficacy and tolerance assessment of a new type of dermocosmetic in infants and children with moderate atopic dermatitis. *J Cosmet Dermatol* 2015; **14**: 107–112.

100 Seite S, Flores GE, Henley JB, Martin R, Zelenkova H, Aguilar L, et al. Microbiome of affected and unaffected skin of patients with atopic dermatitis before and after emollient treatment. *J Drugs Dermatol* 2014; **13**: 1365–1372.

101 Al-Ghazzewi FH, Tester RF. Impact of prebiotics and probiotics on skin health. *Brief Microbes* 2014; **5**: 99–107.

102 Gueniche A, Benyacoub I, Buetler TM, Smola H, Blum S. Supplementation with oral probiotic bacteria maintains cutaneous immune homeostasis after UV exposure. *Eur J Dermatol* 2006; **16**: 511–517.

103 Gueniche A, Knaudt B, Schuck E, Volz T, Bastien P, Martin R, et al. Effects of nonpathogenic gram-negative bacterium *Vitreoscilla filiformis* lysate on atopic dermatitis: a prospective, randomized, double-blind, placebo-controlled clinical study. *Br J Dermatol* 2008; **159**: 1357–1363.

104 Simmering R, Breves R. Pre- and probiotic cosmetics. *Hautarzt* 2009; **60**: 809–814.

105 Bouslimani A, Porto C, Rath CM, Wang M, Guo Y, Gonzalez A, et al. Molecular cartography of the human skin surface in 3D. *Proc Natl Acad Sci USA* 2015; **112**: E2120–E2129.