

The Role of Cutaneous Microbiota Harmony in Maintaining a Functional Skin Barrier

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ABSTRACT

The skin is constantly exposed to various endogenous and exogenous factors that may impact its barrier function at the physical, mechanical, immunological, and microbial levels. These factors have the potential to initiate or exacerbate a variety of inflammatory skin conditions, especially those associated with barrier dysfunction. The barrier function of the skin depends upon a symbiotic relationship between resident microbial communities and host tissue. This symbiosis results from complex signals involved in both the innate and adaptive immune responses. Recent research indicates that both bacterial diversity and the relative abundance of different microbes present on and in the skin, may contribute to skin barrier stability or dysfunction. The objectives of this review are to discuss the relationship between the skin microbiota and skin barrier function and to consider mechanisms that may help its preservation.

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INTRODUCTION

Human skin is a complex barrier organ that provides an ecological niche for a wide range of microorganisms. The majority of these microflora are harmless or beneficial, providing protection against pathogens and playing an important role in modulating the host's cutaneous innate and adaptive immune systems.[1] The symbiosis between the skin and its microbiota (microorganisms on and in the skin, typically identified by 16S ribosomal RNA surveys)[2] depends on a complex "dialogue" and is necessary for healthy skin and an efficient skin barrier function.[1,3]

The skin is constantly exposed to external and internal environmental factors (eg, ultraviolet radiation, pollution, topical medications, and skin care products) that can alter the balanced relationship between the skin and its microbiota.[3] Such disruption may result in increased risk for infections, chronic inflammatory skin diseases (eg, atopic dermatitis, psoriasis, rosacea, acne), and complaints of sensitive, pruritic, and irritated skin.[4]

The objectives of this paper are to review recent information about the relationship between skin microbiota and barrier function, and to consider mechanisms that may aid in its preservation.

THE SKIN MICROBIOTA

A single square centimeter of the human skin contains up to one million microorganisms, including diverse communities of viruses, bacteria, fungi, and mites.[5] While bacteria account for only 0.1% of this total (1 million/cm^2), they are generally considered to be the most important living organisms in this ecosystem. Bacteria are present on the skin surface, deeper layers of the epidermis, the dermis, and dermal adipose tissue.[5]

Evolution in Understanding of Skin Bacteria

Our understanding of microorganisms living on and in the skin has changed dramatically in the last several years. Culture-based studies indicated that *Staphylococcus epidermidis*, other coagulase-negative staphylococci, and coryneforms of the *Actinobacteria* phylum were primary bacterial colonizers of the skin.[6] However, many organisms may be present that are said to be uncultivable or are outcompeted by organisms that grow more readily in culture. The development of culture-independent molecular techniques for identification and quantitation of microbial organisms has revolutionized our view of the skin microbiome. Genomic characterization of bacterial diversity relies on amplification of the 16S ribosomal RNA (16S rRNA) gene by polymerase chain reaction (PCR) directly from skin samples. The 16S rRNA gene exists in all bacteria and archaea but not in eukaryotes excepted for mitochondria. The bacterial landscape obtained by 16S rRNA sequencing is a first step in knowing skin microbiota and then skin microbiome. The main fault of this technology is that it is blind to difference between dead bacteria and living bacteria. Secondly, bacteria have inducible genes that can be expressed and others that are always running. That means that even when we get a global picture of what is there, we ignore the active genes and how this community works. The 16S rRNA contains both conserved regions that serve as binding sites for

PCR primers and variable regions for taxonomic classification after high-throughput sequencing of the PCR products.[6,7] Another crucial point is that there is no international standardization for sampling methods. Because of this, comparisons between different papers can be biased due to the sampling method, the variable 16S rRNA region used, and sometimes by the databases used. Standardization of sampling methods remains a key problem in comparing results from different studies.

Composition

Molecular methods arising from advances in genomic technology have permitted a detailed description of the skin microbiota.[6,8-11] Bacteria on the skin are from four main bacterial phyla, *Actinobacteria, Firmicutes, Proteobacteria*, and *Bacteroidetes*, and the three most common genera are *Corynebacteria*, *Propionibacteria*, and *Staphylococci*.[12] The microbiota of the skin varies across its surface, and four main "environments" have been described: 1) Moist (the axilla, the inner elbow, or the inguinal fold), harboring mostly *Staphylococci* and *Corynebacteria*[12]; 2) Sebaceous (the forehead, the malar crease, the retroauricular crease, and the back), having a higher density of *Propionibacteria*[13,14]; 3) Dry (eg, the upper buttock area), hosting predominantly *Staphylococci*, *Propionibacteria*, *Micrococci*, *Corynebacteria*, *Enhydrobacter,* and *Streptococci*[15]; and 4) Others (sweat glands or hair follicles), hosting facultative anaerobes, such as *Propionibacterium* spp.[12,16,8]The distribution of follicles, eccrine, apocrine, and sebaceous glands contribute to the variable cutaneous microenvironments as do skin pH, moisture, and temperature. This likely selects subsets of bacteria that can thrive in each ecosystem.[17]

Factors Influencing Bacterial Growth

The skin provides a "culture medium" for the growth of bacteria. These microorganisms require water, sources of carbon, nitrogen, and macro-, and microelements. Water is crucial to microbial growth on the skin, and the amount of water available to support this growth is referred to as water activity (a_w). Water activity varies from 0 (no free water available) to 1.0 (all molecules of water are free).[18] Water activity strongly influences the growth of microorganisms and differs considerably between the main environments of human skin described above.[16] *Staphylococcus aureus* is able to grow until a_w of 0.83, *Staphylococcus epidermidis* is less resistant (unable to grow below a_w of 0.87), and *Pseudomonas fluorescens* is unable to grow below a_w of 0.97. Dry skin therefore favors growth of potentially invasive *Staphylococci* and inhibits the growth of commensal organisms. Thus, moisturizers play two important roles in the barrier function of the skin: 1) Preservation of the physical barrier; and 2) Maintenance of the normal composition of the skin microbiota.

The skin's bacterial landscape is highly dynamic with both the composition and relative abundance of bacteria varying considerably across individuals. The diversity and abundance of the cutaneous bacterial flora are said to be influenced by gender, age, and ethnicity. Climate, ultraviolet radiation, pollution, and lifestyle factors including diet, hygiene habits, and drug and alcohol consumption may also influence the composition of the skin microbiota.[19-27]

STRUCTURE AND FUNCTION OF THE SKIN BARRIER

The skin barrier, as well as the microbiota, protects the body against a wide range of external dangers. This barrier consists of the epidermis and several layers below it that influence function and harbor microbes.[3,28,29] The physical barrier of the skin is formed mainly by the stratum corneum, which is composed of dead keratinocytes or corneocytes and proteinaceous crosslinking filaments.[30,31] The corneocytes are surrounded by a proteinaceous structure called the cornified envelope. This structure consists of a layer of highly crosslinked insoluble proteins covalently bound to a layer of lipids. The lipid matrix forms the main permeability barrier against the invasion of bacteria and other hazardous substances.[31-33] Filaggrin (filament aggregating protein) also contributes to the barrier function of the epidermis. The breakdown of filaggrin results in the production of alanine, pyrrolidone carboxylic acid, and urocanic acid, which act as natural moisturizers in the stratum corneum and lower skin surface pH. Histidine released from filaggrin degradation provides protection against ultraviolet light.[33,32] The S-100 calcium binding domain in the molecular structure of profilaggrin may play a role in calcium signaling.[33]

Nucleated keratinocytes in the stratum granulosum and stratum spinosum form cell–cell adhesion junctions that also contribute to barrier function.[30,31] Importantly, the condition of the epidermal barrier depends on physical properties that include the amount of sebum produced, hydration, and pH.[30]

The skin also has a chemical barrier that is comprised of defense molecules that are expressed constitutively or induced and can either directly inhibit microbial growth or serve as activators and mediators of the innate and adaptive immune responses.[34] Keratinocytes protect against infection via the innate production and release of antimicrobial peptides (AMPs). These molecules, which are also produced by mast cells, neutrophils, and sebocytes, provide innate microbicidal action against infectious pathogens (as opposed to antibiotics which have more of a static, or inhibitory, effect). Some AMPs (eg, cathelicidin) also function by triggering inflammatory cell recruitment and cytokine release.[35,36] AMPs can be produced constitutively, or actively induced by proinflammatory cytokines or signaling from pattern recognition receptors (eg, Toll-like receptors [TLRs]).[35]

Role of Skin Microbiota in Protection from Infection and Inflammation

It is becoming increasingly accepted that commensal species of microorganisms that naturally reside on the surface of the

skin are an integral part of the innate immune system. These bacteria contribute to protection against pathogen growth by competing for nutrients and space.[3] Some bacteria directly restrict the growth of competitors via production of antimicrobial compound peptides (AMPs) that can inhibit reproduction of closely related species without affecting the organisms producing them.[3] Those AMPs are called bacteriocins and are very similar to β-defensins secreted by skin cells to regulate specific bacterial population that are overrepresented and detected by the immune system via toll-like receptors (TLR) TLR2 and TLR4, respectively, for gram-positive and gram-negative bacteria.[3]

Commensal bacteria can also provide protection against inflammation. Bacteria from normal skin, such as *S. epidermidis,* have been shown to suppress inflammation by inducing the secretion of interleukin-10, an anti-inflammatory cytokine, by antigen-presenting cells.[37,38] *S. epidermidis*, as all gram-positive bacteria, also secretes specific lipoteichoic acids that inhibit both inflammatory cytokine release from keratinocytes and inflammation triggered by injury through a TLR2-dependent mechanism.[38,35]

Interplay Between Skin Cells and Bacteria in Host Defense and Inflammation

There is a balanced interplay between the host cells and resident and/or transient bacterial populations that is continuously affected by intrinsic (host) and extrinsic (environmental) factors (Figure 1). These factors alter the composition of the skin microorganism community and may influence skin barrier function by inducing an unbalanced microbial state or dysbiosis that may be evidenced in chronic inflammatory skin diseases, such as atopic dermatitis, psoriasis, rosacea, or acne.[20,16,39,40]

The composition of bacterial communities depends on skin characteristics, such as sebaceous gland concentration, moisture content, and temperature, as well as on host genetics and exogenous environmental factors.[7] For example, defects in the skin structural barrier permit penetration of the epidermis by chemical, allergic, and/or infectious agents. This may result in chronic inflammation and a loss of microbial diversity with an associated increase in *Staphylococci*, including *S. aureus*.[41] Skin cells can also affect microbiota by providing specific nutrients or through the synthesis of antimicrobial peptides (Table 1).[10]

The microorganisms that are living on the skin are also under the influence of its water content.[18] The influences of other factors are less well understood,[39] but there is limited information about the effects of some of them. Antibiotics, corticosteroids, radiotherapy, and chemotherapy can all influence the composition of the skin microbiota.[42,12,6,8,4,43,44] It has also been shown that frequent hand washing disturbs skin barrier function, resulting in irritation and changes in the hand skin microbiota.[42]

FIGURE 1. Current model of relationship between skin barrier and skin microbiota.

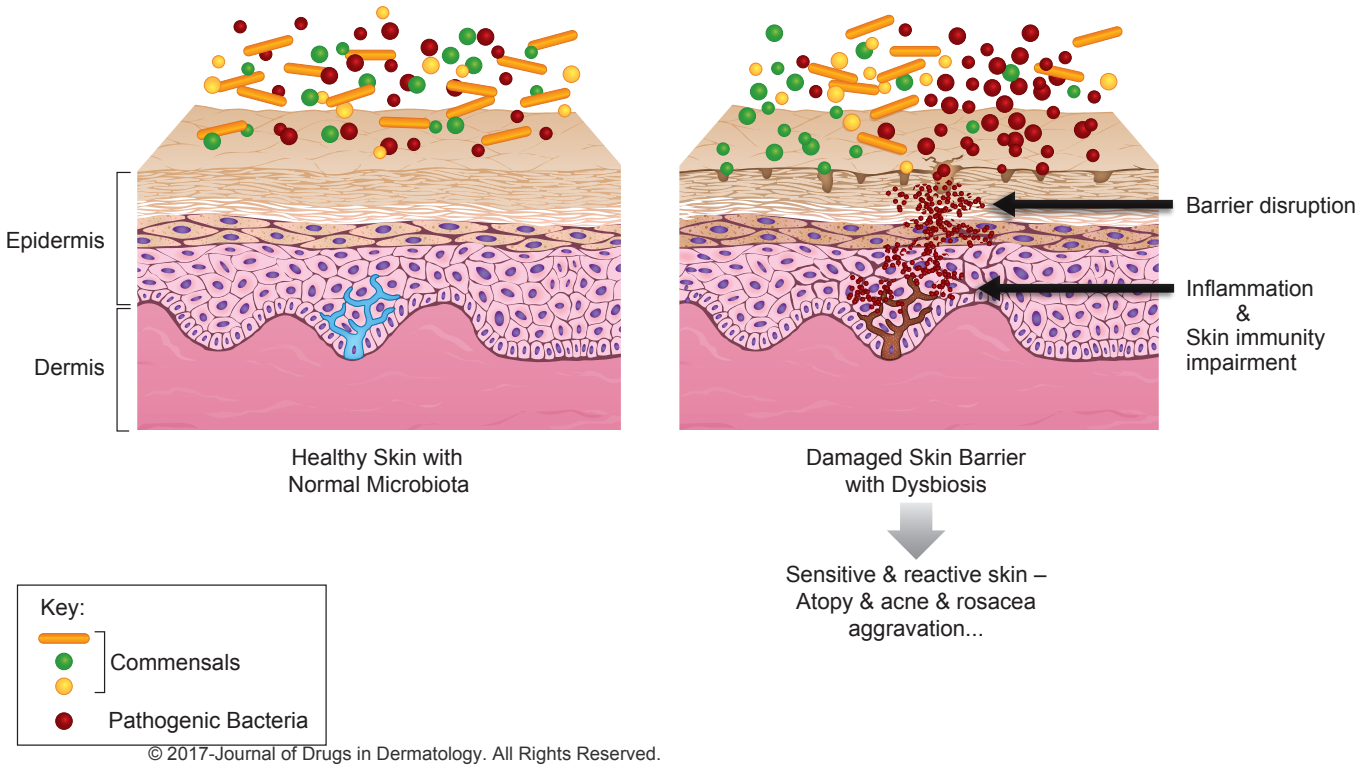

TABLE 1.

Relationship Between Skin Barrier and Skin Microbiota	
How Skin Microbiota Interact With Human Skin Barrier	
Proteases	May affect corneocytes desquamation and many skin proteins (ie, filaggrin) involved in stratum corneum cohesion
Lipases	Break down surface lipids with potentially irritant by-products including fatty acids
Ureases	Virulence factor found in various pathogenic bacteria; essential in host colonization and in maintenance of bacterial cells in tissues
Biofilm	Protect bacterial colonies on the skin
Bacteriocins	Bactericidal peptides regulating bacterial population
Quorum sensing	Needed for microbiota balance; effect not known on the skin
Skin nutrition	Supports commensal bacterial growth
Skin education	Immunology by lipopolysaccharides (Gram-negative bacteria) and teichoic acids (Gram-positive bacteria)
How Human Skin Barrier Interacts With Skin Microbiota	
Provides nutriments	Specific culture medium depending on microenvironment (moist, sebaceous, dry)
Control climate	pH, temperature, moisture, and sweat controlled depending on skin area
Climate and nutriments	Counter-select bacteria growth
Bacterial balance regulation	β-defensins production

Skin microbiota can affect skin barrier function via bacterial enzymes, such as proteases, that may impact corneocyte desquamation or lipases that may break down skin surface lipids (Table 1).[10] Colonization by pathogenic bacteria may play a significant role in the breakdown of the skin barrier in patients with skin diseases.[45] *S. aureus* colonization on the skin is found in up to 90% of patients with atopic dermatitis.[46] This organism produces ceramidase, which breaks down ceramides, an essential component of the skin barrier.[47,48]

The Importance of Maintaining Bacterial Diversity

Changes in the normal composition of the skin microbiota can contribute to the development of inflammation. In patients with inflammatory skin disorders, increasing disease severity correlates with decreased microbial diversity overall and an elevated prevalence of *Staphylococci*, including both *S. epidermidis* and *S. aureus*. Several skin disorders (eg, atopic dermatitis and psoriasis) are characterized by shifts in the skin microbiota, most notably loss of protective bacteria and outgrowth of pathogenic organisms.[5,49,50] This shift has the potential to contribute to chronic inflammation. For example, *S. aureus*-associated molecular patterns bind to TLR2 to initiate long-lasting cutaneous inflammation driven by T helper cells.[51]

MOISTURIZERS FOR MAINTENANCE OF THE SKIN BARRIER AND A NORMAL SKIN MICROBIOTA

Maintaining the normal, highly diverse skin microbiota appears to be important for skin health, and moisturizers may help to maintain this diversity.[52] Moisturizer modifies the water activity of the skin and so changes the growth of a wide range of bacteria with the potential to compete with potentially pathogenic organisms.[53,54]

Actions of Moisturizers

Moisturizers bind water to the stratum corneum, improving the skin surface hydration. This has been shown repeatedly to improve the epidermal barrier function and reduce stinging, scaling, redness, and cracks associated with xerosis.[55] "To moisturize" does not only mean providing moisture, it also signifies preventing moisture evaporation from the skin. Moisturizers can be formulated with emollient, humectant, moisturizing, or occlusive agents; and some formulations have potential prebiotic activity since they may provide food for the skin microbiota.[56] Emollient agents also make the skin softer and more pliable by filling the space between corneocytes and restoring the physical barrier function. Humectants or moisturizing agents are water-soluble substances that help the stratum corneum capture water and rebalance the cutaneous hydrolipidic film. Occlusive agents create a sealed barrier and prevent moisture evaporation from the surface of the epidermis. Moisturizers may also have anti-inflammatory properties that potentially impact the skin microbiota since inflammation has been associated with dysbiosis.[57,58]

Formulation of Skin Care Products

An important focus for the development of skin care products is maintaining an ecological balance in each skin niche.[59,58,5] Classical moisturizers are able to protect the skin, but new-generation

formulations have been specifically developed to manage inflammation and preserve or restore both the skin barrier and the skin microbiota diversity.

Water

Moisturizers can be formulated with deionized water or thermal water. The physicochemical characteristics of thermal water depend on the nature of the geologic materials through which the groundwater has moved. Common soluble minerals include calcium (Ca^{2+}), bicarbonate (CO_3H^-), silicates, iron compounds, sodium and magnesium salts, sulphur compounds, and metals.[61] Trace elements, including selenium or strontium, as well as purity and pH are also important parameters that may influence the specific biological activities of thermal waters. For example, presence of selenium has free-radical scavenging and anti-inflammatory properties and also provides protection against toxic heavy metals.[61-65]

Thermal waters have a unique microbial signature related to their specific mineral content. In comparison to deionized water, thermal water can be viewed as containing prebiotic active ingredients (ie, non-viable food components that confer health benefits associated with a modulation of the microbiota).[56] The presence of specific trace elements in thermal water can drive the growth of beneficial bacterial species particularly if they are already found in its natural microbial content.[54]

The importance of thermal water is supported by results which showed that an emollient containing 50% selenium-rich thermal spring water (TSW) or the use of selenium-rich TSW alone during balneotherapy reduced disease severity and increased the diversity of skin microbiota in patients with either atopic dermatitis or psoriasis.[66,54] In both groups of patients, there was an increase in keratolytic bacteria of the *Xanthomonadaceae* family that are naturally present at low levels on the skin and in TSW and a decrease in *Staphylococcus* spp.[66,54]

Prebiotics

Prebiotics were initially defined as non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria.[67] Prebiotics that might be included in skin products also have the potential to support maintenance of the normal skin microbiome.[60] Relatively little is known about the benefits of this approach, but it has been shown that application of a biomass lysate of the non-pathogenic gram-negative bacterium, *Vitreoscilla filiformis*, helped to restore the skin microbiota in patients with atopic or seborrheic dermatitis.[68-70] It is interesting to note that *V. filiformis* biomass (VFB) prepared from organisms grown in a medium enriched with TSW resulted in more potent stimulation of mRNA expression for and levels of antimicrobial peptides in reconstructed epidermis.[71] Treatment of patients with atopic dermatitis using an emollient containing VFB prepared with selenium-rich TSW vs another recommended emollient yielded greater clinical improvements with the VFB emollient that were associated with significantly increased genus *Xanthomonas*. In contrast, the comparator product was associated with increases in *Staphylococci*.[41] This has been evaluated via high-throughput sequencing approach that targets the V1-V3 region of the bacterial 16S rRNA gene as recommended by Meisel JS et al, 2016.[72] While inclusion of prebiotics in skin preparations appears promising, much more research is required to learn their benefits and limitations.

Other Components

Occlusive agents, such as ceramides, included in moisturizers may be good carbon and nitrogen sources for bacteria. Ceramidase activity has been detected in bacterial skin flora and it has also been noted that skin ceramide levels are reduced in patients with atopic dermatitis.[47] These results suggest that increasing levels of skin ceramides may be important for maintenance of skin health.

Niacinamide (vitamin B_3) is combined with emollients in some skin products and it is also employed in culture media for some bacteria. It may promote skin health as it has been shown to inhibit the growth of methicillin-resistant *S. aureus*.[73]

CONCLUSION

Understanding the complex relationship between normal skin barrier function and the skin microbiome is critical for the rational development of new skin care products.[42,59,60,53,58,54] Appropriately developed formulations have the potential to selectively increase the activity and growth of beneficial microbiota, prevent skin dysbiosis, and restore or maintain efficient skin barrier function.[41] This is particularly important for conditions in which barrier dysfunction may occur, such as with dry, sensitive, and reactive skin; exposure to aggressive cosmetic or hygienic routines; after aesthetic procedures; or when taking therapeutics including antibiotics and corticosteroids. The studies reviewed in this paper suggest that inclusion of prebiotics eg, ceramides, niacinamide, selenium-rich thermal spring water may all increase the efficacy of moisturizers and that some of this benefit may be due to positive effects on skin microbiota.

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REFERENCES

1. Salava A, Lauerma A. Role of the skin microbiome in atopic dermatitis. *Clin Transl Allergy.* 2014;4:33.
2. Whiteside SA, Razvi H, Dave S, et al. The microbiome of the urinary tract—a role beyond infection. *Nat Rev Urol.* 2015;12(2):81-90.
3. Sanford JA, Gallo RL. Functions of the skin microbiota in health and disease. *Semin Immunol.* 2013;25(5):370-7.
4. Zeeuwen PL, Kleerebezem M, Timmerman HM, Schalkwijk J. Microbiome and skin diseases. *Curr Opin Allergy Clin Immunol.* 2013;13(5):514-20.
5. Weyrich LS, Dixit S, Farrer AG, Cooper AJ. The skin microbiome: Associations between altered microbial communities and disease. *Australas J Dermatol.* 2015;56(4):268-74.
6. Grice EA, Segre JA. The skin microbiome. *Nat Rev Microbiol.* 2011;9(4):244-53.
7. Chen YE, Tsao H. The skin microbiome: current perspectives and future challenges. *J Am Acad Dermatol.* 2013;69(1):143-55.
8. Consortium HMP. Structure, function and diversity of the healthy human microbiome. *Nature.* 2012;486(7402):207-14.
9. Lauber CL, Zhou N, Gordon JI, et al. Effect of storage conditions on the assessment of bacterial community structure in soil and human-associated samples. *FEMS Microbiol Lett.* 2010;307(1):80-6.
10. Capone KA, Dowd SE, Stamatas GN, Nikolovski J. Diversity of the human skin microbiome early in life. *J Invest Dermatol.* 2011;131(10):2026-32.
11. Alexeyev OA. Bacterial landscape of human skin: seeing the forest for the trees. *Exp Dermatol.* 2013;22(7):443-6.
12. Grice EA, Kong HH, Conlan S, et al. Topographical and temporal diversity of the human skin microbiome. *Science.* 2009;324(5931):1190-2.
13. Findley K, Oh J, Yang J, et al. Topographic diversity of fungal and bacterial communities in human skin. *Nature.* 2013;498(7454):367-70.
14. Zeeuwen PL, Boekhorst J, van den Bogaard EH, et al. Microbiome dynamics of human epidermis following skin barrier disruption. *Genome Biol.* 2012;13(11):R101.
15. Zouboulis CC. Acne and sebaceous gland function. *Clin Dermatol.* 2004;22(5):360-6.
16. Grice EA, Segre JA. The human microbiome: our second genome. *Annu Rev Genomics Hum Genet.* 2012;13:151-70.
17. Krakauer T, Buckley M. Dexamethasone attenuates staphylococcal enterotoxin B-induced hypothermic response and protects mice from superantigen-induced toxic shock. *Antimicrob Agents Chemother.* 2006;50(1):391-5.
18. Stevenson A, Cray JA, Williams JP, et al. Is there a common water-activity limit for the three domains of life? *ISME J.* 2015;9(6):1333-51.
19. Costello EK, Lauber CL, Hamady M, et al. Bacterial community variation in human body habitats across space and time. *Science.* 2009;326(5960):1694-7.
20. Schommer NN, Gallo RL. Structure and function of the human skin microbiome. *Trends Microbiol.* 2013;21(12):660-8.
21. Kong HH, Segre JA. Skin microbiome: looking back to move forward. *J Invest Dermatol.* 2012;132(3 Pt 2):933-9.
22. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci U S A.* 2010;107(26):11971-5.
23. Dominguez-Bello MG, De Jesus-Laboy KM, Shen N, et al. Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. *Nat Med.* 2016;22(3):250-3. doi: 10.1038/nm.4039. Epub 2016 Feb 1.
24. 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(6):1381-9.
25. Zapata HJ, Quagliarello VJ. The microbiota and microbiome in aging: potential implications in health and age-related diseases. *J Am Geriatr Soc.* 2015;63(4):776-81.
26. Faergemann J, Larkö O. The effect of UV-light on human skin microorganisms. *Acta Derm Venereol.* 1987;67(1):69-72.
27. Blaak J, Kaup O, Hoppe W, et al. A long-term study to evaluate acidic skin care treatment in nursing home residents: impact on epidermal barrier function and microflora in aged skin. *Skin Pharmacol Physiol.* 2015;28(5):269-279.
28. Nakatsuji T, Chiang HI, Jiang SB, et al. The microbiome extends to subepidermal compartments of normal skin. *Nat Commun.* 2013;4:1431.
29. Proksch E, Brandner JM, Jensen JM. The skin: an indispensable barrier. *Exp Dermatol.* 2008;17(12):1063-72.
30. Boer M, Duchnik E, Maleszka R, Marchlewicz M. Structural and biophysical characteristics of human skin in maintaining proper epidermal barrier function. *Postepy Dermatol Alergol.* 2016;33(1):1-5.
31. Blaydon DC, Kelsell DP. Defective channels lead to an impaired skin barrier. *J Cell Sci.* 2014;127(Pt 20):4343-50.
32. López O, Cócera M, Wertz PW, et al. New arrangement of proteins and lipids in the stratum corneum cornified envelope. *Biochim Biophys Acta.* 2007;1768(3):521-9.
33. De D, Handa S. Filaggrin mutations and the skin. *Indian J Dermatol Venereol Leprol.* 2012;78(5):545-51.
34. Christensen GJ, Brüggemann H. Bacterial skin commensals and their role as host guardians. *Benef Microbes.* 2014;5(2):201-15.
35. Gallo RL, Nakatsuji T. Microbial symbiosis with the innate immune defense system of the skin. *J Invest Dermatol.* 2011;131(10):1974-80.
36. Batycka-Baran A, Maj J, Wolf R, Szepietowski JC. The new insight into the role of antimicrobial proteins-alarmins in the immunopathogenesis of psoriasis. *J Immunol Res.* 2014;2014:628289.
37. Chau TA, McCully ML, Brintnell W, et al. Toll-like receptor 2 ligands on the staphylococcal cell wall downregulate superantigen-induced T cell activation and prevent toxic shock syndrome. *Nature Med.* 2009;15(6):641–8.
38. Lai Y, Di Nardo A, Nakatsuji T, et al. Commensal bacteria regulate Toll-like receptor 3-dependent inflammation after skin injury. *Nat Med.* 2009;15(12):1377-82.
39. Grice EA. The intersection of microbiome and host at the skin interface: genomic- and metagenomic-based insights. *Genome Res.* 2015;25(10):1514-20.
40. Rosenthal M, Goldberg D, Aiello A, et al. Skin microbiota: microbial community structure and its potential association with health and disease. *Infect Genet Evol.* 2011;11(5):839-48.
41. Seité S, Zelenkova H, Martin R, Fiefer N. Using a specific emollient to manage skin microbiome dysbiosis. Poster presented at the World Congress of Dermatology, 2015.
42. Holland KT, Bojar RA. Cosmetics: what is their influence on the skin microflora? *Am J Clin Dermatol.* 2002;3(7):445-9.
43. Bensadoun RJ, Humbert P, Krutman J, 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;5:401-8.
44. Vetizou M, Pitt JM, Daillère R, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science.* 2015;350(6264):1079-84.
45. Valdman-Grinshpoun Y, Ben-Amitai D, Zvulunov A. Barrier-restoring therapies in atopic dermatitis: current approaches and future perspectives. *Dermatol Res Pract.* 2012;2012:923134.
46. Baker BS. The role of microorganisms in atopic dermatitis. *Clin Exp Immunol.* 2006;144(1):1-9.
47. Ohnishi Y, Okino N, Ito M, Imayama S. Ceramidase Activity in Bacterial Skin Flora as a Possible Cause of Ceramide Deficiency in Atopic Dermatitis. *Clin Diagn Lab Immunol.* 1999;6(1):101–104.
48. Joo KM, Hwang JH, Bae S, et al. Relationship of ceramide-, and free fatty acid-cholesterol ratios in the stratum corneum with skin barrier function of normal, atopic dermatitis lesional and non-lesional skins. *J Dermatol Sci.* 2015;77(1):71-4.
49. van Rensburg JJ, Lin H, Gao X, et al. The Human Skin Microbiome Associates with the Outcome of and Is Influenced by Bacterial Infection. *MBio.* 2015;6(5):e01315-15.
50. Grice EA. The skin microbiome: potential for novel diagnostic and therapeutic approaches to cutaneous disease. *Semin Cutan Med Surg.* 2014;33(2):98-103.
51. Biedermann T, Skabytska Y, Kaesler S, et al. Regulation of T Cell Immunity in Atopic Dermatitis by Microbes: The Yin and Yang of Cutaneous Inflammation. *Front Immunol.* 2015;6:353.
52. Lynde CW, Andriessen A, Bertucci V, et al. The skin microbiome in atopic dermatitis and its relationship to emollients. *J Cutan Med Surg.* 2016;20(1):21-8.
53. Flores G, Caporaso G, Henley J, et al. Temporal variability is a personalized feature of the human microbiome. *Genome Biology* 2014;15:531.
54. Martin R, Henley JB, Sarrazin P, Seité S. Skin microbiome in patients with psoriasis before and after balneotherapy at the thermal care center of La Roche-Posay. *J Drugs Dermatol.* 2015;14(12):1400-5.
55. Ring J, Möhrenschlager M, Weidinger S. Molecular genetics of atopic eczema. *Chem Immunol Allergy.* 2012;96:24-9.
56. FAO. FAO Technical Meeting Report on PREBIOTICS: Food Quality and Standards Service (AGNS) Food and Agriculture Organization of the United Nations (FAO); 2008. Available at: http://www.aat-taa.eu/index/en/company/download/1262610500.html. Accessed June 15, 2016.
57. Mańkowska-Wierzbicka D, Karczewski J, Dobrowolska-Zachwieja A, Adamski Z. The microbiome and dermatological diseases. *Postepy Hig Med Dosw* (Online). 2015;69:978-85.
58. Seité S, Bieber T. Barrier function and microbiotic dysbiosis in atopic dermatitis. *Clin Cosmet Investig Dermatol.* 2015;8:479-83.
59. Lane ME, Hadgraft J, Oliveira G, et al. Rational formulation design. *Int J Cosmet Sci.* 2012;34(6):496-501.

60. Al-Ghazzewi FH, Tester RF. Impact of prebiotics and probiotics on skin health. *Benef Microbes.* 2014;5(2):99-107.
61. Seité S. Thermal waters as cosmeceuticals: La Roche-Posay thermal spring water example. *Clin Cosmet Investig Dermatol.* 2013;6:23-8.
62. Wollenberg A, Richard A, Bieber T. In vitro effect of the thermal water from La Roche-Posay on the stimulatory capacity of epidermal Langerhans cells. *Eur J Dermatol.* 1992;2:128-9.
63. Moysan A, Morlière P, Marquis I, et al. Effect of selenium on UVA-induced lipid peroxidation in cultured human skin fibroblasts. *Skin Pharmacol.* 1995;8:139-48.
64. Célérier P, Richard A, Litoux P, Dreno B. Modulatory effects of selenium and strontium salts on keratinocyte-derived inflammatory cytokines. *Arch Dermatol Res.* 1995;287:680–2.
65. Staquet MJ, Peugeot-Navarro J, Latorre F, et al. In vitro effects of a spa water on the migratory and stimulatory capacities of human epidermal Langerhans cells. *Eur J Dermatol.* 1997;7:339-42.
66. Seité S, Flores GE, Henley JB, et al. Microbiome of affected and unaffected skin of patients with atopic dermatitis before and after emollient treatment. *J Drugs Dermatol.* 2014;13(11):1365-72.
67. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *J Nutr.* 1995;125(6):1401-12.
68. Guéniche A, Cathelineau AC, Bastien P, et al. Vitreoscilla filiformis biomass improves seborrheic dermatitis. *J Eur Acad Dermatol Venereol.* 2008;22(8):1014-5.
69. Gueniche A, Knaudt B, Schuck E, 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(6):1357-63.
70. Volz T, Skabytska Y, Guenova E, et al. Nonpathogenic bacteria alleviating atopic dermatitis inflammation induce IL-10-producing dendritic cells and regulatory Tr1 cells. *J Invest Dermatol.* 2014;134(1):96-104.
71. Mahe YF, Perez MJ, Tacheau C, 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.* 2013;6:191-6.
72. Meisel J, Hannigan G, Tyldsley A, et al. Skin microbiome surveys are strongly influenced by experimental design. *J Invest Dermatol.* 2016;136:947-956.
73. Kyme P, Thoennissen NH, Tseng CW, et al. C/EBPε mediates nicotinamide-enhanced clearance of Staphylococcus aureus in mice. *J Clin Invest.* 2012;122(9):3316-29.
74. Blaak J, Kaup O, Hoppe W, et al. A long-term study to evaluate acidic skin care treatment in nursing home residents: impact on epidermal barrier function and microflora in aged skin. *Skin Pharmacol Physiol.* 2015;28(5):269-279.

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