Why consider the skin microbiota in dermatological patient management?

SKIN & MICROBIOTA | BASIC

Human skin provides an ecological niche for a wide range of *microorganisms*.[1] As the first line of physical and immunological defense, it is a complex barrier organ resulting from a symbiotic relationship between microbial communities in constant dialogue with the host via complex signals interacting with the innate and adaptive immune systems. This mutualistic relationship leads to a well-controlled but delicate equilibrium, which is essential for healthy skin.[2,3]

Note: Some definitions[2]

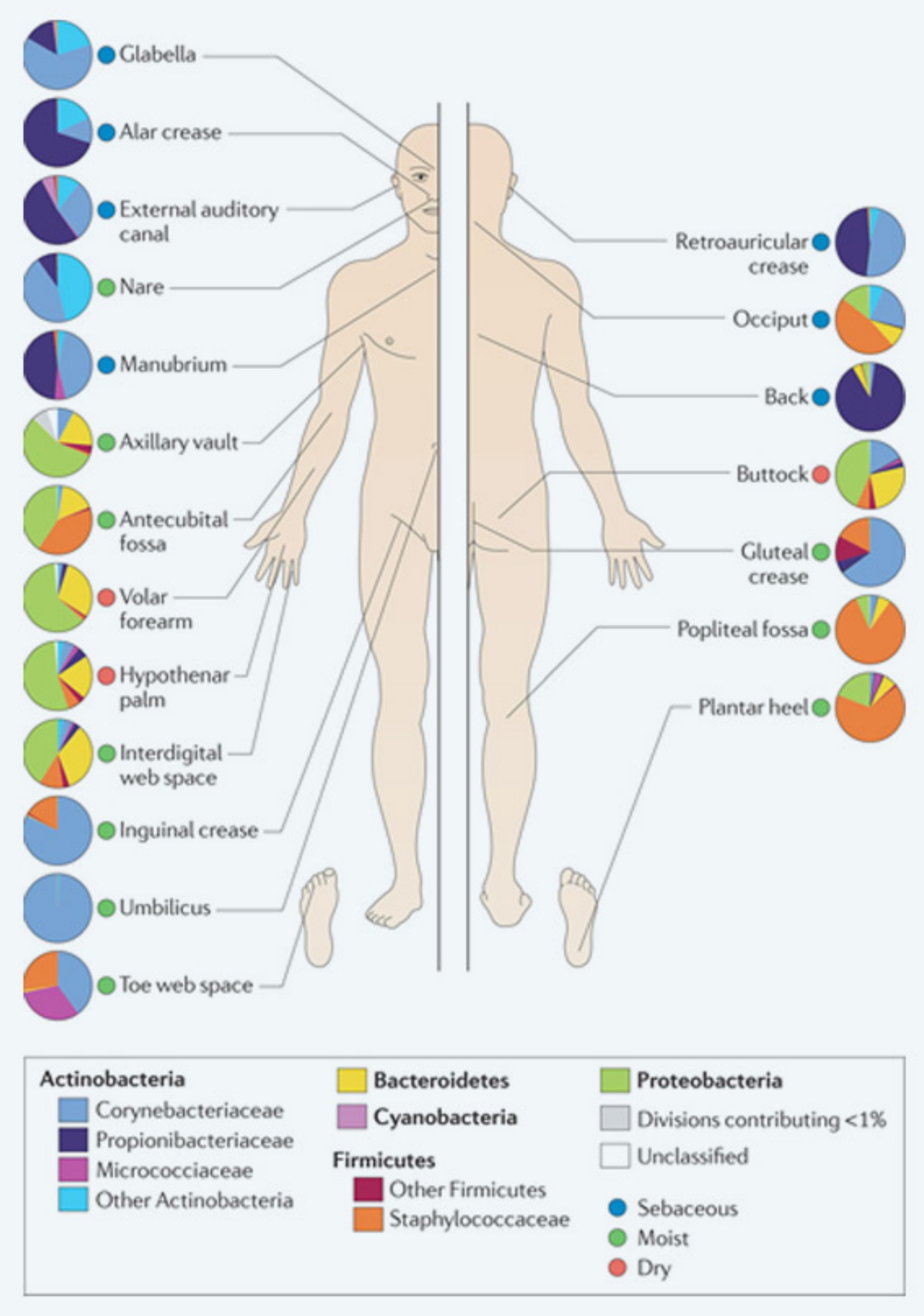
- Microbiota: all the microorganisms (bacteria, phages, fungi, yeasts, viruses, etc) living in a particular environment
- Microbiome: collective genome of indigenous microorganisms
- Metagenome: genetic information of the microbiota
- Dysbiosis: unbalanced diversity of microbiota
- Probiotics: live microorganisms conferring a health benefit when administered in adequate amount
- Prebiotics: nonviable food components conferring a health benefit associated with modulation of the microbiota
- Postbiotics: nonviable bacterial products or metabolic byproducts from microorganisms having a biologic activity

Skin microbiota: a key player for good skin health

The skin is an ecosystem comprising 1.8 m^2 of diverse habitats, with an abundance of folds, invaginations and specialized niches that support a wide range of microorganisms, as well as mites.[4]
An estimated one million bacteria, with hundreds of distinct species, inhabit each square centimeter of skin.[5]

Many of these microorganisms are harmless and in some cases provide vital functions that the human genome has not evolved. Symbiotic microorganisms occupy a wide range of skin niches and protect against invasion by more pathogenic or harmful organisms.[3] They also self-manage their communities, ensuring that no one type of bacteria becomes overdominant; they do this by crowding out or even direct killing with bacteriocins. Bacteriocins are specific peptides synthetized by bacteria.
They may also have a role in educating the billions of T cells found in the skin, priming them to respond to similarly marked pathogenic cousins.[4]

The skin provides many niches in which large populations of microbes are subjected to variable ecological pressures including free water (aw), temperature, pH, the composition of antimicrobial peptides and lipids, etc. In addition, skin structures such as hair follicles and sebaceous, eccrine, and apocrine glands constitute discrete niches that harbor unique microbiota. Analyses of the topographical diversity of microbes that inhabit these niches of human skin using 16S rRNA gene phylotyping revealed that the habitats have significant effects on the microbial composition.[6]



Topographical distribution of bacteria on skin sites (from Grice E.A., Julia A. Segre J.A. The skin microbiome. Nat Rev Microbiol. 2011;9:244–53.)

Locally, microbial–immune interactions in the skin are vital for optimal barrier function, pathogen defense, and tissue repair with the production of key anti-inflammatory and antimicrobial compounds to maintain healthy tissue homeostasis. As in the gut, the metabolome (complete set of small-molecule chemicals found within a biological sample) in the skin reflects the combined functional metabolic activity of the microbes and our host tissues, and is greatly influenced by our environment and behavior.[7]

Thanks to genetic, variability between individuals is high, similar to other sites of the human microbiota, as is temporal variability within the same individual.

However, the dominant types of bacteria that reside on the skin appear to be relatively stable, with the rarer, less abundant types of bacteria accounting for the variability.[6,8]

The skin barrier and microbiota act as 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.[2]

Note:

- Intrinsic factors: hydration, pH, stress, hormones, illness, anxiety, genetics, etc.
- Extrinsic factors: temperature, pollution, UV radiation, washing, inadequate skincare products, anti-inflammatory, antibacterial or immunosuppressive treatments, etc.

Behind several skin conditions, dysbiosis

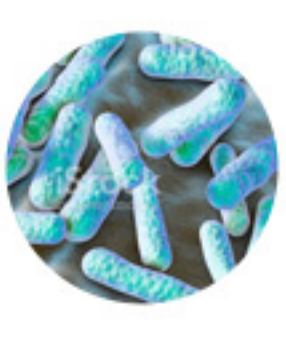
The skin is constantly exposed to various endogenous and exogenous factors that potentially impact this balanced system, creating pathophysiologically relevant situations. The lack of effective compensatory mechanisms could ultimately lead to inflammatory skin conditions such as infections, allergies or autoimmune diseases.[2]

This dysbiosis changes the abundance and diversity of commensal species, which participate in the skin barrier disruption and aggravates chronic skin diseases such as atopic dermatitis, psoriasis and acne.

For example:

Staphylococcus epidermidis is a skin commensal but can be an opportunistic pathogen in immunocompromised hosts.

Staphylococcus aureus has been identified as a resident microbe, yet it is also an important pathogen when over-colonizing the skin.



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.[2]

What changes in the skin microbiota are caused by skin conditions?

- Atopic dermatitis: less diversity and numbers of bacteria
- Acne: much lower levels of *Actinobacteria* including, counterintuitively, *Propionibacterium*, as well as higher levels of *Proteobacteria*. Differences between microbiota of inflammatory and non-inflammatory lesions
- Psoriasis: very low diversity and numbers of bacteria

Disruptions of the skin barrier and the induced inflammation are well known in atopic dermatitis, psoriasis, rosacea, acne, allergy and sensitive skin. However, loss of normal barrier structure and function is also relevant for all humans as they proceed through the skin aging process.[7]

Restoring the microbiota balance: now an achievable goal

The role of the skin microbiota in preventing other, unwanted pathogens from colonizing, and thereby maintaining an ecological balance in each skin niche, has now been confirmed.[2]
The study of the mutualistic interactions between human skin and its microbes has opened a wide range of new therapeutic options for the management of healthy and diseased skin and of skin microbiota, e.g. by selectively increasing the activity and growth of beneficial healthy skin microbiota.[2,6]

The gut–skin hypothesis made in 2010, which referred to a potential gut–brain–skin axis, provided an opportunity to investigate the benefits of oral pre- and probiotics for the skin. In addition to oral pre- and probiotic formulations tailored to the skin, a new generation of skincare products has now been developed, including prebiotics (ingredients that selectively stimulate the growth and/or activity of skin bacteria as sugars, specific oligo elements, etc.) or postbiotics (non-viable bacterial products or metabolic byproducts from microorganisms having a biologic activity), for example lysates of bacteria such as Vitreoscilla filiformis or Lactobacillus. These topical formulations have been designed to support the management of skin diseases such as atopic dermatitis and acne by helping to preserve or restore the skin barrier and skin microbiota, and if necessary by controlling the up or downregulation of innate immunity.[2]

GOING FURTHER

What is a healthy bacterial skin microbiota?

Findings suggest that the skin is inhabited with a more diverse number of bacterial colonies than any other epithelial surface.[2]

The skin microbiota includes two groups:

- *Resident microorganisms, which are a relatively fixed group of microorganisms (the core microbiota) that are found in the skin and reestablish after perturbation. The core skin microbiota is considered to be commensal, meaning that the microorganisms are usually harmless and may provide some benefit to the host.*
- *Transient microorganisms ('tourists') do not take up permanent residency, but emerge from the environment and persist for hours to days before disappearing. Under normal conditions both groups are nonpathogenic.*[2]

Composition

Four main phyla are represented: Actinobacteria, Firmicutes, Proteobacteria and Bacteroides The three most common genera are: Corynebacteria, Propionibacteria and Staphylococci.[2,6,8]
Both the composition and abundance vary considerably between individuals and over time, resulting in an extremely dynamic and greatly fluctuating microbiota.

Other types of organisms also reside on the skin, such as Malassezia sp., a polymorphic yeast sometimes classified as a fungus, and Demodex, a parasitic arthropod. To date, viruses are the least well-known members of the skin microbiota including phages (specific to bacteria).
From a bacteriological standpoint, our skin can be considered a culture medium. Its composition is mainly the result of our genetics, diet, lifestyle and the area we live in. As a result, every human skin is unique and at genus level every microbiota present in the different areas of our skin is unique.[2]

Distribution

In general, the skin is cool, acidic and more dry (arms) than wet (armpit) but distinct habitats are determined by skin thickness, folds and the density of hair follicles and glands.[4]
From a macroscopic standpoint, 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.[2]
The four main environments on human skin are: moist (axilla, inner elbow or inguinal fold), sebaceous (forehead, alar crease (side of the nostril), retroauricular crease (behind the ear) and back), dry (upper buttock area) and others. Further microenvironments include the sweat glands, hair follicles and dermal layers.[2]

Each microbial community has its preferred habitat within the various microenvironments on the skin.
- *Moist regions such as the navel or axilla mostly harbor more Staphylococcus and Corynebacteria species.*
- *Sebaceous sites have a higher density of particularly lipophilic species such as Propionibacteria, which have adapted to this lipid-rich, anaerobic environment.*
- *Drier sites predominantly host Staphylococcus, Propionibacterium, Micrococcus, Corynebacterium, Enhydrobacter and Streptococcus species.*[2,6]

At 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.[2]

Multiple independent detection techniques have shown that bacteria are not only present on the skin surface, but also found in deeper layers of the epidermis and even in the dermis and dermal adipose tissue. These layers have specific microbiota profiles and also contain many specialized cell types such as dendritic cells, melanocytes and Langerhans cells that each express a unique repertoire of functional pattern recognition receptors (PRRs), which respond actively when exposed to components of microorganisms. 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.[2]

Role

Host skin cells constantly sample the microorganisms inhabiting the epidermis and dermis via pattern recognition receptors (PRRs). The portion of activated immune system and how changes are regulated differentiate a commensal organism from a potential pathogen. Some 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 the growth of pathogens such as S. pyogenes and 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. 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's innate immune system and the microbiota.[2]

Skin microorganisms are capable of influencing their host cells, contributing to host immunity. S. epidermis has been shown to (i) induce AMPs boosting host immunity to S. aureus, (ii) activate mast cell-mediated antiviral immunity, (iii) suppress uncontrolled inflammatory reactions during wound healing, inducing the skin's AMP production, and (iv) stimulate cutaneous T-cell maturation.[2]
Therefore, they work in cooperation with the host defense system and endogenous AMPs to protect the skin. Moreover, the microbiota may act as an environmental filter 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 supporting a strong influence of the (genetically determined) immune system on the composition of the microbiota.[2]

On the other hand, after sensing the presence of microbiota through their Toll-like receptors (TLRs), epidermal Langerhans cells are able to instruct naive T cells to mount a Th17 response, which in turn will control AMP secretion by the keratinocytes. Beside the innate immune response, therefore, epidermal dendritic cells seem to educate the adaptive immune system and contribute to the complex dialogue that controls microbial growth in the skin.[2]

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