SKIN UNDER TRIPLE INFLUENCES : GUT, BRAIN, SKIN MICROBIOTA

BIOCODEX
Microbiota Institute

The skin has multiple functions: in addition to separating the body's interior from the external environment[1,2], it also protects against UV rays, plays a role in thermoregulation, gives us our sense of touch, and absorbs and synthesizes compounds.

Its barrier role is threefold. It acts as a **physical barrier** that protects the internal organs against environmental changes and pathogen invasions, a function aided by the continual regeneration of its epithelial cells.[2,3,4] The epidermis, dotted with hair follicles and glands that secrete lipids, antimicrobial peptides, enzymes, salts, and various other compounds, also acts as a **chemical barrier**: its acidic surface (pH between 4.5 and 5.5), which is often dehydrated, rich in salt, and with a relatively low temperature (29-34°C), make it a somewhat inhospitable environment for pathogens. Lastly, the keratinocytes in the epidermis act as an **active immune barrier**, monitoring for the presence of pathogens on the surface of the skin and, if necessary, triggering a host immune response.[2,3,4]

Despite this, the skin allows for the development of a commensal microbiota, or rather various skin microbiota whose composition varies according to the physico-chemical environment prevailing in a given skin area (face, armpits, etc.).

Like its counterpart in the gut, with which it communicates, the skin microbiota protects against pathogens, strengthens immunity and breaks down certain compounds.

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[1] Ederveen THA, Smits JPH, Boekhorst J *et al.* Skin microbiota in health and disease: From sequencing to biology. *J Dermatol.* 2020 Oct;47(10):1110-1118.
[2] Egert M, Simmering R, Riedel CU. The Association of the Skin Microbiota With Health, Immunity, and Disease. *Clin Pharmacol Ther.* 2017 Jul;102(1):62-69.
[3] Barnard E, Li H. Shaping of cutaneous function by encounters with commensals. *J Physiol.* 2017 Jan 15;595(2):437-450.
[4] Byrd AL, Belkaid Y, Segre JA. The human skin microbiome. *Nat Rev Microbiol.* 2018;16(3):143-155.

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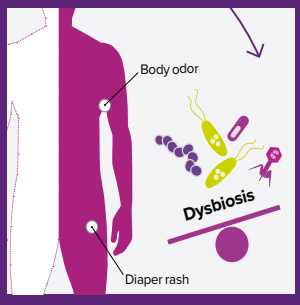

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1

THE SKIN MICROBIOTA

The fourth most populated microbial niche in the human body[2], the skin is home to a complex community of microorganisms.[2] Bacteria, fungi, parasites and viruses live together on the skin in a unique balance specific to each individual, to the point where some investigators speak of an individual microbial fingerprint.[5]

A unique set of skin microbiota for each individual

Each individual is not characterized by one but by multiple skin microbiota. In fact, the skin microbiota varies "horizontally", according to skin area (face, armpits, etc.), but also "vertically", according to the layers that make up the skin epithelium.

BACTERIA, FUNGI, VIRUSES AND PARASITES

Although easily accessible, the skin microbiota remains poorly understood. Its density is believed to be low compared to that of the large intestine, instead resembling that of the small intestine, i.e. around 10^{11} bacteria.[1] It is the fourth largest microbial niche in the body in terms of the number of microorganisms, just after the digestive tract, the oral cavity and the vagina.[2] It hosts **several bacterial phyla** (Actinobacteria, Firmicutes, Proteobacteria and Bacteroidetes), archaea, and fungal species mainly from the genus *Malassezia*.[2,3] Among the bacterial species identified are included *Cutibacterium acnes* and *Staphylococcus epidermidis,* although the strains present differ depending on the individual, the state of their skin (healthy or otherwise) and the sampling site.[3,6]

Lastly, although not well described[2], numerous viruses (papillomavirus, adenovirus, etc.) have been identified on the skin of healthy individuals, as well as phages that target *C. acnes* and *S. epidermidis*, suggesting the existence of a complex virome. **Parasites** (such as *Demodex* mites, etc.), few in number, are even more scantly described.[3]

"HORIZONTAL" VARIATION ACCORDING TO SKIN AREA

The skin is not a homogeneous habitat. The surface of the skin is acidic, salty and aerobic, whereas the invaginations of the hair follicles offer a lipid-rich and anaerobic environment[6]. Three major niches are generally identified based on properties such as pH, temperature, humidity, perspiration levels and lipid content:[1,3,4]

- **sebaceous areas** (face, chest, back) that secrete lipid-rich sebum;
- **dry areas** (forearms, palm of the hand);
- **humid areas** (armpits, elbow crease, nostril, back of the knee and groin), where numerous sweat glands participate in thermoregulation (sweat), acidify the skin and secrete antibacterial peptides.

Some authors distinguish a fourth area in the foot (nails, heel and space between toes)[4] (see table).

These areas are separate ecological niches, each with a unique microbial community: the most exposed and dry areas, such as the hands, are the most diverse; the armpit, which is moist and rich in sweat, is dominated by *Corynebacterium* and *Staphylococcus* species; while lipid-rich areas, such as the face, display much less diversity (*Cutibacterium* bacteria, fungi of the genus *Malassezia*, and *Demodex folliculorum* mites).[3]

Microbiota also vary in density from one skin area to another: from 10^2 bacteria

[5] Bay L, Barnes CJ, Fritz BG *et al.* Universal Dermal Microbiome in Human Skin. *mBio.* 2020 Feb 11;11(1):e02945-19.
[6] Chen YE, Fischbach MA, Belkaid Y. Skin microbiota-host interactions. *Nature*. 2018 Jan 24;553(7689):427-436.

TOP 3 MOST ABUNDANT MICROORGANISMS BY SKIN AREA

	Dry areas	Humid areas	Sebaceous areas	Foot
Bacteria	• *Cutibacterium acnes* • *Corynebacterium tuberculostearicum* • *Streptococcus mitis*	• *Corynebacterium tuberculostearicum* • *Staphylococcus hominis* • *Cutibacterium acnes*	• *Cutibacterium acnes* • *Staphylococcus epidermidis* • *Corynebacterium tuberculostearicum*	• *Corynebacterium tuberculostearicum* • *Staphylococcus hominis* • *Staphylococcus warneri*
Eukaryotes (fungi, parasites)	• *Malassezia restricta* • *Malassezia globosa* • *Aspergillus tubingensis*	• *Malassezia globosa* • *Malassezia restricta* • *Tilletia walkeri*	• *Malassezia restricta* • *Malassezia globosa* • *Malassezia sympodialis*	• *Malassezia restricta* • *Trichophyton rubrum* • *Malassezia globosa*
Viruses	• *Molluscum contagiosum* virus • *Cutibacterium* phage • Merkel cell polyomavirus	• *Molluscum contagiosum* virus • *Cutibacterium* phage • *Human polyomavirus 6* (HPyV6)	• *Cutibacterium* phage • *Molluscum contagiosum* virus • Merkel cell polyomavirus	• *Cutibacterium* phage • Merkel cell polyomavirus • *Alphapapillomavirus*

Source: adapted from Byrd *et al.*, 2018[4]

per cm^2 on the fingertips or back, to 10^6 bacteria per cm^2 on the forehead or in the armpits.[2]

"VERTICAL" VARIATION ACCORDING TO SKIN LAYER

For a long time, it was thought that microbial life in the skin was limited to the epidermis, hair follicles, and sebaceous and sweat glands. However, microorganisms **also seem to live in the deeper layers of the skin,** i.e., the dermis and the underlying adipose tissue.[2]

On the skin's surface, the deeper into the *stratum corneum* the fewer microorganisms are present.[1] Then, from the surface to the subcutaneous regions, the microbiota changes and gradually loses its individual characteristics.[4,5] In the dermis and subcutaneous adipose tissues, there seems to be more Proteobacteria while there are less Actinobacteria and Firmicutes than in the epidermis.[2]

Factors affecting the skin microbiota

The skin microbiota of healthy individuals appears to be relatively stable over periods of a few months or years.[3,4] However, its composition is still influenced by the host and its environment.

HOST-RELATED EFFECTS

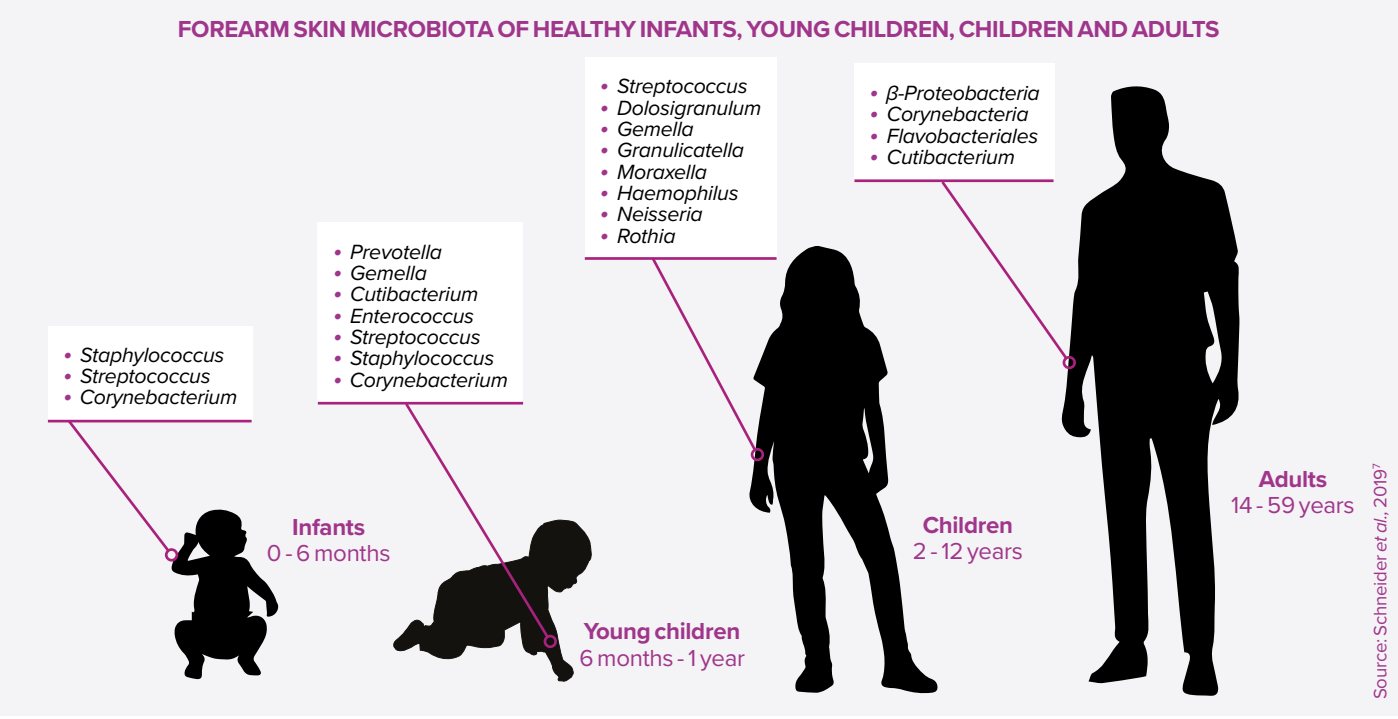
The composition of the skin microbiota is **strongly influenced by the host,** specifically by their age, sex, genes, immune status, concomitant health conditions (dermatological or otherwise), the skin area in question, interactions between microorganisms, diet and stress levels.[2] The initial colonization of a **newborn** baby's skin depends on the mode of delivery[4,7]: children born vaginally acquire vaginal bacteria (*Lactobacillus, C. albicans*), while those born by caesarean section acquire skin microbes (*Staphylococcus, Streptococcus*). Within a few hours of birth, sebum secretion increases sharply. This continues for several days before decreasing.[2] The immature immune system facilitates colonization due to the lack of any inflammatory response.[4] At **puberty**, the skin microbiota undergoes a profound restructuring due to hormonal changes that stimulate sebaceous secretions. It contains more lipophilic organisms (*Cutibacterium, Malassezia*), whereas previously it had been dominated by Firmicutes, Bacteroidetes and Proteobacteria, with a diverse fungal community.[4]

ENVIRONMENTAL EFFECTS

Many external factors also influence the composition of the skin microbiota[2], including lifestyle, domestic and personal hygiene, cohabitation, geographical location, sunlight, occupation (and work clothing), etc. For example, contact with other humans, but also with pets and

[7] Schneider AM, Nelson AM. Skin microbiota: Friend or foe in pediatric skin health and skin disease. *Pediatr Dermatol.* 2019 Nov;36(6):815-822.

objects (telephone, computer keyboard, classroom objects, etc.), modifies the skin microbiota and explains the similarities observed between the microbiota of members of the same household or group.[3] Moreover, the conditions in a given environment affect the different areas of the skin to different degrees. For example, some skin areas (e.g. hand) have more physical contact, others are less exposed to ultraviolet light, etc.[3,4] Despite this, the skin microbiota remains **relatively stable in adulthood,** suggesting reciprocal beneficial interactions between microorganisms and host.[6]



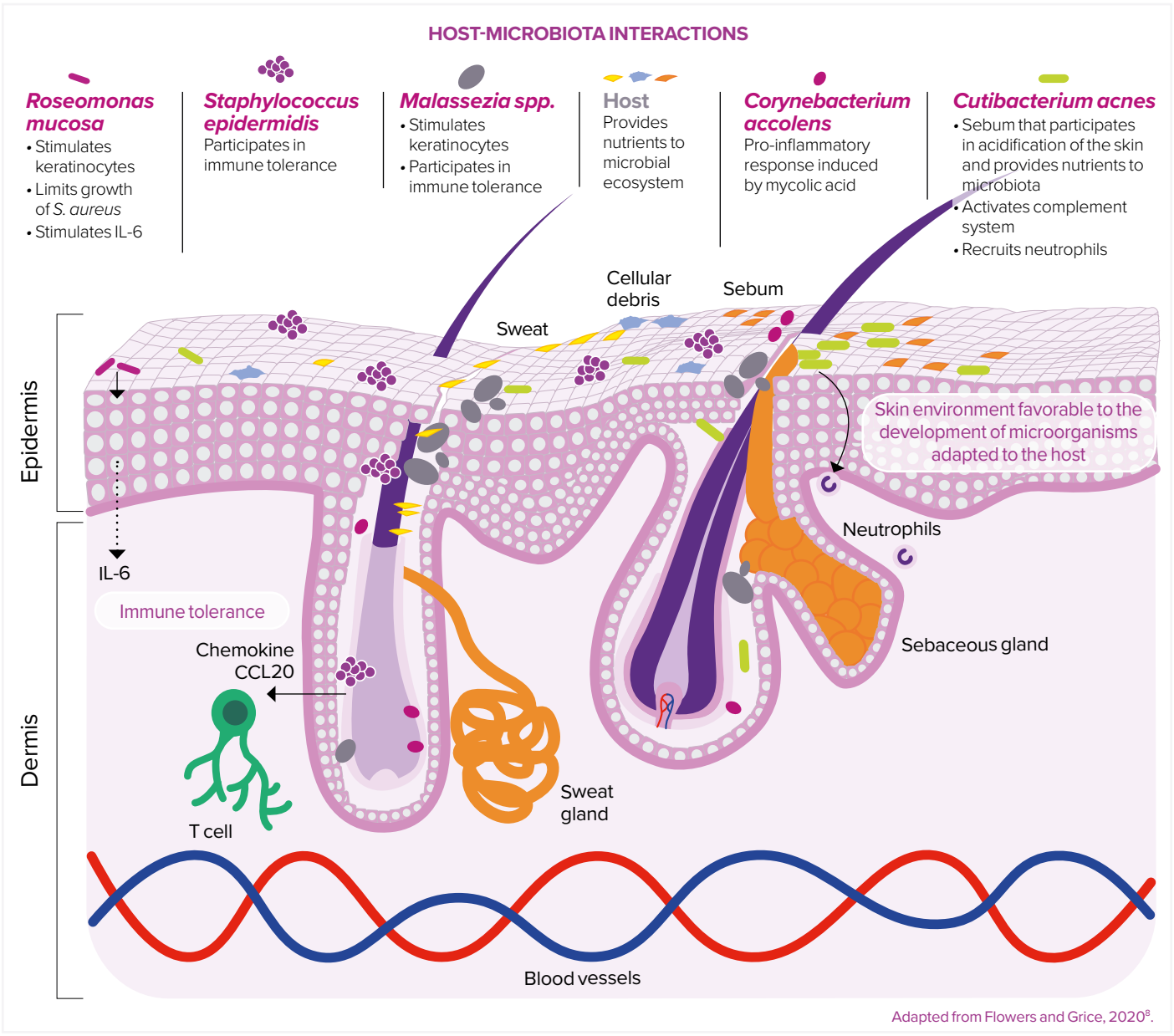
Functions of the microbiota and its interactions with the host

For a long time, the skin microbiota was considered a potential source of infection. Now we know it to be an important factor in host health[2], even if its interactions with the body are only beginning to be understood.

REDUCED COLONIZATION BY PATHOGENS

Although it remains difficult to define, a **"healthy" skin microbiota** is generally considered synonymous with a diversified flora and the presence of commensal bacteria.[2] This balanced microbiota is thought to help **protect against infection**, limiting colonization by pathogens. For example, *C. acnes*, which lives in the sebaceous glands, releases fatty acids from sebum, contributing to the acidity of the skin, which in turn inhibits the proliferation of pathogens.[8] Other bacteria secrete bacteriocins and other antimicrobial factors. For example, *S. epidermidis* releases a protease that destroys *S. aureus* biofilms, while nasal bacterium, *Staphylococcus lugdunensis*, produces an antibiotic peptide that acts against many pathogens, including *S. aureus*, *Enterococcus faecalis*, *Listeria monocytogenes*, *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa*.[2] Lastly, *Corynebacterium striatum* modifies the transcriptional program of *S. aureus*, repressing virulence-related genes and stimulating those associated with commensalism.[6,8] The skin microbiota thus maintains its balance not only by competitive exclusion but also via subtle interactions between microorganisms.[6]

[8] Flowers L, Grice EA. The Skin Microbiota: Balancing Risk and Reward. *Cell Host Microbe*. 2020;28(2):190-200.



Skin microbiota-host interactions promote skin homeostasis and immune responses.

MODULATION OF THE IMMUNE SYSTEM

The skin microbiota also plays a key role in the development and regulation of the **innate and acquired immune systems.**[2] It modulates the expression of innate immune factors (interleukin IL-1α, antimicrobial peptides, etc.) produced by keratinocytes and sebocytes[6], and even produces some of these factors itself. For example, *S. epidermidis* can, in different situations, either **stimulate or reduce inflammation**: it inhibits the release of inflammatory cytokines by keratinocytes and the immune responses of injured skin cells; it reinforces the skin's defense mechanisms against infection by increasing the expression of genes that encode for antimicrobial peptides; and it modulates the expression of skin T cells.[2] *S. epidermidis promotes* tolerance towards the commensal microbiota, while adjusting immune responses to pathogens or those triggered during wound healing.[8] *Roseomonas mucosa, Malassezia spp.* or *Corynebacterium accolens* can also modulate host and keratinocyte immune responses.[8] Lastly, the genetic profile of bacteria also plays a role. *Cutibacterium acnes* strains from acne-prone skin have genes that encode for virulence factors, which could explain the higher pro-inflammatory activity observed. Conversely, strains from healthy skin, which do not have these factors, are thought to promote the production of anti-inflammatory cytokines.[8]

2

SKIN DISEASES ASSOCIATED WITH A DYSBIOSIS

The skin microbiota is a dynamic system in which microorganisms constantly compete to survive. Sometimes this balance breaks down, commensal bacteria become opportunistic pathogens[1,4] and a dysbiosis results: it is a common feature in skin diseases (acne, psoriasis, dermatitis, etc.) and other non-pathological skin conditions (irritation, wounds, odors). However, it is not yet known whether dysbiosis is a cause or effect.

Skin diseases associated with a dysbiosis

Acne, psoriasis, rosacea... Many skin diseases are associated with a dysbiosis. This may have diagnostic or predictive value or even open up novel therapeutic approaches.[2]

SKIN CANCER

Pathophysiology: in many cutaneous neoplasms, dysbiosis appears to be involved in carcinogenesis.[9,10,11,12] Conversely, a healthy microbiota may inhibit the development of tumors by regulating the immune system and controlling inflammation.

Role of the microbiota:

- *S. aureus, Streptococcus pyogenes, Pseudomonas aeruginosa,* the β-human **papillomavirus**, the **Epstein Barr** virus and *Malassezia* or *Candida* fungi may induce a state of chronic inflammation, leading to cancer;[16]
- link between *S. aureus* infection and severity of cutaneous T cell lymphoma.[12]

PSORIASIS

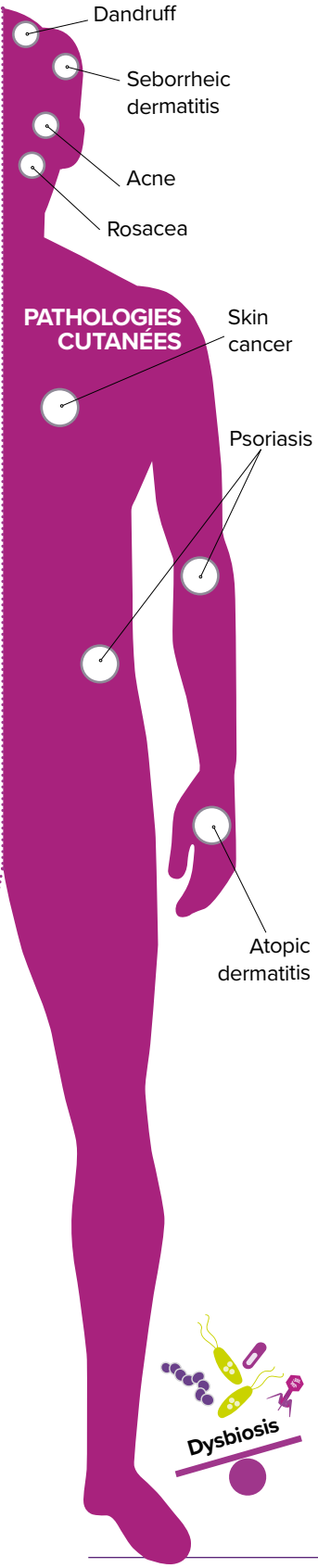
Pathophysiology: multifactorial immune-mediated disease, involving genetic factors, immune system disturbances and environmental triggers.[13]

Prevalence: affects 2%-3% of the population, often appearing between 15 and 20 years of age[11] with two common peaks of incidence (20-30 years of age and 50-60 years of age).[13].

Role of the microbiota:

- psoriasis patients see an **alteration** in the composition of their skin microbiota and a **loss of microbial diversity**[11], which affects not only the lesions, but the skin microbiota as a whole.[11]
- **microorganisms associated with the disease still not clearly identified**[1,11], with numerous contradictory data. However, *S. aureus* thought to be more abundant and to participate in inflammation (by increasing the response of Th17 cells, which release pro-inflammatory cytokines);[11]
- often associated with gut dysbiosis.[14]

[9] Dréno B, Dagnelie MA, Khammari A, et al. The Skin Microbiome: A New Actor in Inflammatory Acne. *Am J Clin Dermatol.* 2020 Sep;21(Suppl 1):18-24.
[10] Heng, A.H.S., Chew, F.T. Systematic review of the epidemiology of acne vulgaris. *Sci Rep* 10, 5754 (2020). https://doi.org/10.1038/s41598-020-62715-3
[11] Ellis SR, Nguyen M, Vaughn AR, et al. The Skin and Gut Microbiome and Its Role in Common Dermatologic Conditions. *Microorganisms*. 2019;7(11):550.
[12] Yu Y, Dunaway S, Champer J, Kim J, Alikhan A. Changing our microbiome: probiotics in dermatology. *Br J Dermatol.* 2020;182(1):39-46.
[13] Rigon, R. B., de Freitas, A. C. P., Bicas, J. L., Cogo-Müller, K., Kurebayashi, A. K., Magalhães, R. F., & Leonardi, G. R. (2020). *Skin Microbiota as a Therapeutic Target for Psoriasis Treatment: Trends and Perspectives. Journal of Cosmetic Dermatology.* doi:10.1111/jocd.13752



ACNE

Pathophysiology: multifactorial chronic inflammatory disease involving hyperseborrhea, abnormal keratinization of follicular ducts and a dysbiosis of the skin microbiota associated with a predominance of virulent *C. acnes* phylotypes.[9]

Prevalence: 8th most common skin disease, affecting 9.38% of the world's population (all ages), with higher prevalence in adolescents, reaching 35%-100% in some countries.[10]

Role of the microbiota:

- loss of balance between the different *C. acnes* phylotypes (the more virulent phylotype IA$_1$ becomes dominant and induces inflammation by activating the innate immune system);[9]
- loss of reciprocal control between *C. acnes* (maintains acidic pH, inhibits the development of *S. epidermidis*) and *S. epidermidis* (anti-inflammatory activity, limits the proliferation of *C. acnes*);[9]
- suspected secondary pro-inflammatory role (folliculitis) of opportunistic fungal species of the pilosebaceous apparatus (*Malassezia* and possibly *Candida*);[11]
- additional effect of **diet** on acne severity (interaction with gut microbiota).[9]

ATOPIC DERMATITIS (ECZEMA)

Pathophysiology: chronic inflammatory skin disease with a strong genetic component involving a disruption of the skin barrier and immune system (inflammatory Th2 cells), resulting in increased susceptibility to infections and allergens.[11,15]

Prevalence: up to 20% of infants and 3% of adults worldwide[11], and up to 10% of adults in developed countries.[14]

Role of the microbiota:

- patients see a **loss of diversity** in the skin microbiota[11,12], both in lesions and healthy areas;
- increase in content of **staphylococci, with a proliferation of *S. aureus*** linked to a lower production of antimicrobial peptides by keratinocytes via the influence of Th2 cells.[15] Increased presence of *S. epidermidis* in less severe forms;[12]
- a higher density of colonization with *S. aureus* correlated with more inflammation and increased disease severity.[11]

SEBORRHEIC DERMATITIS (SD) AND DANDRUFF

Pathophysiology: chronic skin disease involving a complex interaction between the *Malassezia fungus*, keratinocytes, and the inflammatory response induced by an altered lipid composition in the skin.[12,18]

Prevalence: three peaks of incidence (early childhood, adolescence and from the age of 50 onwards). Half of adult population thought to be affected by DS and dandruff.[11,18]

Dysbiosis/role of microbiota:

- **hydrolysis by *Malassezia* of skin lipids** into free fatty acids that trigger an inflammatory response;[16]
- increased presence of *Malassezia* species, with *M. restricta, M. globose* and *M. furfur* the most commonly associated with seborrheic dermatitis. The first two species are the most virulent (they produce irritating oleic acids, leading to IL-8 and IL-17 activation);[17]
- *Actinetobacter*, *Staphylococcus* and *Streptococcus* dominate microbiota in the lesions;[11]
- correlation between disease severity and decreased bacterial diversity; no correlation with *Malassezia* abundance.[12]

ROSACEA

Pathophysiology: chronic inflammatory disease whose pathophysiology is not fully understood. Factors include neurovascular reactivity, genetic susceptibility, dysfunction of the innate immune responses, and comorbid gastrointestinal conditions.[17]

Prevalence: between 0.9% and 10% of the population in the US and Europe.[11]

Role of the microbiota:

- *Demodex folliculorum* (a sebaceous gland mite) stimulates the production of inflammatory peptides and cellular growth factors. This mite may also carry *Bacillus oleronius*, a pro-inflammatory bacterium;[11]
- a variant of *S. epidermidis*, more virulent than the commensal bacterium, also thought to be involved;[11]
- often associated with a gut dysbiosis.[18]

[14] Szántó M, Dózsa A, Antal D *et al.* Targeting the gut-skin axis-Probiotics as new tools for skin disorder management? *Exp Dermatol.* 2019 Nov;28(11):1210-1218.
[15] Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. *Lancet.* 2020 Aug 1;396(10247):345-360.
[16] Squarzanti DF, Zavattaro E, Pizzimenti S *et al.* Non-Melanoma Skin Cancer: news from microbiota research. *Crit Rev Microbiol.* 2020;46(4):433-449.
[17] Tutka K, Żychowska M, Reich A. Diversity and Composition of the Skin, Blood and Gut Microbiome in Rosacea-A Systematic Review of the Literature. *Microorganisms.* 2020;8(11):1756.
[18] Adalsteinsson JA, Kaushik S, Muzumdar S et al. An update on the microbiology, immunology and genetics of seborrheic dermatitis. *Exp Dermatol.* 2020;29(5):481-489.

Non-pathological skin conditions associated with a dysbiosis

Changes in the skin microbiota can also be seen in non-pathological skin conditions. The skin is constantly exposed to various endogenous, exogenous and lifestyle factors that can affect the physical, mechanical or microbial properties of the skin barrier.[19]

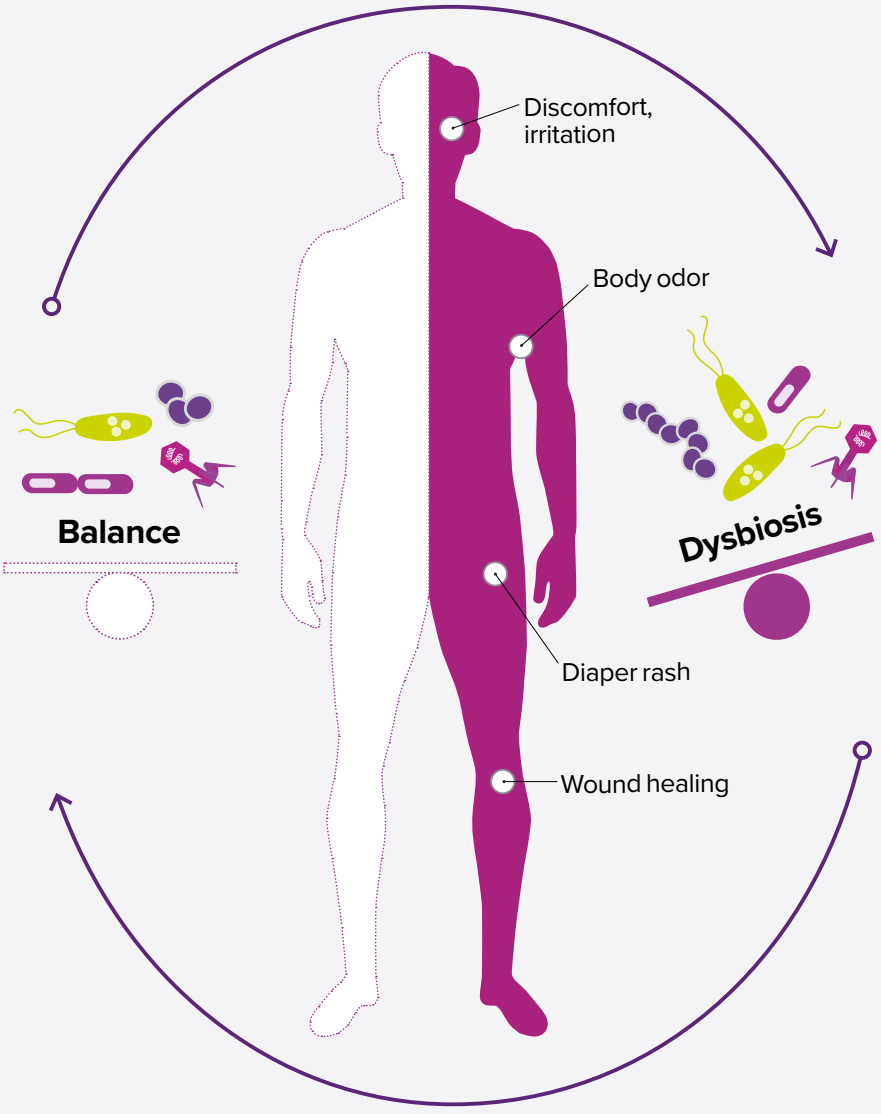
DISCOMFORT, IRRITATION, DIAPER RASH

Sensitive skin "tightens", tingles or burns in response to stimuli that would not normally cause such sensations. It is seen both in people with normal skin and in those with a disruption of the skin barrier.[19] A hyperreactive cutaneous nervous system, the skin barrier and the skin microbiota are thought to be involved.[19] An alteration of the *stratum corneum* in sensitive subjects may contribute to penetration by chemical, environmental and microbial agents associated with increased skin sensitivity.[19]

Diaper rash only affects skin exposed to diaper friction, excessive hydration and a variable pH, and in constant contact with

Skin sensitivity may be linked to a hyperactive cutaneous nervous system, to the skin barrier and the skin microbiota.

SKIN DYSBIOSIS IS ALSO CHARACTERISTIC OF NON-PATHOLOGICAL SKIN CONDITIONS



Adapted from Barnard and Li, 2017[3].

[19] Seite S, Misery L. Skin sensitivity and skin microbiota: Is there a link? *Exp Dermatol.* 2018 Sep;27(9):1061-1064.

urine and feces. *Candida albicans* and *Staphylococcus aureus* are potentially involved.[20]

WOUND HEALING

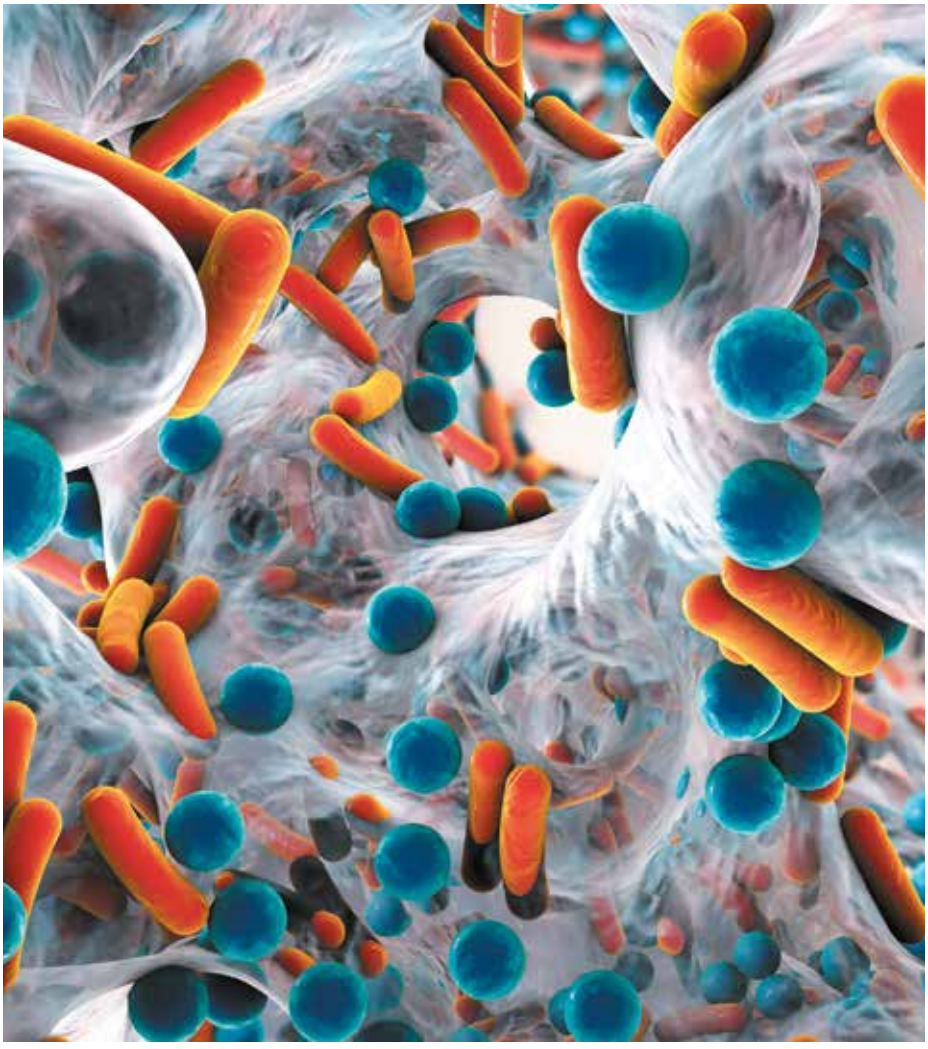
As a result of the physical tear of skin tissue, the wound healing process begins with **inflammation** that results from close cooperation between immune cells and bacteria involved in the process.[21] Commensal bacteria such as *Staphylococcus, Streptococcus*, *Pseudomonas* and *Corynebacterium* have both positive and negative effects on wound healing. They stimulate the host immune system and reduce invasion by other pathogenic microorganisms, but this loss of microbial diversity is often accompanied by prolonged inflammation, which may slow wound healing.[21]

This close relationship between host and skin microbiota in wound healing processes could open the door to novel therapies, such as creams rich in antimicrobial peptides, biofilm-destroying probiotics or anti-inflammatory bacteria.[12,21]

BODY ODOR

Human body odors result from the **metabolization by bacteria** of sweat components (amino acids, fatty acids and glycerols), leading to the production of malodorous molecules, e.g. the "sulfurous" or "sour" odor of acetic acid produced by *Staphylococcus spp.* in children and adolescents, or the "sour" odor of thiols produced by *Corynebacterium* and *Staphylococcus spp.* in adults.[7]

The repeated use of deodorants and antiperspirants alters bacterial diversity in the armpit, favoring staphylococci over *Corynebacterium*, which may have counterproductive effects in adolescents.[7]



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Bacterial biofilms can form during wound healing.

EXPERT OPINION
DR MARKUS EGERT

Could probiotics be a third option for dealing with body odors, in addition to the two classical strategies, alcohol-based deodorants and antiperspirants?

I think it's possible that the regular, long-term application of a body odor product containing live microorganisms could change the microbiota of the armpit so that it's less prone to producing odors. However, I suspect this would have a very mild effect and would probably be less effective than the antimicrobial effect of alcohol. Also, probiotics would not be able to prevent underarm dampness (sweat production) with the same effectiveness as the aluminum chlorohydrate that blocks sweat pores in antiperspirants.

[20] Šikić Pogačar M, Maver U, Marčun Varda N et al. Diagnosis and management of diaper dermatitis in infants with emphasis on skin microbiota in the diaper area. *Int J Dermatol.* 2018;57(3):265-275.
[21] Johnson TR, Gómez BI, McIntyre MK, et al. The Cutaneous Microbiome and Wounds: New Molecular Targets to Promote Wound Healing. *Int J Mol Sci.* 2018;19(9):2699.

3

THE GUT-SKIN AXIS

Laced with blood vessels, packed with nerves, heavily involved in the immune system and massively colonized by microbial communities, the gut and the skin have a number of things in common[22]. But that's not all. Recent years have seen growing evidence for the existence of a link between the gut and the skin (the gut-skin axis) or even the gut-brain-skin axis[23].

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[22] O'Neill CA, Monteleone G, McLaughlin JT, Paus R. The gut-skin axis in health and disease: A paradigm with therapeutic implications. *Bioessays.* 2016;38(11):1167-1176.
[23] Salem I, Ramser A, Isham N, Ghannoum MA. The Gut Microbiome as a Major Regulator of the Gut-Skin Axis. *Front Microbiol.* 2018 Jul 10;9:1459.

MOLECULES SYNTHESIZED BY GUT BACTERIA THAT MAY DIRECTLY OR INDIRECTLY AFFECT THE SKIN

Molecule	Synthesizing bacteria	Potential/documented effects on the skin
Short-chain fatty acids (SCFAs), e.g. butyrate, acetate, proprionate	*Bacteroides, Bifidobacterium, Propionibacterium, Eubaterium, Lactobacillus, Prevotella*	Anti-inflammatory effects
Tryptamine	*Lactobacillus/Bacillus* spp.	Itching
Trimethylamine	*Bacillus* spp.	Prevents keratinocyte fragility
Acetylcholine	*Lactobacillus/Bifidobacterium* spp.	Barrier function
GABA	*Lactobacillus/Bifidobacterium* spp.	Inhibits itching
Dopamine	*Eschericia/Bacillus* spp.	Inhibits hair growth
Serotonin	*Eschericia/Streptococcus/Enterococcus* spp.	Synthesis of melatonin

Source : O'Neill *et al.*, 2016[22]

Psoriasis, atopic dermatitis and rosacea: gut-skin axis involved

The gut microbiota appears to play an active role in the pathogenesis of various skin diseases, including psoriasis, rosacea and atopic dermatitis. Three mechanisms are at play: the composition of the skin microbiota, the skin's barrier effect and the skin's immune response.

Skin ulcers or psoriasis in patients with inflammatory bowel disease (IBD), dermatitis and psoriasis in celiac patients, a gut dysbiosis and *H. pylori* infection in people with rosacea... There are many examples of associations between digestive and skin conditions.[22]
Although the gut-skin axis is not fully understood, several explanations have been put forward.

COMPOSITION OF THE SKIN MICROBIOTA

The gut microbiota may influence the composition of the skin microbiota.[23] **Short-chain fatty acids** (SCFAs, e.g. acetate, propionate) produced by the gut microbiota via fiber fermentation in the gut **may modify the predominance of certain microorganisms** or microbial profiles in the skin. For example, gut bacterium *Propionibacterium* (see table) mainly produces acetate and propionate. Propionic acid has an antimicrobial effect against certain skin pathogens, particularly methicillin-resistant *Staphylococcus aureus.*[23] In contrast, commensal skin bacteria *S. epidermidis* and *Cutibacterium acnes* have been shown to tolerate wider shifts in SCFAs.[23]

INTEGRITY OF THE SKIN BARRIER

Children with atopic dermatitis also seem to suffer from a gut dysbiosis. A damaged gut barrier sees increased **penetration by food antigens, bacterial toxins and pathogens**.[14] For example, gut bacteria, especially *Clostridiales difficile*, can produce free phenol and p-cresol, which can disturb the skin barrier and reduce keratin production.[14,22,23]
A low level of vitamin D has been associated with atopic dermatitis and psoriasis. Vitamin D may be regulated by the gut microbiota and may participate in a signaling mechanism between microbiota and host.[14]
In the case of acne, microbial metabolites may regulate various skin functions (cell proliferation, lipid metabolism, etc.) via other metabolic pathways.[14] A high glycemic load, typical of adolescent meals in developed countries, in-

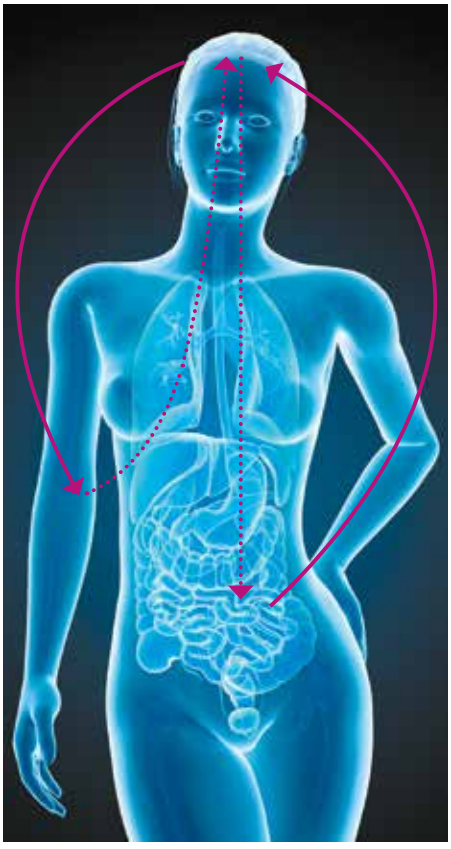
fluences insulin metabolism, ultimately triggering sebaceous gland hyperproliferation, lipogenesis and hyperplasia of keratinocytes, thereby contributing to the development of acne.[14,23] This appears to be a two-way process, with the metabolic pathway in turn affecting the composition of the gut microbiota via the gut barrier. This may result in a vicious circle via a positive feedback cycle of inflammation.[23]

IMMUNE RESPONSE OF THE SKIN

The mechanisms by which the gut microbiota acts on the skin microbiota may also involve the modulating effect of gut microorganisms on systemic immunity.[22] Some gut microbes and metabolites facilitate anti-inflammatory responses[24]. For example, SCFAs are thought to exert **local and remote anti-inflammatory effects**, particularly on the skin.[22] Conversely, other metabolites may participate in the inflammatory loop and the appearance of skin diseases. For example, filamentous bacteria may promote the accumulation of pro-inflammatory Th17 and Th1 cells.[23]

In the case of rosacea, some authors suggest a link with *Helicobacter pylori*. This bacterium may exert pro-inflammatory effects via peptides.[11,22]

Other mechanisms have been mentioned in psoriasis, involving a decrease in beneficial species such as *Faecalibacterium prausnitzii*[13] or *Akkermansia muciniphila*, with the latter thought to strengthen the integrity of the gut epithelium and protect against inflammatory diseases.[11] Psoriasis patients whose blood contains bacterial DNA, have significantly higher levels of systemic inflammatory response markers, including IL-1β, IL-6, IL-12, tumor necrosis factor, and interferon γ.[11]



A gut-brain-skin axis?

Should we go further than a gut-skin axis and include the brain also?

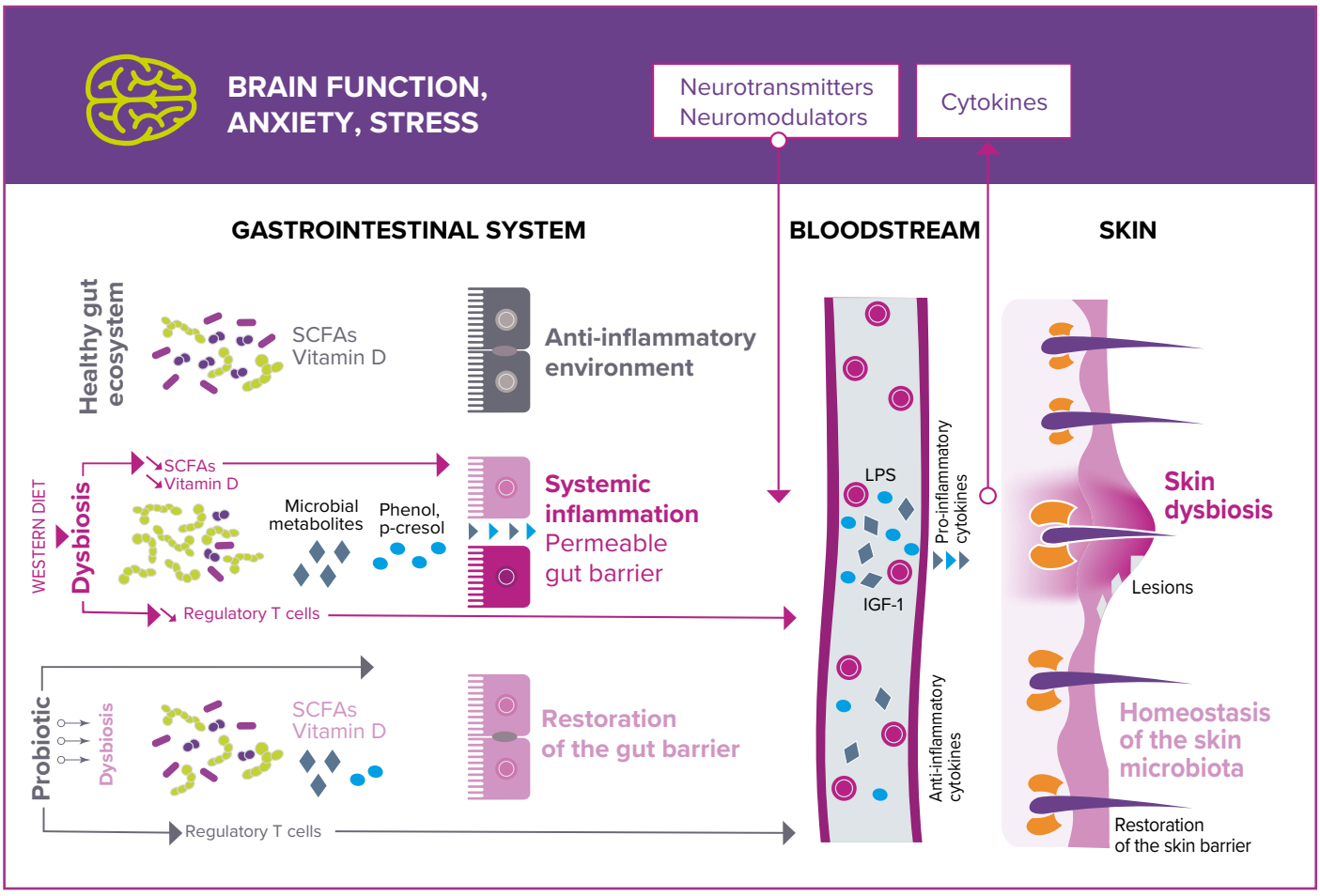
As early as 1930, dermatologists John Stokes and Donald Pillsbury[25,26], suggested that emotional states such as anxiety or depression can alter the gut microbiota and induce local or systemic inflammation[27]. They recommended the use of fermented milk to reintroduce beneficial microorganisms. More precisely, stress leads to the secretion of neurotransmitters (serotonin, norepinephrine and acetylcholine). These neurotransmitters increase **gut permeability**, leading to **local inflammation**. At the same time, they also provoke **systemic inflammation** via the bloodstream.[11,23]

For example, stress hormone cortisol is thought to alter the composition of the gut microbiota and blood levels of

Is the gut-brain-skin axis a two-way axis, i.e. can the skin in turn act on the gut via the nervous system?[22]

[24] Forbes JD, Van Domselaar G, Bernstein CN. The Gut Microbiota in Immune-Mediated Inflammatory Diseases. *Front Microbiol.* 2016 Jul 11;7:1081.
[25] Lee SY, Lee E, Park YM, Hong SJ. Microbiome in the Gut-Skin Axis in Atopic Dermatitis. *Allergy Asthma Immunol Res.* 2018;10(4):354-362. doi:10.4168/aair.2018.10.4.354.
[26] Stokes JH, Pillsbury DH: The effect on the skin of emotional and nervous states: theoretical and practical consideration of a gastrointestinal mechanism. *Arch Dermatol Syphilol* 1930, 22:962-93.

CONTRIBUTION OF THE GUT-BRAIN-SKIN AXIS TO SKIN INFLAMMATION



Adapted from Szántó *et al.*, 2019[14], Lee *et al.* 2018[25]

A gut dysbiosis makes the gut barrier more permeable to pro-inflammatory cytokines which, via the bloodstream, are thought to play a role in skin dysbiosis. In addition, a gut dysbiosis may modify the production of various neurotransmitters and neuromodulators, also affecting skin function. By restoring the gut barrier, probiotics may help restore skin homeostasis.
LPS = lipopolysaccharides; IGF-1 = insulin-like growth factor 1

neuroendocrine molecules (tryptamine, trimethylamine and serotonin), ultimately affecting the skin barrier and skin inflammation.[25]

ACNE AND ATOPIC DERMATITIS

This gut-brain-skin axis is implicated in certain skin diseases. For example, upregulation and strong expression of substance P (a neurotransmitter and neuromodulator of the central and peripheral nervous systems) are observed in both **acne** and gut dysbiosis. Substance P is known to trigger the expression of many pro-inflammatory mediators implicated in the development of acne (IL-1, IL-6, TNF-α, PPAR-γ).[22,23]
The gut-brain-skin axis is also thought to be involved in **atopic dermatitis**.[25] An altered gut microbiota may modify the production of various neurotransmitters and neuromodulators, affecting the functioning of the skin barrier and immune system, two key parameters of the pathophysiology of atopic dermatitis.[25] Tryptophan produced by the gut microbiota is thought to cause skin itching, while lactobacilli and bifidobacteria may inhibit these sensations.[25] Moreover, some researchers ask whether the gut-brain-skin axis is a two-way axis: can the skin in turn act on the gut via the nervous system?[22]

[27] Bowe WP, Logan AC. Acne vulgaris, probiotics and the gut-brain-skin axis - back to the future?. *Gut Pathog.* 2011;3(1):1. Published 2011 Jan 31. doi:10.1186/1757-4749-3-1

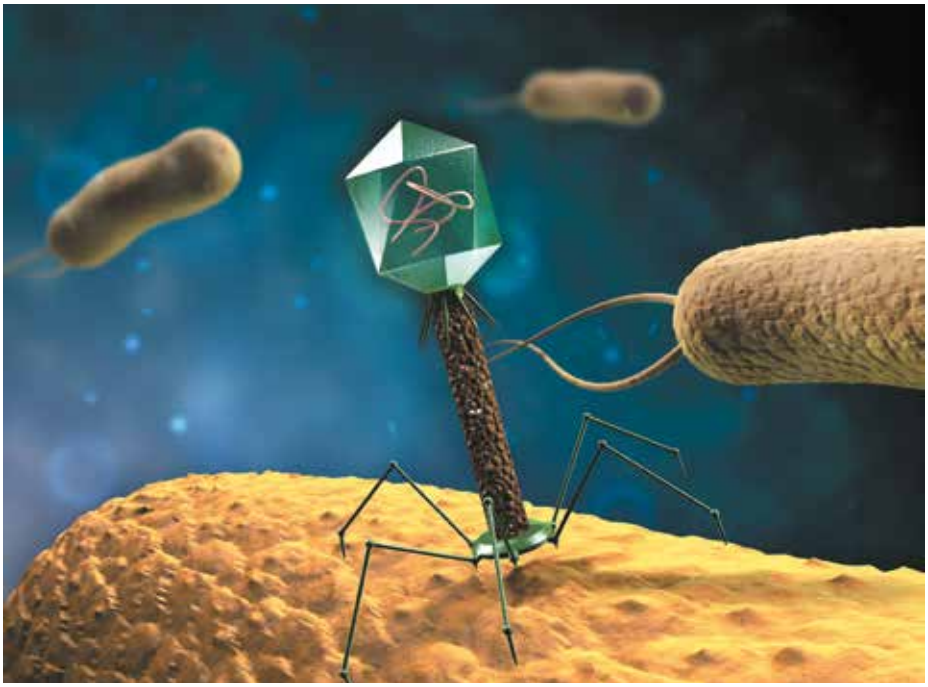
4

MODULATING THE SKIN MICROBIOTA

Preventing and treating dysbiosis without eliminating pathogens: novel therapeutic strategies aim to rebalance the skin microbiota directly via topical applications, or indirectly via oral solutions that modulate the gut ecosystem.

Modulating the skin microbiota via topical applications

The first clinical trials seem to support the use of topical applications to rebalance the skin microbiota. However, further trials are needed to confirm these results.



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For acne, creams containing *S. epidermidis* or bacteriophages of *C. acnes* that preferentially target pathogenic strains have shown positive results.[12]

In general, there have been few clinical trials evaluating the topical application of probiotics in skin diseases.[12] For **acne**, creams containing *S. epidermidis* or bacteriophages of *C. acnes* that preferentially target pathogenic strains have shown positive results.[12] The application of *R. mucosa* in patients with **atopic dermatitis** may reduce lesion severity, the need to use topical steroids and the presence of *S. aureus.*[28,29] The limited availability of microbial candidates on the skin has forced researchers to also use other sources of microorganisms. Derived from thermal spring water, *Vitreoscilla filiformis* may be beneficial in **seborrheic dermatitis:** one study

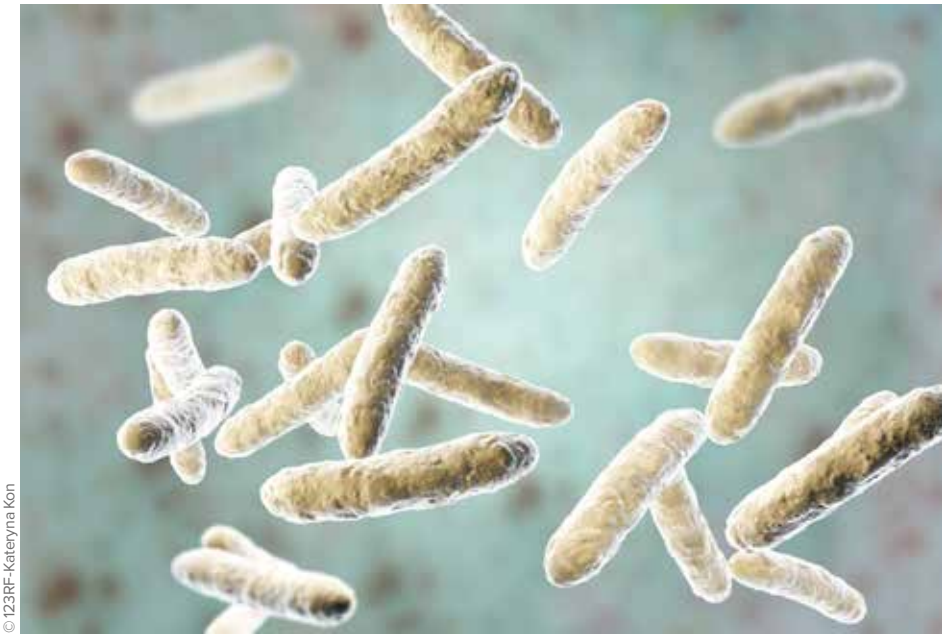
[28] Myles IA, Earland NJ, Anderson ED, *et al.* First-in-human topical microbiome transplantation with Roseomonas mucosa for atopic dermatitis. *JCI Insight.* 2018;3(9):e120608.
[29] Drago L, Toscano M, De Vecchi E, Piconi S, Iemoli E. Changing of fecal flora and clinical effect of L. salivarius LS01 in adults with atopic dermatitis. *J Clin Gastroenterol.* 2012;46 Suppl:S56-S63.

reported a reduction in erythema, desquamation and pruritus by soothing the inflammation.[12] In **acne**, *Nitrosomonas eutropha* decreases lesion severity[12], while the topical use of bacterial products (*E. faecalis* enterocins) reduces lesions by 60% compared to controls.[12] An alternative strategy corrects the dysbiosis by using sucrose to promote the growth of *S. epidermidis* over *C. acnes*.[9] Scientific data are scant for **skin cancer** and non-existent for **rosacea**. In murine models of UV-related cancers, a molecule produced by *S. epidermidis* was shown to inhibit tumor proliferation.[12,16]

Modulating the skin microbiota with oral solutions

The existence of a gut-skin axis suggests the possibility of influencing the skin microbiota by modulating the gut microbiota. Pre- and probiotic oral solutions are therefore an option.

In numerous murine models, a *Lactobacillus*-enriched diet reduces skin sensitivity, rash, inflammation, dermatitis, etc., and improves skin phenotype (increased dermal thickness, enhanced folliculogenesis and increased sebocyte production).[23] These beneficial probiotic effects have been confirmed by several interventional studies in humans involving lactobacilli and/or bifidobacteria.[23] Managing skin diseases by modulating the gut microbiota will most likely involve probiotics (beneficial live bacteria), prebiotics (bacterial substrates) and symbiotics (combinations of pro- and prebiotics).[23]



In mice, a Lactobacillus-enriched diet reduces skin sensitivity and improves skin phenotype.[23]

A lack of adverse effects makes oral probiotics of even greater interest for the management of skin diseases.[14]
For example, in **atopic dermatitis**, daily consumption of probiotics (*Bifidobacterium*) and prebiotics (galacto-oligosaccharides) improves skin hydration in healthy adult women.[14] To take another example, oral *Lactobacillus* supplementation reduces skin sensitivity and strengthens the skin's barrier function in adults[29] and children[30]. Several clinical trials have shown probiotics to have a positive effect when taken alone or in a cocktail (lactobacilli, bifidobacteria and/or *S. thermophilus*), with a reduction in lesions and severity in the case of **acne.**[12,23] The positive effects of oral probiotics may be due to their ability to reduce systemic oxidative stress, regulate cytokines and reduce inflammatory markers.[9] In the case of **psoriasis**, there are still few clinical data, but two studies in humans show beneficial effects: a reduction in inflammation markers with *B. infantis*; a reduction in the severity and appearance of lesions with *B. longum*, *B. lactis* and *L. rhamnosus* alongside a topical corticosteroid treatment.[13] There were similar results for **seborrheic dermatitis**, with inflammation and symptoms relieved by oral *L. paracasei*.[12] Some probiotics may even protect against **skin cancer**.[16] However, clinical trials are still required to identify the most effective formulation of probiotic strains, the optimal duration of supplementation and the patients most likely to benefit.[14]

[30] Niccoli AA, Artesi AL, Candio F, et al. Preliminary results on clinical effects of probiotic Lactobacillus salivarius LS01 in children affected by atopic dermatitis. *J Clin Gastroenterol.* 2014;48 Suppl 1:S34-S36.

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PROBIOTICS: A COMPLEMENTARY THERAPEUTIC OPTION

Long considered a source of infection, today microorganisms are often classified as either "good" or "bad". Is this black or white view appropriate?

Microbes are neither "good" nor "bad"; nor are they our "friends" or "enemies". We can't apply this humanized classification to them. Even the most harmless microbe can cause death if the immune system is weakened. However, it is well known that many microorganisms can benefit their host under certain circumstances, whereas others are generally pathogenic.

For example, *Staphylococcus* are very abundant on human skin. *Staphylococcus aureus* has quite a bad reputation: it is often associated with wound infections and several skin disorders, it carries many virulence genes, and its multidrug-resistant form (methicillin-resistant S. *aureus*, or MRSA) is a major cause for concern in hospital environments. At the same time, numerous recent studies have shown that *Staphylococcus epidermidis* can stimulate the immune system and the skin's defenses and even destroy *S. aureus* biofilms. On the other hand, *S. epidermidis* is a major cause of implant-related infections and can also become resistant to multiple antibiotics, whereas many people are colonized by *S. aureus* without experiencing any problems. Therefore, it's not always a good idea to try to improve skin health by simply lowering the ratio of *S. aureus* to S. *epidermidis* on the skin. A good balance between the two should be sought.

"Probiotics can be beneficial to our health."

Which microorganisms are involved in atopic dermatitis?

While microorganisms are probably not the main cause of the disease, they make a significant contribution to its pathology. Affected skin areas can be characterized by a microbial dysbiosis: an increased abundance of *S. aureus* and a reduced presence of typical skin bacteria such as *Cutibacterium* and *Corynebacterium*. *S. aureus* may benefit from a weakening of the skin barrier, possibly the result of altered antimicrobial peptide production in the skin and/or mutations in filaggrin genes[1], leading to dryness and cracking of the skin. Inflamed skin is usually treated with antibiotics, which risks causing severe damage to the beneficial part of the skin's microbiota, as well as antibiotic resistance. Probiotic strategies which aim to increase/restore the abundance of coagulase-negative staphylococci (CoNS) are considered optional and/or complementary.

Can topical and/or oral probiotics prevent or cure skin diseases? What part can they play in therapeutic strategies, now and in the future?

The addition of live microorganisms (probiotics) can certainly benefit the host's health, for example, by reducing the abundance of pathogens or stimulating the host's defenses and immune system. Due to the existence of a gut-skin axis, oral probiotics can also have a positive impact on the skin.
However, for most (if not all) major skin diseases, the role of the skin microbiota remains unclear. Although such diseases see marked changes in the structure (community composition) and function (physiological properties) of the skin microbiota, it's not usually clear whether these changes are the cause or effect of the underlying disease. This is the classic chicken and egg conundrum.

Therefore, in my opinion, it's a little too early to hope that a simple probiotic cream or capsule can make a significant therapeutic contribution to the prevention or cure of serious skin diseases. Furthermore, research in the gut has shown that, compared to conventional chemical therapies, the effects of probiotics are rather mild and influenced by so many factors that it's difficult to extrapolate them from highly standardized animal models to humans. Only robust clinical trials could show the effectiveness of probiotics. However, although it's too early to give a definite opinion for the most serious diseases, to me probiotics seem to be an additional therapeutic option for managing less serious skin disorders and a valuable strategy for improving skincare products. Since it now seems clear that a balanced and diversified microbiota is a characteristic of healthy skin, it makes full sense to preserve and protect such a state, including with probiotic approaches, for example in the case of blemished, sensitive or irritable skin, etc. ●

1. protein in the skin's stratum corneum that contributes to protective functions

The skin hosts **complex microbial communities** that vary according to skin area (sebaceous, dry or humid). These microbial communities also change through the layers of the skin epithelium, from the epidermis to the dermis. Although relatively stable over periods of a few months or years, the composition of the skin microbiota is still **influenced by the host** (age, sex, genes, immune status, etc.) **and the environment** (lifestyle, hygiene, cohabitation, geographical location, etc.).

An important factor in host health, the **skin microbiota helps protect against infection** both by competitive exclusion and via subtle interactions between microorganisms. It also plays a key role in the development and regulation of the innate and acquired immune systems.

Sometimes, **the balance between the different microorganisms breaks down**.
These imbalances are associated with skin diseases such as acne, psoriasis, atopic dermatitis, skin cancer, rosacea, seborrheic dermatitis and dandruff. They are also observed in non-pathological skin conditions such as irritation, diaper rash, wounds or body odor.

But which microorganisms are involved?

More surprisingly, skin diseases are often associated with gut dysbiosis. **The gut microbiota may play its own role in the development of skin diseases.** The search for the mechanisms involved is ongoing. Secretion of bacterial metabolites transported by the blood? Stimulation of the host immune system? Involvement of a gut-skin axis, or even a gut-brain-skin axis?

Lastly, researchers are currently studying various **therapeutic strategies** to restore the balance of the skin microbiota involving topical applications or oral probiotics.
While these strategies are promising, their therapeutic potential has yet to be confirmed.

This report provides a full overview of our current understanding of the skin microbiota, its associated microorganisms and proposed mechanisms of action. These mechanisms reach far beyond the skin, and potentially involve the gut microbiota and the brain.

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