

The integumentary system and its microbiota between health and disease

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The aim of the present investigation was to evaluate the essential physiological functions of the skin microbiota in human health and diseases. The main characteristics of the normal microbiota in the different anatomical sites have been reported in relation to the main factors, such as the effect of age, on its composition and stability for the eubiosis condition. Moreover, the present overview analyzed the functions and composition and the correct functionality of the skin microbiota in the light of current knowledge. According to several evidence is important preserving the eubiosis of the commensal microbes of the microecosystem (symbiotic and pathogenic), and probiotics are able to counteract the conditions of dysbiosis. Also, it has been shown that there is a crosstalk between gut and skin microbiota that affects human health and is still being studied, and its relationship to the current pandemic SARS-CoV-2.

The integumentary system is the largest organ in the human body and acts as a natural barrier to prevent the entry of pathogens from the external environment by participating in the regulation of the hydro electrolytic balance, temperature and other (1). At the same time, the skin has a complex and dynamic ecosystem inhabited by thousands of germs including bacteria, archaea, fungi, and viruses. On about 2m² of skin surface, about 1 million bacteria live per square centimeter for a total of over 10¹⁰ bacterial

cells. Indeed, a discovery by the Human Microbiome Project (HMP) in 2007, was launched to identify and characterize microbes present in various parts of the body (2, 3).

The communities living in different locations in the body are by no means uniform but vary greatly in their composition. Historically, the detection and characterization of skin germs has relied on their culture by pre-washing swabs from its surface. In using DNA sequencing techniques to detect and

Key words: human microbiota, skin microbiota, dysbiosis, probiotics, immune modulation, gut-skin axis, oro-cutaneous conditions, SARS-CoV-2

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0393-974X (2020)

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identify microbial genes, it has become clear that cultured microbes represent only a small fraction of the total organisms interacting on the surface of the human body and have sought to describe the diversity of microbes that live in our body and the microbial communities that inhabit them have collectively called it “microbiome” (4). These play a vital role in its physiology and skin homeostasis. During the life of a person, all keratinized skin cells, immune cells and germs, interact to maintain the natural and immune barrier of the skin healthy and to restore balance when dysbiosis or injury phenomena. There is a complex link between skin germs and their host (5, 6).

The structure of the integumentary system

The skin of an adult covers an area of approximately 2 m² and consists of three layers: (a) epidermis, (b) dermis, and (c) hypodermis and skin appendages (hairs, nails, sebaceous glands, eccrine and apocrine sweat glands) (6, 7).

The epidermis, which is the outer layer of the skin, provides immediate protection from external factors. It is a graduated squamous epithelium in which 90% of its cells are keratinocytes. These cells synthesize a series of structural proteins such as keratins. As the keratinocytes move from the basal layer, they differentiate to produce a variety of protein and lipid products. These cells undergo an apoptotic process in apoptosis in the granular layer before becoming the depleted and nucleated cells that form the stratum corneum. The skin is a site of lipid production, and the stratum corneum's ability to act as a hydrophobic barrier is largely due to its design. Dead keratinocytes with a strongly bound protein membrane are found within a metabolically active lipid layer composed of keratinocytes. Also, important skin cells are Langerhans cells which are dendritic cells derived from the bone marrow. Their main function is the effective presentation of foreign antigens in lymphocytes. The epidermis is attached to but separated from the underlying skin through the basement membrane. The latter acts as an anchor for the skin but allows the free circulation of cells and nutrients between the skin and the dermis (6, 7).

Dermis, just below the skin, contains blood vessels, nerves and skin components (hair follicles and

secretory and reactive sweat glands). The dominant skin cells are the collagen-producing fibroblasts. In addition to fibroblasts, there is a large population of other cell types such as mast cells, monocytes, macrophages, T lymphocytes, and dendritic cells. Finally, Hypodermis layer, lies deeper and consists mainly of adipose and connective tissue (7).

Hair follicles sweat glands and sebaceous glands are skin structures that penetrate the skin. There are two types of sweat glands: Eccrine and Apocrine. The eccrine glands, which are distributed almost throughout the human body, present in various numbers (the highest density in the palms, soles of the feet and head, much less on the trunk and limbs) and have pores that are directly open to the skin. Its water-based secretion (directly to the surface of the skin) is useful for cooling the body and thus, they play an essential role in thermoregulation with the evaporation (8). Also contains salt and electrolytes which contribute to skin acidification. Overall, the result of this process is the creation of a cool, dry and slightly acidic environment. This environment is not very conducive to microorganisms and plays an important role in reducing germs that can survive and multiply on the skin. The sweat glands are therefore actively involved in the innate immunity of the host with the produce molecules of antimicrobial peptides (AMPs) (7, 8).

The apocrine glands, which are present from birth, are activated after adolescence and have a more limited distribution, mainly found in areas such as the axillae, under the breasts (and around the nipples), genitals and perianal area. These glands secrete their contents, an odourless fatty blend of proteins, lipids and steroids, into the hair follicles (7, 9).

The sebaceous glands are small releasing exocrine glands in the epidermis connected to the hair follicles near the top of the pores (areas with a high density of sebaceous glands, such as the face, chest and back) (Fig. 1). They consist of modified keratinocytes (sebaceous cells) and secrete sebum, a substance rich in lipids that lubricates the hair and skin, thus promoting the growth of lipophilic and anaerobic microorganisms, such as *Propionibacterium acnes*, which hydrolyzing triglycerides in the sebum thus maintaining the acid pH of the skin. The composition

of normal flora is influenced by the essential fatty acid deficient (EFAD) skin lipids and in vitro experiments are effective against *Streptococcus pyogenes*, *S. aureus*, *S. epidermidis*, *Micrococcus* spp., and a *Coryneform*. Hair follicles and sebaceous glands represent an anoxic environment that hosts anaerobic microorganisms (6, 7).

DISCUSSION

The development of human skin microbiota

The development of microbiota of the skin begins at birth. The bacterial microbiota bio location and individuality shape the structural and functional composition of the skin. Thus, the variations of quantity and stability of the microbial community depend on the specific characteristics of the skin area e.g., the palms or soles of the feet, the skin is thick and hairless (dry type skin), while others such as axilla have thin skin and wide number of eccrine glands (moist skin) and consequently can have zone with more greasiness with a wide number of sebaceous and eccrine glands, such as face, scalp and torso (sebaceous or oily skin). The microbiota, although individualized, changes systematically between different environment and aging (10, 11).

At first the skin is sterile in the womb, and it has been shown that the fetus comes into contact with microorganisms belonging to the maternal microbiota and have been isolated from meconium (obtained from healthy newborns) by caesarean section lactic acid bacteria. Such a finding indicates that the embryos are not completely sterile and that there may be an outflow of congenital bacteria from the mother to the baby. All isolated strains belong to the genus *Enterococcus*, *Streptococcus*, *Staphylococcus* or *Propionibacterium* (12). The skin is therefore colonized by microorganisms at birth. This original microbial members have a very little variety throughout the body and is largely shaped by the way babies are born - babies born with normal births will be colonized by germs in the mother's vagina, while babies born with cut cesarean section acquire a skin flora more similar to that found in the mother's skin (13). The process of microbial synthesis of the skin flora progresses mainly over

several weeks, combined with exposure to the surrounding environment and body anatomy of children, it shows an increasing variety as they grow up. However, within six weeks of birth, the microbial composition has significantly evolved, expanded and differentiated, and within the first 6 weeks of life the baby's microbiota undergoes substantial reorganization, driven primarily by the body itself and not by the birth pattern (14). The skin microbiota of the new-born is different from that of an adult, due to particular differences in the structure and function of the skin. The baby's skin is dominated by *Firmicutes* (mainly *Staphylococci*), followed by *Actinobacteria*, *Proteobacteria* and *Bacteroidetes*. However, early microbial colonization is expected to affect the development of immune function in the skin. The first colonization dominated by *Staphylococci* (the stratum corneum of a new-born is relatively better hydrated than of an adult). As a person ages, the microbial communities differentiate and become similar to those of an adult organism from the age of 12-18 months (15).

In adulthood, based on sequencing of the ribosomal 16S RNA gene, most bacterial skin inhabitants belong to four genera: *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Proteobacteria* and these inhabitants are present in different proportions and *Actinobacteria* are the most abundant inhabitants of many skin sites. Despite the constant exposure of the skin to the environment, the microbial composition remains unexpectedly stable over time, raising the hypothesis of its resistance to pathogens (16). The skin has the most diverse bacterial communities of any epithelial surface studied to date. Wet areas (navel, groin, sole of foot, front of elbow and bridge of knee) the most abundant microbes that colonize are *Staphylococcus* and *Corynebacterium*, of the genera *Firmicutes* and *Actinobacteria* respectively (5, 17). Sebaceous glands, such as the forehead, the side of the nostrils, the crease behind the ear and the back appear to house the least diverse germ populations and the *Propionibacterium* species of the genus *Actinobacteria* are the most common isolates of the sebaceous regions (such as the face and trunk) probably due to their ability to survive in these anaerobic and lipid-rich environments (4).

The dry areas of the skin (forearm, some areas of the hand and buttocks) have been shown to have the greatest variety in microbial populations, with different aspects of the four main genes. However, it is unclear what percentage of these organisms can actually survive or reproduce on the skin. However, we must not forget that fungi, parasites and viruses reside in the skin, so microbial diversity is not limited to bacteria but also microorganisms such as fungi that play an important role in the stability of the microbial community and then in the health balance. In normal human skin, the commonly recognized fungi are *Malassezia* spp. representing up to 80% of fungi depending on the anatomical position of the skin. They dominate the trunk and arm while the feet, are colonized by a more diverse combination of *Malassezia*, *Aspergillus*, *Cryptococcus*, *Rhodotorula*, *Epicoccum* and others (18, 19).

Another important factor to consider for microbiota diversity are individual behavioural factors that alter the condition of the skin's surface. Indeed, some species, such as *Cutibacterium acnes*, will tend to colonize multiple areas of the skin of the same individual but others, such as *Staphylococcus epidermidis*, will tend to colonize different areas. Transgenic classification

of the human microbiota has focused primarily on species composition. However, the skin barrier is not only its epidermis but also the underlying layers, which influence its function and also host the germs. In fact, DNA sequencing from the skin and dermal adipose tissue has shown (via 16S bacterial ribosomal RNA), a diverse and partly distinct microbial community in the subcutaneous areas of the skin, hair follicles and sebaceous glands (20-22).

Skin microbiota and innate - adaptive immunity

The skin, the largest organ in the human body that hosts a wide and complex variety of natural (innate) and adaptive immune functions. Within the skin, both innate and adaptive mechanisms contribute to immune function. Despite the strong immune system present in the skin barrier, the skin favours colonization by microorganisms. Immune defence is normally distinguished in an innate immune response that offers immediate protection from invading pathogens and an adaptive or acquired immune response that takes longer to develop but is specialized and provides long-term protection. Mechanisms of immunity against infection include anatomical barriers, phagocytes, soluble molecules

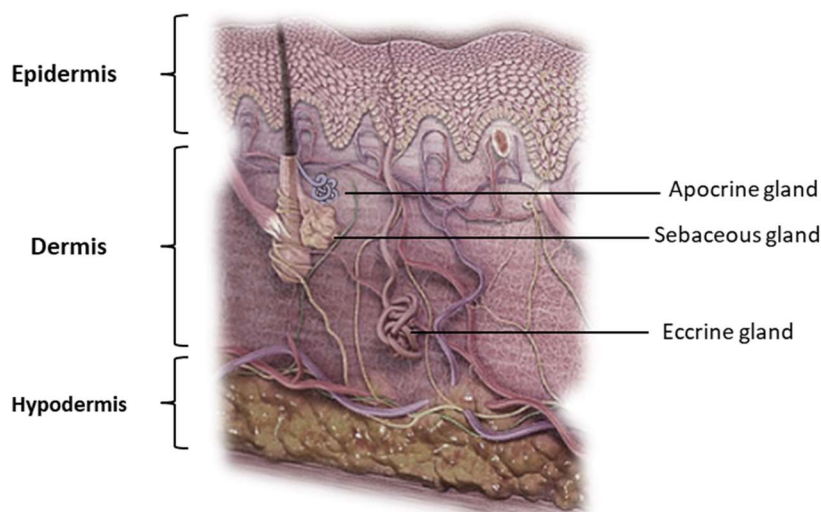


Fig. 1. *The integumentary system.*

such as the complement system and acute phase proteins, natural cytokines (NK cells) and dendritic cells. When innate immunity fails to provide effective protection against a pathogenic invader, the adaptive immune system is mobilized (7, 23, 24). The anatomy of the skin and its physical/chemical properties are the first line of defence against the pathogens that tend to invade. The outer surface of the skin consists of a lipid and protein layer, keratinized cells, hair follicles and glands that secrete lipids, antimicrobial peptides, enzymes, salts and many other compounds. While the skin surface is mostly drier acidic and high salinity with an aerobic environment, the interior of the hair follicles is relatively anaerobic and even richer in lipids. Skin lipids such as sapienic acid may have antimicrobial activity while others, such as triglycerides, can be metabolized by microbes into free fatty acids monoacylglycerols and diglycerides which can act against other microbes or play a stimulating role for host cells (7, 25, 26). As we have reported, antimicrobial peptides (AMPs) contribute significantly to innate dermal immunity and this system, combined with the skin's unique ionic, lipid and natural barrier, is the first line of defence against entering pathogens in the skin. The immune system is made up of a complex network of cells, proteins and lymphatic organs strategically placed to ensure defence against pathogenic bacteria (17, 23, 24).

There are two types of adaptive immune responses: humoral immunity associated with antibodies produced by B lymphocytes and cellular immunity associated with T lymphocytes, which synthesize and release cytokines and thus enact their action on other cells. These actions are together on natural immunity to maximize the effectiveness of the immune response. Keratinocytes are the first to be actively involved in the skin's immune response. These epithelial cells express a series of pattern recognition receptors (PRRs) that detect germs. Hence, it is the keratinocytes that express a series of antimicrobial peptides, cytokines and chemokines, and the activation of PRRs increases the expression of these molecules, resulting in direct antimicrobial effects, as well as activation and formation of additional immune cells. Recent evidence supports the idea that Langerhans cells (LC), found in the skin,

are involved in promoting tolerance to autoantigens and related microbes through the induction of regulatory T cells under normal conditions (27, 28). Furthermore, there are many cells that function in the dermis and are involved in innate and adaptive immunity such as dendritic cells, macrophages, mast cells, natural killer (NK) cells and a variety of T cells including CD8 + memory T cells, CD4 cells + TH1, TH2 and TH17, NKT cells and regulatory T cells (Treg) (10, 23, 24, 29). Under eubiosis, the skin is filled with very different T cells. Therefore, due to the sheer number of possible antigens expressed by the microbiota, it predicts that a significant fraction of these T cells residing in the skin are specific to normal flora. Due to the unusual pressure exerted by the microbiota on the immune system, the largest number of immune cells in the body are found in areas colonized by diners. In particular, healthy human skin is home to approximately twenty billion effector lymphocytes, making it one of the largest reservoirs of memory T cells in the body. The production of antibodies by B lymphocytes and the control of their production by the dermal microbiota is still not very well understood (28, 30, 31).

Interactions between the skin germs and the host

The germ-microbial interactions actually contribute to human health in several ways. Initially, the presence of beneficial microbes in the skin results in competition for nutrients and space, thereby significantly affecting the tendency of pathogens to grow when they enter the skin's surface. In fact, the alteration of the normal flora by means of broad-spectrum antibiotics generally favours opportunistic infections by microorganisms that rapidly colonize the dysbiotic environment. Furthermore, microbes as we have mentioned produce fatty acids and bacteriocins which inhibit the growth of many pathogens. But if the external defences are violated by a lesion or a pathogenic microorganism, the special soluble proteins and cells of natural immunity are activated (23, 27, 28, 32). Protein agents, called bacteriocins, are a natural weapon of bacteria since they have the ability to destroy other harmful bacteria. They are able to inhibit the growth of even closely related species of pathogenic bacteria, while

having no effect on the microorganisms that produce them (27). There are many networks of germ-microbial interactions that can govern host disease in a strain- and environment-dependent manner. *S. epidermidis* is generally beneficial to the host but is also a leading cause of death in premature infants and nosocomial infections (33). *S. epidermidis* is one of the most abundant members of the skin bacterial community and a related species of the pathogenic *Staphylococcus aureus* (although *S. epidermidis* can cause severe infections, it is an opportunistic pathogen under certain conditions) (22, 34). *Staphylococcus epidermidis*, acts as a barrier against colonization pathogens and inhibits the excessive development of opportunistic pathogens already present. (e.g., *S. epidermidis* and *Staphylococcus hominis* have been shown to secrete antimicrobial peptides that kill *S. aureus* and transplantation of these species into the skin of patients with atopic dermatitis has resulted in reduced colonization with *S. aureus*). *S. epidermidis*, detected by keratinocytes via the Toll type 2 receptor, has been shown to improve host defense against *S. aureus* infection through increased expression of these antimicrobial peptides which against a large variety of skin pathogens, including Gram-negative bacteria, fungi, viruses and parasites (22, 35). *S. epidermidis* is able to inhibit the formation of bio membrane from *S. aureus* by producing a serine protease, Esp, which also enhances the antimicrobial effects of Human β defensin 2 (HBD2). Some strains of *S. epidermidis* cause activation of specific IL-17 T cells and CD8 + (cytotoxic) T cells that protect the skin from infection by causing keratinocytes to produce AMP, a phenomenon called heterologous protection (36). In addition to their protective role, these specific commensal T cells also promote wound healing (12, 30, 35, 36). The *Staphylococcus* species that populate the skin are involved in beneficial microbial-microbial interactions for the host by the production of a variety of immunomodulatory molecules, such as wall acids and polysaccharides. It has recently been discovered that substance-producing *Staphylococcus epidermidis* 6-N-hydroxyaminopurine (6-HAP) can regress skin cancers and thus the skin microbiota plays an important role in the body's defence, including for

skin cancer (37, 38). According to recent research, another common skin resident, *Corynebacterium striatum*, suppresses co-cultured *S. aureus* genes and stimulates genes involved in commensalism and *Corynebacterium accolens* in another study it appears to inhibit the growth of *Streptococcus pneumoniae*, a common respiratory pathogen. In particular, a lipoprotein lipase hydrolyzes triolein which releases oleic acid, inhibiting the growth of pneumococci (39). Another common bacterium is *P. acnes* which has shown that it is able to inhibit the growth of growth of methicillin-resistant *Staphylococcus aureus* (MRSA) by fermenting glycerol (a metabolite normally found in human skin) into a series of short-chain fatty acids that carry to a reduction of the intracellular pH within *S. aureus*, thus inhibiting its growth. This suggests that *P. acnes* can prevent the development of pathogens in human skin and could also be used to develop new therapies for MRSA infections (40).

In conditions of eubiosis, AMPs in the skin are mainly produced by keratinocytes, but also by mast cells and sweat glands and that a significant contribution also comes from symbiont bacteria, which produce AMPs and TLR ligands. The main groups of AMPs found in the skin are defensins, cathelicidin, dermcidin and a group of proteins/peptides including the RNase7 and S100 proteins (41-43). Dermcidin (DCD) with natural broad-spectrum antibacterial activity and in areas of the body with a high probability of contact with pathogenic microorganisms, a large amount of DCD peptides was also detected in sweat. 9 Cathelicidin (one of its two LL-37 fragments is anti-Gram-) and β defensins have strong antimicrobial activity against Gram-positive and Gram-negative bacteria (44). Therefore, some AMPs are expressed components of host cells, while others they can be stimulated by specific members of the normal flora, or produced microbes (including *Cutibacterium's* thiopeptides) (45, 46). Under inflammatory conditions, large numbers of AMPs are produced by the penetration of immune cells (e.g., neutrophils). The basic functions then of all AMPs produced are the activation of the host's innate immune response against pathogens. Most symbiotic germs on the skin behave as neutral

or reciprocal under normal conditions. These microbes play an important role in the maturation and homeostasis of skin immunity through their effect on host cell function. Finally, germs can increase the expression of the complement system made up of a group of more than 20 precisely regulated and functionally linked proteins that promote inflammation and destroy pathogenic invaders (35, 47-49).

Thus, microbiota produce their own AMPs thus acting to enhance the production of AMP by keratinocytes. Hence useful for maintaining inflammatory homeostasis by suppressing the release of excess cytokines after minor skin damage. These observations suggest that the normal microflora of human skin protects the skin in various ways, a conclusion that supported by many lines of evidence linking diseases with an imbalance of microflora

such as atopic dermatitis, acne, psoriasis. Therefore, microbiota regulates the expression of various intrinsic immune factors such as: (a) Interleukin IL-1, (b) antimicrobial peptides (AMPs) which naturally produced by keratinocytes and sebaceous glands and (c) complement. The microbiota enhances the activation of lymphocytes both in the normal state and during infection, which acts as an endogenous adjuvant to the skin's immune system. (Fig. 2) (5, 36, 50, 51).

Skin microbiota dysbiosis and diseases

Several studies have found differences in the germs present in diseased skin compared to those present in healthy skin. Thus, the microbiota contributes significantly to normal immune development and skin function, and it makes sense to link diseases to changes in its composition. While

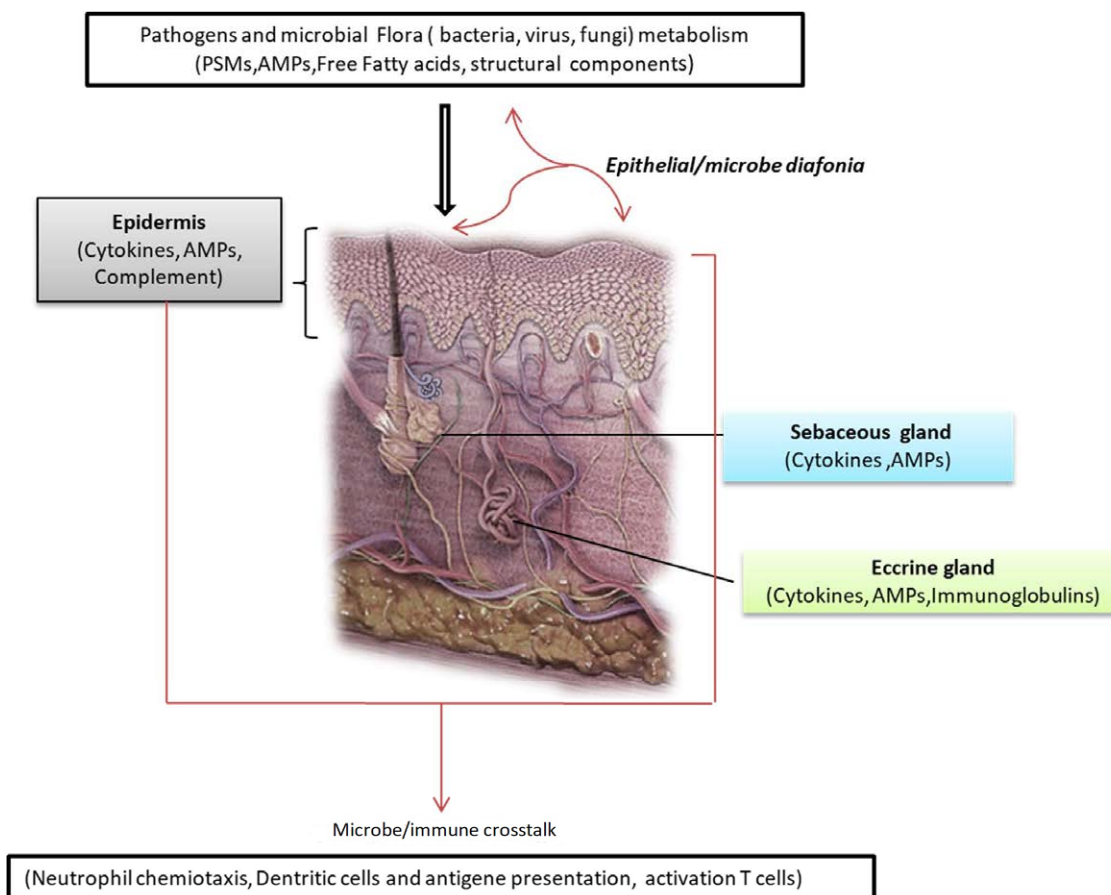


Fig. 2. Defence axis between epithelial/microbe and microbe/immune system. The microbiota located in Integumentary system inhibit the installation of other pathogenic microbes.

studies show that many diseases cause dysbiosis, but on the other hand, it is not entirely clear whether changes in the microbiota lead to disease or whether certain conditions lead to an imbalance in microbial communities (Fig. 3). Many germs considered relatively harmless commensals can actually cause severe infections under immunosuppressive conditions, e.g., the germs present in chronic non-healing ulcers as well as the rates of coagulase-negative staph infections observed in hospitals. So even apparently beneficial microorganisms can take on a pathogenic role when they find the right opportunity (52, 53).

It has been observed that traditional pathogens often populate the skin surface asymptotically e.g., one of the most important skin pathogens is *S. aureus*. Although more than 30% of healthy people are asymptotically colonized by *S. aureus* it can still become pathogenic through furuncle or cellulitis or even more severe infections through penetration into any organ of the body (e.g., bones osteomyelitis, bacterial endocarditis, sepsis and more). *S. aureus* has also been implicated in the pathogenesis of chronic diseases such as atopic dermatitis and systemic lupus erythematosus with renal and dermal dysfunction (52-59). Mycobacterium is another

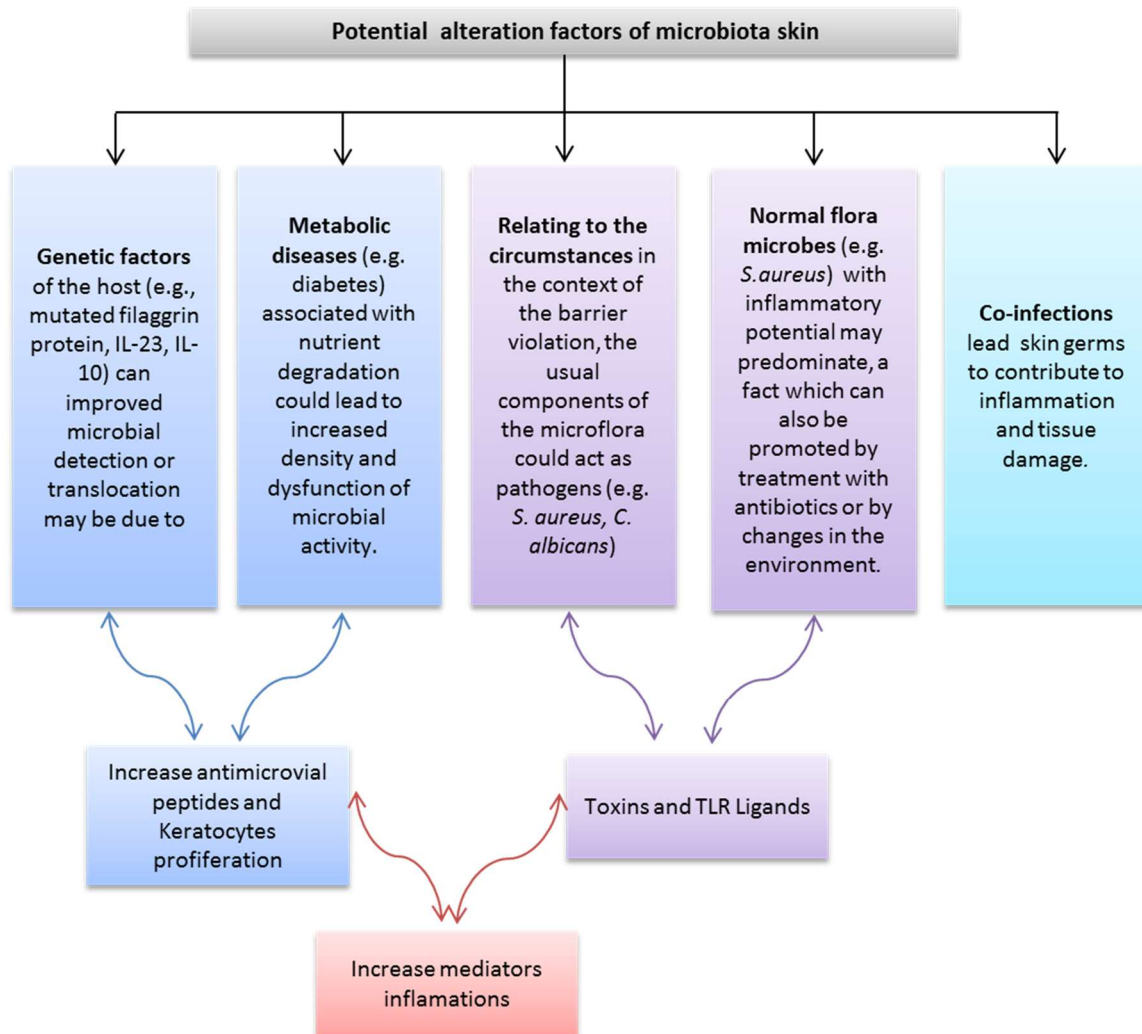


Fig. 3. Potential factors through which the skin microbiota can trigger the onset or exacerbation of its disorders. In most cases, but also combinations of different scenarios may be required to activate pathologies. In turn, the induced inflammation can alter microbial communities.

important pathogenic genus of the skin, a bacterium belonging to the *Actinobacteria*. Mycobacteria are a diverse genus of organisms including the etiologic agents of *Mycobacterium tuberculosis* and *Mycobacterium leprae*, and other species that cause hospital or wound infections (e.g., *M. kansasii*, *M. chelonae* and *M. marinum*). *M. tuberculosis* generally causes pulmonary or systemic infections thus producing a particularly wide range up to cutaneous manifestations. Furthermore, mycobacteria show similarities to *Corynebacterium* which lives on the skin but has very different effects on the host. The *M. leprae*, also causes a wide range of diseases, including various skin manifestations, nerve damage, bone and eye damage. The incubation period for *M. leprae* is usually 2-12 years (60-64). Furthermore, numerous bacteria present in the normal microbial flora of the skin often cause infections in chronic and incurable wounds, usually occurring in diabetic patients and the elderly. Another group of microorganisms, Herpes viruses are often pathogenic to the skin, including Human herpesvirus 3, with recurrent episodes (HSV1 and HSV2). However, after the acute phase of the infection, the herpes viruses remain dormant within the host, in a latent state for the life of the host (65-67). On December 31, 2019, a new Coronavirus strain was reported in Wuhan, China, identified as a new Coronavirus beta strain β -CoV from Group 2B, with a genetic similarity of approximately 70% to SARS-CoV, called Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused a pandemic infection that continues to this day (68). The most common skin manifestations associated with COVID-19 infection include a maculo-papular or papulovesicular rash, urticarious lesions, livedo reticularis and others. The most common areas involved are the trunk, hands and feet, with little itching experienced and no demonstrated correlation, between skin lesions and COVID-19 severity (69-77).

Common skin disorders such as Dandruff, hidradenitis suppurativa, acne, atopic dermatitis, and psoriasis have associated with dysbiosis of the skin flora. Dandruff is a mild inflammatory condition characterized by peeling of the skin on the scalp and *Malassezia* species suggested as the main cause of dandruff in the 1800s, a view that still prevails

today by studies shown to increase in abundance in dandruff-affected skin. Furthermore, because *Malassezia* found in the common fungal microbiota, it is not the only cause of the disease alone, but there may be other active mechanisms involved in the etiology. However, recent work has shown that dandruff microbial communities are more complex. A molecular analysis of the 26S rRNA gene from fungal communities confirmed the relative abundance of *Malassezia* in the dermis of the scalp (17, 78, 79). and that *Penicillium*-related dermatitis and *Filoblastidium floriforme* are associated with the severity of dandruff. In general, all germs living on or in a host fall into a range, with some showing almost no aggressive behavior and others appearing mainly with infectious and invasive phenotypes i.e., there is an alternation of microbes between passive and aggressive behavior. For example, *P. acnes* produces coproporphyrin III that induces the formation of *S. aureus* in the biofilm, which leads to a negative effect on the host but on the other hand *P. acnes*, ferments glycerol into short chain fatty acids, thus suppressing growth methicillin-resistant pathogenic *S. aureus* USA300. A similar range of harmful and beneficial effects has demonstrated for other microbes (33, 40, 80).

The pathogenesis of hidradenitis suppurativa (HS) is still under study; however, several factors indicate a possible involvement of the dermal microbiota. The composition of germs in HS differs significantly from that of healthy individuals. In total, the following types of 5 microbes were identified: *Corynebacterium species* (type I), *Acinetobacter* and *Moraxella species* (type II), *Staphylococcus epidermidis species* (type III), *Peptoniphilus species* and *Porphyromonas* (type IV) and *Propionibacterium V acnes* (The microbiota types consisted mainly of type I or type IV and Type IV was not detected in healthy controls). Several species, including *Propionibacterium*, showed significantly greater relative abundance in healthy controls against HS skin, suggesting that *Propionibacterium* may be part of the pathogen in HS via a dysbiotic condition of the microbiota and HS (81).

Acne is a chronic and inflammatory skin disease characterized by anomalies in the production of

sebum, bacterial proliferation that will lead to inflammation (most affected areas are the face, neck, chest, shoulders and back). This is because these areas have a large number of sebaceous glands and sometimes an excess of sebum produced, which can clog the pores, creating a favorable environment for bacteria to grow. In fact, in adolescent acne vulgaris there is a sebaceous hypersecretion that leads to the obstruction of the pores. This process causes the rupture of the follicular wall causing the influx of neutrophils and the formation of vesicles, a process ability of *P. acnes* to activate keratinocytes (82, 83). The contribution of *P. acnes* to the pathogenesis of acne is however unclear (84) which would be the main germ associated with the development of acne is that it too is an important member of the symbiotic flora of the skin. The strain level analysis of the 16S rRNA gene showed that although the amounts of *P. acnes* did not differ significantly between healthy and acne patients and the relative proportions of the different strains differed between the two skin conditions. Furthermore, genomic comparisons of different *P. acnes* strains show that genomes related to Acne conserves several chromosomal genomic regions and linear plasmid sites, thus suggesting that specific genes may be present at these sites that contribute to acne pathology (85).

Atopic Dermatitis (AD) is a chronic and recurrent inflammatory skin disease, occurring more often in children than in adults and is associated with dysbiosis. Patients with AD show disruption of the skin barrier, modification of T lymphocyte function with suppression of antimicrobial responses (86). It has long been associated with *Staphylococcus aureus* colonization and infection and that targeted antibiotic treatment can sometimes temporarily ameliorate the disease (87). In patients with atopic dermatitis, *Staphylococcus aureus* strains develop as biofilms in the skin and produce proteases that degrade host AMPs such as cathelicidin LL-37 (this type of AMP, in addition to its antimicrobial properties, has numerous immunomodulatory properties that can contribute to the development of autoimmune diseases) (88, 89). It has been observed that over 90% of patients with AD exhibit colonization with *S. aureus* and is recognized by innate immune receptors such as

Toll-type receptors on the surface of keratinocytes that produce antimicrobial peptides such as the β -defensins (HBD-2 and HBD-3), interleukin IL-8. In the presence of Th2, IL-4 and IL-13 induce STAT6 phosphorylation by inhibiting $\text{INF-}\gamma$ and $\text{TNF-}\alpha$. This subsequently inhibits the production of HBD-2 and HBD-3, causing a decrease in the production of IL-8 leading to the change of neutrophils in the skin. These cascades of events help allow *S. aureus* to grow (89). However, the host has developed mechanisms to prevent *S. aureus* from invading any layer of skin and subcutaneous tissue. In addition to a variety of AMPs produced, adipose tissue contributes to the innate immune response. Following a breakdown of the skin barrier and subsequent *S. aureus* infection, lipid cells proliferate rapidly, expanding subcutaneous fat thereby increasing cathelicidin production (90). AD lesions have also been reported to contain high levels of lipoic acid and an immunostimulant derived from Gram-positive bacterial walls, the presence of which further suggests the role of bacterial components in disease (91). Defects in various aspects of epidermal function have been implicated in AD. Mutations in the gene that codes for the protein filaggrin, an essential component of the formation of the epidermal barrier, have been associated with atopic dermatitis and other disorders (92, 92). Furthermore, mutations observed in the receptors and signaling molecules that detect various microbial bacteria, such as TLR2, CARD4 and CD14, and reduced expression or function of antimicrobial peptides such as defense, dermicidin and caliclidine. Although *S. aureus* may contribute in part to the pathogenesis of the disease, the role of the microbial community as a whole with an association between increased disease severity and reduced bacterial diversity of the microbiota. Furthermore, fungal communities shown to change in composition as disease severity progresses (93-96).

Many observational studies suggest that a role played by dysbiosis of the skin microbiota in the pathogenesis of psoriasis and that the type of knee psoriasis is triggered by streptococcal infection. Analysis of bacterial microflora with approaches based on the 16S rRNA gene suggests an under-representation of *Propionibacterium* and a greater representation of genus *Firmicutes* in its psoriatic

plaques than in healthy ones. In psoriasis, plaques can give an idea of the role of germs in activating, spreading and maintaining plaques. Instead, culture studies of psoriasis-related organisms identified *Malassezia*, group A and B β -hemolytic *Streptococci*, *S. aureus*, and *Enterococcus faecalis*. Analysis of evidence of the fungal microflora of the association of *Malassezia* with psoriasis (97).

The gut/skin axis

The gastrointestinal tract is undoubtedly the main place for the growth of microorganisms in the human body and according to estimates that are, more about 3.8×10^{13} (13) bacteria colonize the large intestine of a 70 kg human. The gut microbiota interacts with its host and performs many of the basic functions with metabolic reactions such to maintain human health (98, 99). The interaction between intestinal microbes and the host's immune system is widely recognized to promote the smooth functioning of the intestinal immunity system. The bacteria of the symbiotic flora produce antimicrobials such as bacteriocins and hydrogen peroxide that inhibit the growth of others with pathogenic behaviour. The intestine is a humid environment with a neutral pH rich in polysaccharides and various sources of carbon and nitrogen with more aerobic areas in the intestinal crypts than in the hair bulbs of the skin and a thick layer of mucus that allows it to support much larger microbial biomass (100-103). Conversely, skin performs its functions of protection, thermoregulation, water retention and immune protection when it is in a state of balance. The skin differs from the intestine in its physical and chemical properties. The skin is more dry and less moist, acidic, rich in a high salt lipid environment with no exogenous nutrient sources and therefore has a low microbial biomass. Additionally, the material within the crypts regularly exchanged for material in the intestinal tract due to peristalsis, while the hair follicles have narrow openings filled with sebum and keratinocyte fragments, making them more isolated. The intestine and the skin are highly vascularized organs with important immune and neuroendocrine roles, and it appears that they are uniquely connected by purpose and function (7, 10). Thus, it appears that there is a bi-directional link between gut and skin

that connects the gastrointestinal microbiota of the skin for homeostasis of the body. We must mention that there is also other important bowel cross talk such as the gut/pulmonary and gut/brain (104, 105). It is known that certain gastrointestinal disorders are often accompanied by skin manifestations and in particular the intestinal microbiota participates in an active world in many inflammatory disorders (106, 107). The gut microbiota thus contributes on Integumentary system allostasis and homeostasis after any inflammatory process based on its role with innate and adaptive immunity. Excessive production of pro-inflammatory cytokines leads to intestinal barrier damage. This a condition of severe intestinal dysbiosis that leads to inflammation beyond intestinal and therefore systemic of low grade with involvement of the skin. As a consequence, we will have various skin manifestations such as atopic dermatitis, eczema, acne and others. It has been noted that in some cases in conditions of dysbiosis, the increase of the final products of the metabolism of aromatic amino acids by *Clostridioides difficile* (i.e., free phenol and p-cresol). This will be capable of an imbalance of production between T_H1 and T_H2 lymphocytes in the intestine with involvement of the skin. The free phenol and p-cresol passage into the circulation and consequently their accumulation in the skin leads to an alteration of the skin barrier which can cause electrolytic alterations with dehydration and keratinization disruptions (106-108). In fact, in the new viral pandemic infection SARS-Cov-2 which also presents with skin symptoms, as we have previously mentioned, alterations of the intestinal microbiota have been observed. These skin manifestations could be partly justified thanks to this over immune process of crosstalk gut/skin, but further studies are still ongoing. The intestinal microbiota become unbalanced (dysbiosis) in many viral inflammatory situations. In the case of SARS-Cov-2, changes of various bacterial species have been observed in the fecal microbiota in some patients. The following are reported: over represented *Actinomyces*, *Streptococcus*, *Rothia*, *Veillonella*, *Clostridium hathewayi*, *Actinomyces viscosus*, *Bacteroides nordii*, *Coprobacillus*, *Clostridium ramosum*, *Faecalibacterium prausnitzii* (act on the

severity of the infection), *Firmicutes* (has a potential influence on the intestinal ACE2 expression), *Corynebacterium*, *Ruthenibacterium*, and reduce *Eubacterium ventriosum*, *Faecalibacterium* taxus *fecalaceae*, *Lachnospiraceae*, *Bifidobacterium*, *Lactobacillus* (31, 33). Finally, some *Bacteroides* spp (*B.dorei*, *B.thetaiotaomicron*, *B.massiliensis* and *B. ovatus*) have a protective effect against the viral inflammation (69, 70, 109-118).

Some studies report the link between intestinal dysbiosis and the skin some diseases and this has shown in many studies through the administration of probiotics (104). The probiotics fight the spread of pathogens, strengthen normal flora and contribute to the creation of a strong immune system, creating a healthy environment that encourages healing and recovery in a natural way. Studies have shown the significant effect of probiotics on building a strong immune system (113). The beneficial bacteria they contain play an important role in helping the body to stay healthy so that it can fight some diseases. Thus, Probiotics help the restore balance of microbiota and lead to the eubiosis. The genera *Lactobacillus* and *Bifidobacterium* species are the most commonly used probiotics (115, 119-122, 123-157).

In several studies on animals but also on humans have shown the benefit in some skin diseases such as, atopic dermatitis, acne vulgaris, psoriasis and others through the administration of probiotics. Some studies report the link between intestinal dysbiosis and atopic disease. After metagenomic analysis of fecal samples from patients with atopic dermatitis, the reduction of *Faecalibacterium prausnitzii* was noted. In a study involving 300 individuals with acne, strains of *L. acidophilus* and *L. bulgaricus* were administered, an improvement of 80% of patients was noted. In another randomized, double-blind, placebo-controlled study, *B. infantis* 35624 was administered to 26 patients with plaque psoriasis and an improvement in systemic inflammation was noted, with decreases CRP and TNF- α . This is probably a demonstration of how the gut microbiota can affect skin health (104, 158).

However, due to the continuity of skin and mouth microbiota, the interaction of these close ecological systems is obvious and may have both positive and

negative effects. In fact, it is well known that a lip infection by Herpes virus 1-2 may diffuse to the oral cavity, leading to glossitis and mucositis, and angular cheilitis can be complicated by *Candida albicans* superinfection, moreover in young children and immune suppressed patients.

Conclusions

Different germs have evolved to thrive in different ecological locations in our body. Skin microbiota regulates and contributes to skin immunity through their effect on host cell function. More and more studies have begun to shed light on the relationships that skin microbiota germs share with their host. It has observed that, as immune factors and host behaviours shape the composition of these communities, the microbes themselves present in the skin also significantly influence the functions of human immunity. Therefore, to understand the microbial flora of the skin, it is important to recognize that unlike all other studied areas of the microbiota, such as the intestine and oral mucosa, the skin has the greatest variety of variables that affect its surface characteristics and a wide variety of cell types predisposed to interact with germs. Given the great diversity of skin environments, it makes sense to predict that each microenvironment will support very different populations of microorganisms. The study of the microbial communities that populate the skin revealed the great temporal and spatial diversity of the microbiota components that observed both between different individuals and within the same person. Although several discoveries have made about the importance of microbial communities, much less is known today about the role of skin microbes in developing and maintaining our immune system. Therefore, today the skin's immune system be considered a collective mixture of elements made up of the host and the microbes acting in a mutual relationship. However, persistent dysbiotic conditions can lead to skin diseases and there is a crosstalk between intestinal and skin microbiota that affects the human health and is still being studied. In this light view, some dermatological manifestations in the course of many diseases, including the new pandemic infectious SARS-Cov-2, could find

an answer. Finally, Probiotics have shown to be effective in promoting eubiosis and thus preventing or accelerating the healing process.

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