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Review

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The microbiome and aging

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Abstract

The microbiota changes as the host ages, but also the relationship between host and bacteria impacts host aging and life expectancy. Differences in the composition of certain bacterial species in the human gut and skin microbiome have been identified between the elderly and the young. In this sense, it has been suggested that the manipulation of the microbiota of older adults would be an innovative strategy in the prevention and treatment of age-related comorbidities.

Keywords: Microbiome, aging, skin aging, skin cancer, probiotics

INTRODUCTION

Humans are practically sterile during gestation, but, as early as birth, the whole body surface, including the oral cavity, gut, and skin, are colonized by an enormous variety of microbes, fungal, archaeal, bacterial, and viral[1]. There is a very complex relationship between the resident microbial communities and the human cells. These species and their metabolic products play an important role in a wide range of biological functions[2]. In normal life, these microbes are necessary for many functions, such as developing and maintaining our immune system or digesting food. However, the dysfunction of the human microbiota is considering a relevant factor in many diseases[1,3].

The skin, the largest organ of the human body[3], is in direct and continuous contact with the external environment, and, consequently, it is exposed to the microorganisms that inhabit it[4]. In addition, these skin commensal microbial communities interact with each other, as well as with the host cells and the immune system[3]. In this sense, it is clear that the immunological system of the host modulates the composition of these communities, and, conversely, the microbes present on the skin have a great impact on human immune system[3,5].

Different factors influence the diversity in the composition of this ecosystem. In fact, the anatomy and physiology of the skin determine the skin bacterial diversity, such as the axillae, forehead, palms, fingers, or feet[2]. Even on a particular niche of the body, the skin microbiota is still complicated by a combination of both external and internal factors, including, but not limited to, gender, age, environmental conditions such as pollution and the climate, genetics, hormones, cosmetics, diet, immune response, and lifestyles in general[5-8].

In this regard, different distributions of microorganism species have been identified in sebaceous, moist, or dry locations[6,8,9]. In addition, areas more exposed to the outside environment may contain a greater proportion of "transitory" microorganisms, compared to less exposed ones[6,9].

The perception of the skin as an ecosystem can help us to understand the delicate balance between host and microorganisms and how the alteration of any of them can result in skin diseases or infections[4].

The objective of this article is to review the existing evidence in relation to the microbiome and aging, especially that of the skin, and the possibility of manipulating the microbiome to prevent and treat age-related comorbidities and premature skin aging.

This is a narrative review of the subject. We obtained the articles by searching in PubMed. The search terms were *microbiome*, *aging*, *skin*, and *skin cancer*. To identify the articles relevant to the purposes of the review, we read abstracts, results, and, when necessary, the full texts to ascertain which ones contain pertinent information.

THE TECHNIQUES FOR SKIN MICROBIAL ANALYSIS

There are two main sampling methods for collecting resident skin microbiota. On the one hand, skin swabbing using a sterile cotton swab is a simple, quick, and non-invasive method for large-scale skin sampling. However, this method can accurately collect only resident microbiota from the stratum corneum; therefore, it does not provide a full spectrum picture of the skin microbiota, particularly in some specific subniches, such as the dermis. On the other hand, punch biopsies are invasive but offer the best representation of skin microbiota in deep epidermis, dermis, and glands such as the sebaceous gland. Nevertheless, due to its invasive nature, the latter is rarely used for qualitative analyses[10].

Regarding the technique, it must be sterile to ensure that bacterial DNA sequences are not introduced into the sample from sampling equipment, lab reagents, clinicians, *etc.*[11]. Additionally, cold storage at -20 or -80 ℃ or in liquid nitrogen is a standard practice to limit further microbial growth and long-term DNA degradation[10].

Once the samples are obtained and properly stored, there are several methods to extract DNA, including the REPLI-g Midi kit (Qiagen, Limberg, The Netherlands), Qiagen DNA Extraction Kit (Qiagen), and DNeasy DNA Extraction kit (Qiagen)[11]. These techniques recognize the specific DNA or RNA (16S ribosomal

RNA) fingerprint sequences that each organism contains, which allows identifying, characterizing, and measuring the true relative abundance of each bacterial operational taxonomic units[10].

Finally, the essential portion of accurate microbiome analysis is the bioinformatics processing. Generally, large-scale computing clusters and specific bioinformatic pipelines must be established to understand and analyze these diverse bacterial communities from the millions of sequencing reads[11].

THE MICROBIOME OF THE SKIN

The majority of the "regular" bacterial inhabitants of the skin are included in four phyla: *Actinobacteria*, *Proteobacteria*, *Bacteroidetes*, and *Firmicutes*[3]. The three most common genera are *Propionibacteria*, *Corynebacteria*, and *Staphylococci*[6].

The commensal microbes of the skin have also been classified as resident or transient depending on if they belong to the fixed microbiota or not[3,10]. The fixed microbiota tends to reestablish after disturbance. It is considered as commensal, which means that these microorganisms are normally harmless and most likely provide some benefit to the host. Transient microorganisms are temporarily found in the skin. They come from the environment and persist for hours or days and then disappear[10]. Under normal circumstances, both groups are nonpathogenic[10]. Recent research has shown that, even though the skin is constantly exposed to the environment, the healthy human skin microbiome is stable[12,13].

The body site is one of the most influential factors in the types of microbes inhabiting the skin[3]. The three main types of environments on the human skin are sebaceous, dry, and moist. Moist areas mostly include the body folds: the navel, axilla, antecubital and popliteal fossa, or groin. Sebaceous areas include the forehead, nasolabial folds, retroauricular crease, middle chest, and back, whereas the upper buttock area, forearm, and hypothenar palm are drier sites[3,6,8-10]. Other microenvironments include the hair follicles, sweat glands, and dermal layers[10].

The microbial communities found in these cutaneous environments are different. *Corynebacterium* and *Staphylococcus* genera, of the phyla *Actinobacteria* and *Firmicutes*, respectively, are the most abundant microbes colonizing moist regions. The diversity of the microbes present in sebaceous sites is lower. In this anaerobic lipid-rich environment, there is a higher density of *Propionibacterium*, a lipophilic genus. The dry areas of the skin show the highest diversity in microbial inhabitants, predominantly *Staphylococcus*, *Propionibacterium*, *Micrococcus*, *Corynebacterium*, *Enhydrobacter*, and *Streptococcus* species[3,10]. Additionally, even microenvironments such as sebaceous, apocrine, and eccrine glands and hair follicles are associated with their own singular microbiota. In this sense, whereas *Propionibacterium* is especially adapted to the anaerobic environment rich in lipids of the sebaceous follicles, Gram-positive bacteria of the genera *Corynebacterium, Micrococcus*, *Staphylococcus*, and *Propionibacterium* are the main microbiota of the axillar area, rich in sebaceous glands[10].

Although microbiota research has focused primarily on identifying bacteria, we have to keep in mind that other types of microorganisms also live on the skin[3,10]. The fungal community is similar all over the body regardless of physiology. The genus *Malassezia* predominates at the head, trunk, and upper extremities, whereas feet are colonized by a combination of *Malassezia*, *Aspergillus*, *Epicoccum*, *Rhodotorula*, *Cryptococcus*, and other genera[13]. *Demodex* is a tiny mite that is also present in normal skin, especially inside the follicles, although its role as a commensal organism remains uncertain[14]. To our knowledge, there is little information about the viral composition of the cutaneous microbiota.

All these communities of bacteria, viruses, fungi, and mites present in different skin ecosystems can influence the health of the host in both senses, either as a protective mechanism disease or by contributing to the initiation or development of different dermatoses and cutaneous infections[11,15].

Regarding the biological mechanisms that could explain the relationship between the alteration in the skin microbiota and the development of disease, its role inducing inflammation and modulation of the immune response is considered very important[16-18]. All these microorganisms can produce beneficial or pathogenic substances, and the interaction among them can also participate in the pathophysiology of some dermatoses. Examples of dysbiosis related to skin diseases include: increase density of pathogenic bacteria, such as in atopic dermatitis; reduced bacterial diversity, such as in psoriasis; increase of commensal organisms, such as in acne; and alterations of microenvironments and colonization by unique species, such as in chronic wounds[11] [Table 1].

THE MICROBIOME AND AGING

The microbiota changes as the host ages, but also it seems that the relationship between the host and the microbiota impacts host aging and life expectancy[19]. The changes in the microbiota with age have been extensively studied in the human gut[20]. In this sense, there is a proliferation of opportunistic *Proteobacteria* at the cost of symbionts *Firmicutes* and *Bacteroidetes* with age, as well as less abundance of *Bifidobacterium* (*Actinobacteria*) compared to younger adults[21] [Table 2]. These changes associated with age have been related with different factors implicated in dysbiosis and disease: dietary changes, especially those related with a scarce consumption of fibrous foods, and increased antibiotic administration, among others[22]. Furthermore, aging and dysbiosis have in common the inflammation, which is a known risk factor for the progression of several diseases related with age. Smith *et al.*[23] conducted an interesting study in African turquoise killifish by recolonizing middle-age fish (after being treated with antibiotic) with the gut microbiota from young fish. Surprisingly, they found that this change was associated with a significant increase in life expectancy. In addition, they also performed the opposite experiment: they recolonized young fish with the microbiota from middle-aged fish, finding that the metabolism of hyaluronic acid, a fundamental component of the extracellular matrix associated with skin aging, was increased in this model[23].

THE MICROBIOME AND SKIN AGING

The skin structure and function change with age, and this could be due not only to intrinsic factors such as cellular metabolisms, the immune system, or hormone changes, but also to extrinsic factors such as ultraviolet irradiation[24]. In this sense, the microbiota also changes over the lifetime[5], not only due to age, but also due to geography, age, diet, lifestyle, and pollution, among others[8,25-27] [Figure 1].

Skin aging is characterized by a decrease in sebum and hydration levels as well as immune dysfunction, which results in significant alterations in skin physiology[28]. These physiological changes also imply changes in the cutaneous ecology, inducing a disbalance of cutaneous microbiota[29].

The composition of the microbiome is different in old and young skin[7,30,31]. In puberty, the density of lipophilic bacteria proportionally increases with the increase of sebum levels, whereas it is much lower in elderly skin[5,32]. Moreover, metagenomic studies have shown a decrease of *Actinobacteria* in older skin[32,33]. However, the number of total bacteria increases in older people; specifically, more *Corynebacterium* species are found on the aged skin[34]. Shibagaki *et al.*[33] found that the diversification of skin microbiome in older skin is related to chronological and physiological skin aging, but it is related to the oral bacteria composition. Another study suggests that gut, oral, and skin microbiomes predict chronological age, being

Table 1. Dysbiosis related to skin diseases

Atopic dermatitis	Psoriasis	Acne vulgaris	Chronic wounds	AK/cutaneous SCC
90% of AD patients are colonized with *Staphylococcus aureus* on both lesional and non-lesional skin (compared with less than 5% of healthy individuals) There is an increase in anaerobic bacterial species, including *Clostridium* and *Serratia*	Higher levels of *Proteobacteria* on the trunk Higher levels of *Streptococcus* and *Propionibacterium* in lesions	Different *Propionibacterium acnes* strains between acne patients and healthy controls	Proliferation of several different anaerobic bacteria, including *Staphylococcus*, *Serratia* and *Clostridium*	Higher relative abundance of *Propionibacterium* and *Malassezia* on nonlesional skin than in AK/SCC lesions *S. aureus* overabundance in AK/SCC
Increased microbial load at the lesion site	Less microbial diversity in psoriatic lesions	Similar relative abundance of *P. acnes* between both groups but colonization of the affected follicles by multiple bacterial species in addition to *P. acnes*, including other commensal microorganisms, such as *Streptococcus epidermidis*	Decreased bacterial diversity Opportunistic colonization of specifically adapted microbes	More studies are required to expand and confirm these findings

AK: Actinic keratosis; SCC: squamous cell carcinoma.

Table 2. Dysbiosis in aging

	Actinobacteria	*Bacteroidetes*	*Firmicutes*	*Proteobacteria*
Gut	Decrease of *Bifidobacterium*	Unchanged or decrease Not seem to be related to the ageing	Changes in the proportion: decrease in *Clostridium* and increase in *Bacilli*	Enrichment in facultative anaerobes, notably "pathobionts" (opportunistic components that can induce pathology, such as *Enterobacteriaceae*)
	Actinobacteria is not highly represented in the human gut	*Bacteroidetes* and *Firmicutes* dominate the gut microbiota (93%-95%)		There is a proliferation of opportunistic *Proteobacteria* at the cost of symbionts *Firmicutes* and *Bacteroidetes*
Skin	Lower abundance in the older group, in relation to the decrease in the *Propionibacterium* genus. However, *Corynebacterium* significantly increase in the elderly	Increase	Increase; however, *Staphylococcus* genus is significantly decreased in the older group	Increase, especially the *Acinetobacter* genus
	Actinobacteria is the predominant phyla in the skin			
Oral	Increase in *Actinomyces*		Increase in *Lactobacillales* and *Staphylococcus*	Increase in *Enterobacteriaceae* and *Pseudomonas*
	Oral bacteria contribute to bacterial diversification and alteration in the older skin: *Streptococcus* and *Veillonella* (F), *Rothia* (A), *Prevotella* (B), *Haemophilus* (P), and *Fusobacterium* are members of the core taxa of the oral bacterial community that are significantly enriched in the older skin microbiome.			

A: *Actinobacteria*; B: *Bacteroidetes*; F: *Firmicutes*; P: *Proteobacteria*.

the skin microbiome the most accurate to predict it, on average yielding predictions within 4 years of chronological age[35] [Table 1].

Nevertheless, some authors consider that changes in skin microbiota are also a consequence of aging, rather than a cause[34].

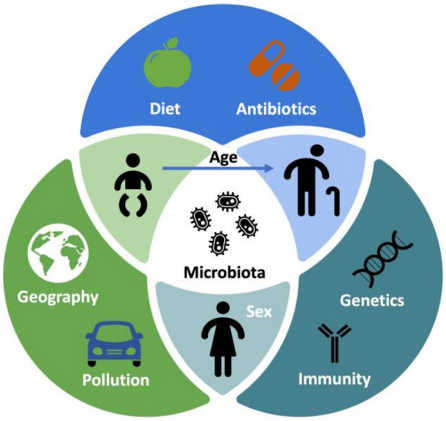

Figure 1. External and internal factors that influence the composition of the microbiome.

As research on the skin microbiome progresses, there is growing interest in finding ways to help the skin to recover and regenerate from the numerous microorganisms living on it. In this sense, the manipulation of the gut microbiota of older adults could be an innovative strategy in the prevention and treatment of age-related comorbidities; therefore, a balanced skin microbiota could help to prevent premature skin aging[26]. Recently, oral and topical probiotics have been proposed as a therapy for restoration of the microbiota balance, supporting skin barrier function, as well as protecting against environmental factors, especially ultraviolet radiation-induced skin damage[36-38]. The following are some examples of relevant effects in the skin caused by different microorganism: *Streptococcus thermophiles* enhance ceramide levels of the stratum corneum when is topically applied on the skin[39]; and some probiotics help to restore the balance between free radical removal and production, which may slow aging[40]. On the other hand, oral and topical compounds are being investigated to know their potential therapeutic effect on the modulation of the skin microbiome[41]: *Orobanche rapum* extract stimulates skin rejuvenation and protects the cutaneous microbiota, inducing healthier skin[42]. In addition, the term "Photobiomics" has recently been introduced, referring to the use of low levels of visible or near-infrared light to modify the gut microbiome through photobiomodulation[43].

THE MICROBIOME AND SKIN CANCER

The occurrence of malignancies increases with age. The association between the microbiome and malignancies is a recent and not very well studied hypothesis also in skin cancer. Different studies suggest the role of microbiome in the tumoral genesis and/or progression, especially the gastrointestinal one. Additionally, the gut microbiota seems to play an important role in the response to immunotherapy, and, perhaps, this could also be extrapolated to the skin microbiota[16,17].

Some of this work indicates that dysbiosis may promote cancer. In normal circumstances, the microbiome does not induce a pro-inflammatory response due to the tolerance that the immune system has developed to commensal bacteria, preserving homeostasis[17]. When these mechanisms are disrupted or new pathogenic microorganisms enter into this balanced system, dysbiosis occurs and the immune system is activated towards the microbiome, causing inflammation[18,44] or modifying the local immune response, which can trigger the tumoral growth in the intestine[16,17]. It has also been reported that intestinal inflammation enhances the possibility of the microbiota to produce genotoxins that cause damage to DNA, promoting the development of tumors[45].

Focusing on skin cancer, Mrázek *et al.*[46] conducted a study on pigs, showing that the bacterial diversity was significantly different between normal skin and melanoma surface. They found that *Trueperella* and *Fusobacterium* genera were present in the microbiome of melanoma samples, which also had an increased amount of *Streptococcus* and *Staphylococcus* compared to the microbiome of normal skin. Moreover, *Fusobacterium nucleatum* increased with age in animals with progressive melanoma, whereas it diminished when animals had regressive disease. The authors concluded that *Fusobacteria* might be associated with tumor progression, and, as a possible mechanism, they proposed a tumor-based immune evasion: *F. nucleatum* - bound tumors are protected against the immune system, inhibiting natural killer cell cytotoxicity through the interaction of the fusobacterial protein Fap2 with the inhibitory receptor TIGIT of the immune cells. *F. nucleatum* can bind to different tumor types, including melanoma[46].

Recent studies suggest that some microorganisms of the skin microbiome can suppress tumor growth[47]. In this sense, dysbiosis would be potentially harmful because the host microbiota loses its protective function and/or gains a harmful microbial community. This study describes a strain of *Staphylococcus epidermidis* common in the microbiota of the skin that produces 6-N-hydroxyaminopurine (6-HAP), a molecule that inhibits DNA polymerase activity[47]. In culture, 6-HAP selectively inhibited the proliferation of tumor cell lines but did not inhibit normal keratinocytes. Intravenous injection of 6-HAP in mice suppressed melanoma growth without evidence of systemic toxicity. Colonization of mice with a strain of *S. epidermidis* producing 6-HAP reduced the chronic ultraviolet radiation skin damage and developing of tumors compared to mice colonized by a control strain that did not produce 6-HAP[47]. *S. epidermidis* strains producing 6-HAP have been found in the metagenome from the skin of multiple healthy human subjects, suggesting that the microbiome of some individuals may protect against skin cancer[47]. These findings show a new role for skin commensal bacteria in host defense against skin cancer induced by ultraviolet radiation.

Wang *et al.*[48] proposed an *in vitro* model irradiating with co-cultures of human melanocytes and commensal skin bacteria containing *Propionibacterium acnes* and *S. epidermidis*. Commensal *S. epidermidis* and its byproduct lipoteic acid (LPA or TLR2 ligand, which has specific anti-inflammatory action on keratinocytes, increasing UVB resistance) promote melanocyte survival after UVB irradiation; this effect is due to an upregulation of TRAF1, CASP5, CASP14, and TP73; however, *P. acnes* induces apoptosis of UVB-irradiated melanocytes mediated by TNF-alpha production. The apparently opposite effects can be explained by the different location and concentration of *P. acnes* in the normal skin. *P. acnes* is found primarily in hair follicles, whose environment is critical for the maintenance of stem cells. Considering that DNA damage in these cells can result in severe mutations, *P. acnes* may have been accepted during evolution in the hair follicle niche to contribute to the health of the stem cell niche. By contrast, *S. epidermidis* is more present in dry areas of the body, especially on the inter-follicular epidermis. As mentioned above, LTA helps melanocytes to escape from UVB-induced apoptosis, which is crucial to preserve viable inter-follicular melanocytes during sun exposure, preventing their transformation into tumoral cells[48]. Other studies that support this perspective include previous observations from the intestinal microbiome probing that microbes may suppress tumor growth by the production of short-chain free fatty acids[49,50]. Additionally, skin microbiota potentially produce cis-urocanic acid by degrading L-histidine, which plays a role in the immunosuppression induced by UV radiation and suppresses melanoma growth[47].

To our knowledge, there are few human studies investigating the relationship between the skin microbiome and skin cancer. One of them did not find significant differences in the diversity or abundance of bacterial genera between the microbiome of cutaneous melanomas and melanocytic nevi, although the cohort was relatively small (17 nevi and 15 melanoma)[51].

Regarding non-melanoma skin cancer, a recent study investigated the microbiomes of actinic keratosis (AK) and cutaneous squamous cell carcinoma (SCC) in immunocompetent men either longitudinally or cross-sectionally[52]. *Propionibacterium* and *Malassezia* were relatively most frequently found in healthy perilesional areas, whereas *Staphylococcus* was more abundant in both AK and SCC, with a predominance of the *S. aureus* species. Particularly, eleven Operational Taxonomic Units (OTUs) of *S. aureus* were identified in the participating subjects; six of these were significantly associated with SCCs, with OTUs 50 and 216 present in all patients, suggesting their specific involvement in progression from AK to SCC[52]. Lately, these results have been confirmed, finding an overabundance of *S. aureus* in SCC and AK compared with basal cell carcinoma samples. Consequently, as *Malassezia* was decreased in SCCs, it is hypothesized that this yeast could be protective against *S. aureus* over-colonization[53] [Table 1].

According to this local possible pathogenic effect of the skin microbiota in the promotion and/or progression of skin cancer, a recent study established the role of the gut microbiota in the response to anti-PD-1 immunotherapy in patients with metastatic melanoma. A significant association between the presence of some specific bacteria such as *Bifidobacterium longum*, *Collinsella aerofaciens,* and *Enterococcus faecium* and a positive clinical response to the therapy was found[54]. According to this, reconstitution of germ-free mice with fecal material from responders improved tumor control, enhanced T cell responses, and increased efficacy of anti-PD-L1 therapy. These results suggest that commensal microbiome may modulate anti-tumor immunity in cancer patients[54].

CONCLUSION

Multiple studies indicate that age plays a critical role in modifying the human microbiota.

Furthermore, it appears that the microbiota may interact with ultraviolet radiation, facilitating skin damage and skin cancer or protecting against them. This knowledge opens the possibility of modulating the microbiota to maintain or improve health during aging. Thus, topical and oral probiotics are a promising therapy in the prevention of premature skin aging.

DECLARATIONS

Authors' contributions

Conceptualization, investigation, writing original draft: Abadías-Granado I
Investigation, writing original draft: Sánchez-Bernal J
Conceptualization, supervision, writing, review and editing: Gilaberte Y

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Consent for publication

Not applicable.

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