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Review

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The microbiome and dermatological diseases*

Mikrobiom a choroby skóry

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Summary

The human skin harbours hundreds of species of commensal organisms, collectively known as the skin microbiota. The composition of the microbiota can be modified by various factors, such as host genotype, diet, antibiotics, hygiene, and pathogen infections, among others. Changes in these factors can cause microbiome disruption known as dysbiosis, leading to the outgrowth of potential pathogenic bacteria or a decrease in the number of beneficial bacteria. Dysbiosis has been implicated in some dermatological diseases. This mini-review aims to discuss the topic of the skin microbiota and its potential effects on various skin diseases.

Key words: **skin microbiota • dysbiosis • skin disease • dermatological disease**

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Introduction

The microorganisms inhabiting the human body are collectively known as the microbiota. They colonize the most environmentally exposed surfaces such as the skin, mouth, gut and vagina immediately after birth [43]. Estimated at approximately 100 trillion organisms, most of which are bacteria, the microbiota numbers about 10 times the total cells of the human body [43]. The majority of microbes reside in the gastrointestinal tract, have a profound influence on human physiology and nutrition, and are crucial for human life [7,37]. The suggested total number of bacteria inhabiting a healthy human gut is approximately 10^{14} [11]. Their collective genome, referred to as the metagenome, is estimated to contain at least 100 times more unique genes than the human genome [43]. Of the 70 known bacterial divisions and the 13 divisions of Archaea that have been described to date, only two phyla predominate within the intestine: the Bacteroidetes (16.3%) and the Firmicutes (65.7%) [23,25]. The fact

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that the bacteria within the human intestine represent such a small fraction of the total bacteria found on the planet suggests that these bacteria are highly evolved and specialized to live within the mammalian intestine. Numerous studies have identified important roles for bacterial signals in promoting the optimal digestion of food [37], maintaining epithelial homeostasis [3], modulating fat metabolism [6], promoting angiogenesis [74], supporting resistance to infection [69], and promoting normal development and regulation of immune cell homeostasis [15], among others. The composition of the intestinal microbiota can be modified by various factors, such as host genotype, diet, antibiotic ingestion, pathogen infections and other life events [73]. Changes in these factors can cause microbiome disruption known as dysbiosis, leading to the outgrowth of potential pathogenic bacteria or a decrease in the number of beneficial bacteria [33]. Though it is widely accepted that shifts in the gut microbiota composition and density can affect local immune responses, it is becoming clear that these changes can also alter host immunity and inflammation in organs distal from the intestine [10]. Accumulating evidence indicates that dysbiosis is not only a marker of various inflammatory diseases but also a trigger, leading to altered immune responses that underlie these diseases [35,65]. Intestinal dysbiosis has been recently implicated in numerous inflammatory and autoimmune diseases, including inflammatory bowel diseases (IBD) [48], coeliac disease [70], rheumatoid arthritis [68], diabetes mellitus type I [84] and II [62], multiple sclerosis [55], and allergies [36], among others. A strong association with dysbiosis has also been found in obesity [76], metabolic syndrome [79], atherosclerosis [82], and cancer [49]. Despite our growing understanding of the roles that intestinal bacteria play in normal development and regulation of the human immune system, little is known about the microbiota inhabiting the skin, the largest organ of the body. This mini-review aims to discuss the topic of skin microbiota and their potential effects on various skin diseases.

Skin microbiota

The skin is an ecosystem composed of 1.8 m^2 of diverse habitats with an abundance of folds, invaginations and specialized niches that support a wide range of microorganisms. The primary role of the skin is as a physical barrier, resisting penetration by microorganisms and potential toxins while retaining moisture and nutrients inside the body. The skin is also a primary interface with the outside environment and, as such, is colonized by a diverse group of microorganisms, including bacteria, fungi, viruses and mites.

Although human skin is a rather inhospitable environment, very poor in nutrients, acidic, desiccated, with continual shedding of superficial skin cells, it is inhabited by one billion bacteria per square centimetre on average [29]. The microbiota of the skin is characterized by the same four predominant phyla as in other body sites: Actinobacteria, Firmicutes, Proteobacteria, and Bacteroidetes [18,28]. The proportions, however, differ significantly: whereas Actinobacteria members are more abundant on skin, Firmicutes and Bacteroidetes members are more abundant in the gastrointestinal tract. A common feature of gut and skin microbial compositions is a low diversity at the phylum level, and a high diversity at the species level.

Additionally, microbial profiling has revealed that the relative distributions of bacterial phyla and families differ significantly among various skin sites [24]. These differences in microbial distribution reflect differences in skin temperature, humidity, glandular distribution, environmental exposure, etc [24]. Some regions of the skin, for instance, are partially occluded, such as the groin, axillary vault and toe web, and are higher in temperature and humidity. These regions are inhabited by microorganisms preferring moist conditions, such as Gram-negative bacilli, *Corynebacterium* spp. and *Staphylococcus* [63]. Other areas, characterized by a high density of sebaceous glands, including the face, chest and back, are preferentially inhabited by lipophilic microorganisms, such as *Propionibacterium* spp. and *Malassezia* spp. [63]. Arm and leg skin, due to the relative desiccation and fluctuations of surface temperature, harbour fewer organisms than other skin areas [63]. There are also various factors specific to the host (age, location and sex), as well as environmental factors (occupation, clothing choice, antibiotic use, hygiene, UV exposure, etc) that significantly affect the composition of skin microbial flora [30]. Despite bacterial diversity at different sites, skin microbial composition seems to be more similar between skin sites than among other body habitats.

Generally, bacterial skin populations can be categorized as: i) transient (contaminant, non-reproducing), ii) temporary residents (not typically resident, yet can colonize), and iii) resident (growing and reproducing) flora [53]. The 'normal' resident skin flora includes *Propionibacterium acnes*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Corynebacterium diphtheria*, *Corynebacterium jeikeium* and *Pseudomonas aeruginosa*. The roles of resident bacteria are highly varied and not fully understood.

Microbiota-cutaneous immune system interactions

In addition to being a physical barrier, the skin is an immunological barrier [12]. The skin immune response is crucial in infection and wounding, but also modulates the commensal microbiota residing on the skin. Keratinocytes continuously sample the microbial antigens through pattern recognition receptors (PRRs) capable of recognizing pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide, flagellin, nucleic acids from Gram-negative bacteria, mannan and zymosan from fungal cell walls, and peptidoglycan and lipoteichoic acid from Gram-positive bacteria. The key PRRs involved in recognition of these microbial components are Toll-like receptors (TLR), nucleotide oligomerization domain receptors (NODs), and mannose receptors [60]. The acti-

Tab. 1

Ligand	Microbiota	Target	Immunological effect	Reference
LTA	*Stapphylococcus epidermis*	TLR-2 ligation on keratinoytes	Suppression of TLR-3-mediated inflammation (wound healing)	[42]
unspecified	*Vitreoscilla filiformis*	TLR-2 ligation on DCs	Induction of IL-10 production and differentiation of Tr1 cells	[80]
PSA	*Bacteroides fragilis*	DCs TLR-2 ligation on FOXP3+ Treg cells	Induction of FOXP3+ Treg cells Stimulation of IL-10 production	[64,66]
unspecified	*Clostridium spp.*	Gut epithelial cells	Induction of FOXP3+ Treg cells	[4,50]
SCFAs	*Various gut microbiota*	GPR43 ligation on FOXP3+ Treg cells	Maturation and proliferation of FOXP3+ Treg cells	[72]

Abbreviations: DC – dendritic cell; FOXP3 – forkhead box P3; GPR – G protein-coupled receptor; IL- interleukin; PSA – polysaccharide A; SCFA – short-chained fatty acid; TLR – toll-like receptor; Treg – regulatory T cell; Tr1 – T regulatory 1 cells.

vation of keratinocyte PRRs by PAMPs initiates the innate immune response, resulting in the secretion of cytokines, chemokines and antimicrobial peptides (AMPs), such as cathelicidins and β-defensins that altogether effect the adaptive immune response [14]. Secretion or release of AMPs provides innate antibiotic-like actions against infectious pathogens, and some of them, such as cathelicidin LL-37, also trigger inflammatory cell recruitment and cytokine release [52]. Keratinocytes, different immune cells and skin microorganisms are involved in a constant interplay modulated by a variety of signals of both host and microbial origin.

Despite being constantly exposed to large numbers of microorganisms, the skin can discriminate between harmless commensal microorganisms and harmful pathogens. The mechanism responsible for this discrimination is not fully understood, but involves the induction of tolerance by commensal microorganisms. In the steady state, both the skin Langerhans cells (LCs) and dermal dendritic cells (dDCs) maintain the tolerance through induction of FOXP3+ regulatory T cells, which can act in a bacteria-specific manner [78]. While LCs have been demonstrated to promote skin resident Treg cell proliferation [71], it seems that mainly dDCs present self-antigens in the skin draining lymph nodes [5,9]. Suboptimal DC activation and very low doses of antigens, or a combination of these factors, have been linked to the induction of bacteria-specific Treg cells [78]. Recently, numerous PAMPs of commensal origin have been identified capable of inducing Treg cells (Table 1). Markers typical for skin resident Treg cells are CD44 and CD103, indicating that the majority of skin Treg cells are of memory/effector type [22,67,75]. Skin Treg cells also express high levels of IL-10 and TGF-β, two potent immunoregulatory cytokines [75].

Accumulating evidence indicates that microorganisms are capable of modulating the host immune response. A large number of Gram positive bacteria such as *Lactococcus*, *Streptococcus* and *Streptomyces* species are able to produce factors that inhibit other bacteria [27]. *Staphylococcus epidermidis*, for instance, the dominant commensal bacterium, can selectively inhibit skin pathogens such as *Staphylococcus aureus*, group A *Streptococcus* and *Escherichia coli* by phenol-soluble modulins (PSM), such as PSMγ and PSMδ [17]. PSMs function in a similar mechanistic manner as various AMPs, creating pores and causing membrane leakage and membrane perturbation in bacteria. PSMs can also enhance the antimicrobial activity of the host AMPs [27]. It has been recently found that a small molecule of <10 kDa produced by *Staphylococcus epidermidis* can trigger keratinocyte expression of AMPs through a TLR2--dependent mechanism [41]. Similarly, co-cultivation of differentiated human primary keratinocytes with live *Staphylococcus epidermidis* enhances production of various AMPs and RNases [27]. Moreover, keratinocytes pre-incubated with *Staphylococcus epidermidis*-conditioned media strongly enhanced AMP production by keratinocytes activated by *Staphylococcus aureus* [83]. This suggests that commensal bacteria are capable of sensitizing keratinocytes towards pathogenic bacteria and amplifying the innate immune response. It has also been demonstrated that lipoteichoic acid (LTA) produced by *Staphylococcus epidermidis* inhibits both inflammatory cytokine release from keratinocytes and inflammation triggered by injury through a TLR2-dependent mechanism [42].

Dysbiosis and skin diseases

Various skin diseases, such as psoriasis and atopic dermatitis, are strongly associated with dysregulation of the skin immune response, which affects and/or results from the changes in the microbiota (Table 2).

Atopic dermatitis is a chronic inflammatory and pruritic skin disease characterized by flares and remissions. Atopic dermatitis lesions are characterized by low levels of AMP production, despite the presence of skin inflammation, and are regularly infected with pathogens, including *Staphylococcus aureus*, which can be isolated from

Tab. 2

Disease	Defect in innate immunity	Microbiota	Reference
Atopic dermatitis			
	Lower expression of cathelicidin (LL-37), dermicidin and hBDs compared to psoriatic lesions Increased expression of RNase7 and psoriasin Upregulation of Th2 cytokines Defective TLR2 and TLR9 signalling pathways	↑ *Staphylococcus aureus* ↑ various bacterial infections	[19,32,45,54,57,77]
Psoriasis			
	Excessively high expression of cathelicidin and hBDs Upregulation of proinflammatory cytokines (Th1/Th17) Upregulation of TLR1, TLR2 Downregulation of TLR5	↑ *Firmicutes* ↓ *Propionibacterium* ↓ *Actinobacteria* ↓ bacterial infections	[19,28,31,58,77]
Acne			
	Upregulation of TLR2, TLR4 Upregulation of proinflammatory cytokines Activation of complement	↑ *Propionibacterium acnes*	[20,30,40,77]
Rosacea			
	Excessively high expression of cathelicidin High expression of kallikrein 5 activating hCAP18 to LL-37 Upregulation of TLR2	↑ Staphylococcus epidermis ↓ diversity if bacteria	[34,40,85,86,87]

Abbreviation: hBD – human beta defensin; hCAP – human antibacterial cathelicidin; Th – T helper; TLR – toll-like receptor; ↑ - increase; ↓ - decrease.

more than 90% of patients [19,57]. Interestingly, RNase7 and psoriasin are induced in atopic dermatitis skin and the AMP induction is upregulated by barrier disruption [32]. It is believed that the upregulation of Th2 cytokines in atopic dermatitis lesions at least partially accounts for the suppression of the innate immune response observed in AD [54]. Inhibited induction of some but not all AMPs is thought to contribute to the susceptibility of atopics to infection. Polymorphisms within genes encoding TLR2 and TLR9 have also been associated with atopic dermatitis [77].

Psoriasis is a chronic inflammatory skin disease mediated by T cells, which trigger keratinocytes to hyperproliferate and perpetuate the disease. The disease has been strongly associated with Th1 and Th17 cytokine profiles. Psoriatic lesions are characterized by high production of cathelicidins and hBDs as well as by a strong innate immune response [19,31]. Keratinocytes from psoriatic plaques express high levels of TLRs 1 and 2 [77]. In psoriatic lesions, the representation of *Propionibacterium* and *Actinobacteria* species is lower than in normal skin, while *Firmicutes* species are overrepresented [28]. It seems, therefore, that psoriasis is, in part, associated with substantial alteration in the composition and representation of the cutaneous microflora; however, the disease has not been linked to any clear microbial component, although the guttate subset of psoriasis has been associated with streptococcal infections [58].

The commensal skin bacterium *Propionibacterium acnes* is associated with the common teenage malady acne, which is an inflammatory disorder of the pilosebaceous unit. *Propionibacterium acnes* and other lipophilic microorganisms secrete lipases, proteases and hyaluronidases that injure the tissue [20]. It has been found that *Propionibacterium acnes* is capable of activating classical and alternative complement pathways, leading to the formation of C5a, an anaphylatoxin that induces the secretion of proinflammatory cytokines, including TNF-α, IL-1β, and IL-8 by monocytes [77]. *Propionibacterium acnes* also produces low-molecular weight, serum-independent chemotactic factors that attract neutrophils through the epithelium wall, into the lumen of sebaceous follicles [30]. It has been shown that there is a positive correlation between the severity of acne lesions and the upregulation of TLR2 and TLR4 [40,77].

In rosacea, similarly to psoriasis, the upregulation of cathelicidin and TLRs has been observed, driving inflammation and abnormal blood vessel growth by mechanisms of cell activation [40,86,87]. These defects in innate immune mechanisms could impact the homeostasis of skin-resident microflora, which may disrupt the skin barrier and induce abnormal inflammatory responses. Although no specific pathogens have been isolated in the lesional skin of rosacea [47], the dysbiosis has been implied in the pathogenesis of the disease. The predominance of *Staphylococcus epidermidis* has been observed in

the lesional skin, while other bacteria have been recorded at much lower levels compared to peripheral non-lesional skin [85]. In addition, studies have also revealed increased microbial loads or immune hyperactivity to the following microorganisms: *Demodex folliculorum*, *Bacillus oleronius*, *Helicobacter pylori*, and *Chlamydophila pneumonia* [34].

Conclusions

Recent studies have shown that skin microbiota contribute to the protection against pathogenic microorganisms as well as against overgrowth of opportunistic pathogens. A great example of such a role is provided by *Staphylococcus epidermidis*, the most common skin bacterium capable of inhibiting the colonization and biofilm formation by *Staphylococcus aureus* [39]. *Staphylococcus epidermidis* has been demonstrated to produce the glutamyl endopeptidase protein, which can synergize with the human AMP β-defensin 2, interfering with *Staphylococcus aureus* colonization. It has also been shown that cutaneous commensals exert their effect against pathogens by augmenting IL-1 signalling and amplifying the response in accordance with the local inflammatory milieu [51]. It is worth mentioning that the IL-1 pathway is an evolutionary conserved mechanism of the innate immune system that may have arisen as an early mediator of host skin-commensal cross talk, implying the possibility of coevolution. Therefore the maintenance of normal skin microflora may be crucial to maintain healthy skin. The composition of the skin microbiota, however, can be modified by various factors, such as diet, antibiotic ingestion, hygiene, pathogen infections, etc. Changes in these factors can cause dysbiosis, resulting in the outgrowth of potential pathogenic bacteria or a decrease in the number of beneficial bacteria, ultimately leading to induction and/or exacerbation of the disease.

The picture becomes even more complicated when taking into account the cross-talk between the skin and other organ systems that can be assumed based on the number of skin conditions that commonly co-manifest with non-cutaneous disorders [81]. The existence of a specific communication axis between the skin, the gut, and the brain has been recently postulated, since both the gut and skin exhibit similar neuronal and inflammatory activity [2]. Though currently it is widely accepted that shifts in the gut microbiota composition and density can affect local immune responses, it is becoming clear that these changes can also alter host immunity and inflammation in organs distal from the intestine [10]. There is convincing evidence indicating the association between gut dysbiosis and numerous inflammatory and autoimmune diseases, including dermatological diseases [16,61]. Current data suggest, for instance, that acne vulgaris has a strong gut microbial involvement [13]. The link between gut dysbiosis and psoriasis seems also plausible. First of all, there is a known association between psoriasis and Crohn's disease (CD), a chronic inflammatory disease of the gastrointestinal tract resulting, at least partially, from a breakdown of immune tolerance to the gut microbiota [46]. CD patients are five times more likely to develop psoriasis compared with a control population [38,88]. Conversely, patients with psoriasis are at greater risk of developing CD than the general population [44]. Both diseases feature increased permeability of the intestine [56]. In addition to a similar peak age of onset, the two diseases show an overlap in their immunopathogenic pathways (Th23/Th22/Th17 axis), genetic mutations and response to biologic therapies, implying similar pathology [26].

It also seems that any deviations from the normal microbiota during childhood may alter the outcome of immune development and potentially predispose individuals to various inflammatory and autoimmune diseases later in life. It has been observed, for instance, that normally, intestinal colonization of neonates is dominated by transmission of bacteria from the maternal vaginal flora [21]. However, infants born by Caesarean section are initially colonized more by bacterial species of epidermal origin, and are predisposed to development of allergies and asthma later in life [8]. Recent studies have also demonstrated the association between Caesarean section and low intestinal microbial diversity in infants and subsequent development of atopic dermatitis [1,59].

In conclusion, accumulating evidence indicates that resident commensals are necessary for optimal host skin immune fitness. Still, much has to be learnt about the interactions between skin commensals and the cutaneous immune system. Understanding the role of microbiota in maintaining skin homeostasis is not only of prime importance for human health, but might also help to develop new therapeutic strategies.

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