Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2022;31:105-109
doi: 10.15570/actaapa.2022.16

Skin and gut microbiota dysbiosis in autoimmune and inflammatory skin diseases

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Abstract

The human body is inhabited by complex communities of microorganisms. Changes in the composition and function of the skin and gut microbiota are linked to various skin diseases. The microbiota is an important modulator of the immune system and thus maintains homeostasis. Conversely, the immune system can also change the composition of the microorganism community. Thus, it is still unknown whether certain skin diseases are caused by primary changes in the local and/or remote microbiota, or whether dysbiosis is only a secondary consequence of the dermatoses themselves. Expanding knowledge of skin and gut microbiota dysbiosis in skin diseases may possibly lead to better understanding of their pathophysiologies and to the discovery of new molecular markers for their earlier diagnosis and targeted treatment; for example, using specific microbes to replace missing ones. This narrative review provides an overview of current knowledge about skin and gut microbiota dysbiosis in psoriasis, atopic dermatitis, hidradenitis suppurativa, seborrheic dermatitis, acne vulgaris, rosacea, and lichen sclerosus.

Keywords: microbiota, dysbiosis, skin, autoimmune, inflammatory

Received: 30 August 2022 | **Returned for modification:** 1 September 2022 | **Accepted:** 5 September 2022

Introduction

The skin and mucosal membranes have a host defense function by creating a barrier against noxious external factors. This barrier is complex. Functionally, its components can be subdivided into four different levels: a physical, chemical, immune, and microbial barrier. Because microbes in the microbial barrier can be found on the skin surface and on certain mucous membranes, they represent the outermost barrier and as such are the first defense against environmental invaders (1, 2). All microorganisms that inhabit a specific part of the body, including opportunistic, commensal, and pathogenic microorganisms, are united under the single term *microbiota* (2). The human microbiota consists mainly of bacteria and viruses, while archaea, fungi, and other eukaryotes represent a minor proportion (3). The term *microbiome* is broader and describes the collection of microorganisms and their genomes and the environment that the microbes inhabit, including the host epithelium, the immune system, and products produced by both microbes and the host (4). To better define complex microbial communities of the oral cavity, skin, nostrils, and gastrointestinal and urogenital tracts, the Human Microbiome Project (HMP) was founded in 2007 (5). When analyzing microbiota and microbiome, one often encounters the terms *alpha* (α) and *beta* (β) *diversity*, which represent the diversity of microbes within the sample or among the samples investigated, respectively. In recent years, culture-based methods of studying microorganisms have been replaced by molecular methods, including polymerase chain reaction (PCR), DNA fingerprinting, and especially next-generation sequencing (NGS), which is becoming increasingly sensitive, rapid, and cost-effective. Amplicon sequencing analyses usually target one marker gene; namely, the ubiquitous gene for 16S ribosomal ribonucleic acid (rRNA) in bacteria and archaea, and the internal transcribed spacer (ITS) region, and the 18S rRNA gene in fungi and other single-cell eukaryotes. The 16S rRNA gene contains nine variable regions that can be amplified and used for taxonomic profiling of the bacteria (and archaea) in the sample because they are phylogenetically diverse for a particular genus and species. Metagenomic shotgun sequencing, unlike 16S rRNA sequencing, fragments and amplifies the entire extracted DNA; that is, most or all of the genetic material in the sample. In addition to taxonomic classification, it makes it possible to study the functional potential of the microbes. Even more complex than metagenomics is metatranscriptomics, with which, through the amplification of microbial messenger RNA, direct information about their function can be obtained (6).

Normal skin and gut microbiota

The skin microbiota is taxonomically very diverse, both among different hosts and between individual skin regions of the same host. Microorganisms can be present in the skin up to the superficial part of the subcutaneous tissue. Whereas the microbiota of the epidermis is significantly influenced by environmental factors, the microbiota of the dermis is more stable and most likely universal to all skin regions. The composition of the skin microbiota changes during development and depends on the age of the subject (7). In newborns, it depends on the method of delivery. It stabilizes at about 3 years of age and again goes through hormonally conditioned dramatic changes at puberty, especially due to the secretion of sebum. Its third period of evident changes occurs with age, when sebum secretion decreases (8). The total number of microbes in the skin microbiota is estimated at 10^{12} (9). The largest share is represented by bacteria (60%), followed by viruses (30%) and eukaryotes (10%), whose representatives are mainly fungi (10). Part of the skin microbiota are also archaea, which represent up to 4.2% of all prokaryotes (11). The most dominant bacterial phyla of the skin microbiota are *Actinobacteria* (36–51%), *Firmicutes* (24–34%), *Proteobacteria* (11–16%), and *Bacteroidetes* (6–9%) (12, 13). Molluscum contagiosum, human papillomavirus, and Merkel cell polyomavirus are often part of the skin virome (10).

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Of the fungi, the genus *Malassezia* is the most predominant. In addition to sex, age, and geographical area, the diversity and composition of the microbial population depends on physiological characteristics of the skin, such as temperature, pH, exposure to ultraviolet rays, humidity, and the amount of sebum secreted. On the basis of these physiological factors, different skin areas can be classified into three topographical categories, including dry areas (e.g., underarms), which are mainly colonized by Betaproteobacteria, moist areas (e.g. the groin and popliteal areas), where the genera *Staphylococcus* and *Corynebacterium* predominate, and, finally, sebaceal areas (e.g., the face), with a predominance of the lipophilic genus *Cutibacterium*, followed by *Staphylococcus* and *Corynebacterium* (12–14). Figure 1 shows topographical skin regions with their characteristic bacterial species.

The highest number of microbes is found in the gut. Bacteria again represent the largest proportion of gut microbiota. Their total abundance is estimated from 10^7 in the stomach to up to 10^{14} per gram of content in the colon. The main bacteria inhabiting the small intestine are from the phyla *Firmicutes* and *Proteobacteria*.

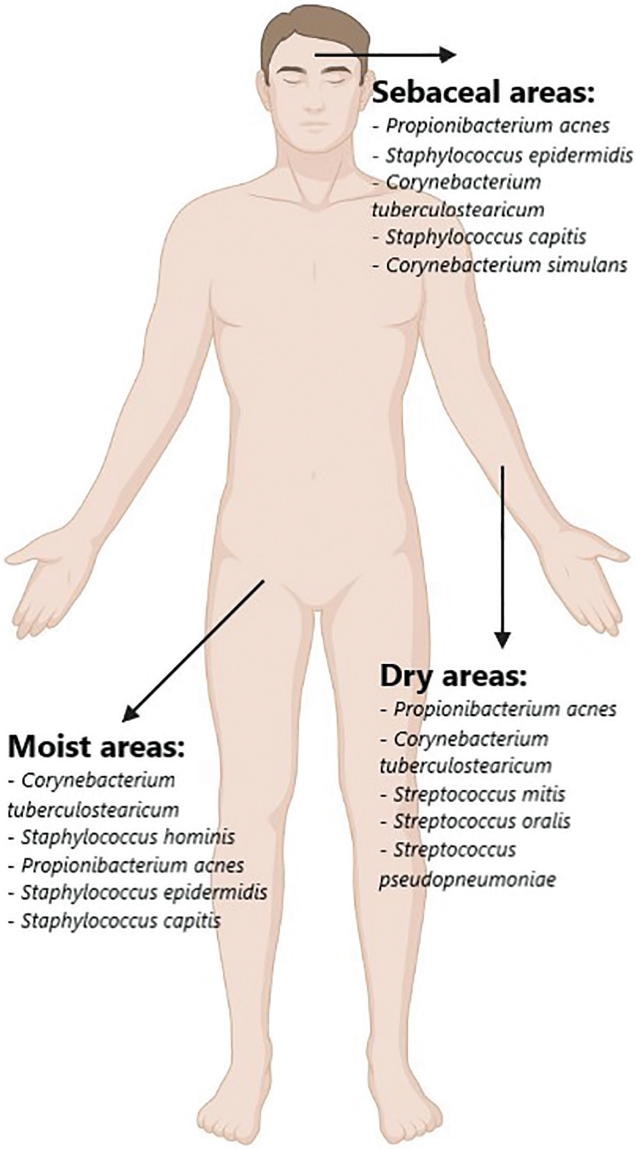

Figure 1 | Skin topographical microenvironments based on the physiology of the skin site with the top five abundant bacterial species (Byrd et al., 2018). Created by BioRender.

Anaerobes predominate in the large intestine, with the majority of bacteria belonging to the phyla *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Verrucomicrobia* (*Akkermansia*), and *Proteobacteria* (15).

Skin and gut dysbiosis in autoimmune and inflammatory skin diseases

Skin and gut dysbiosis associated with various autoimmune and inflammatory skin diseases is presented in Table 1.

Interplay between microbiota dysbiosis and host immune system

The microbiota is an important modulator of the immune system and, vice versa, the immune system can also influence changes in the composition of the microbial community, which is called dysbiosis or disruption of the microbial balance. It results in the absence of usual microbes and the presence of microbes with unfavorable effects. With the loss of beneficial functions of commensal microorganisms or due to harmful functions of pathogenic microorganisms, activation of the immune system can occur, thereby possibly causing or aggravating diseases. However, it is still unknown whether changes in the local and/or remote microbiota are the primary event in the development of certain skin diseases, or whether dysbiosis is only a secondary consequence of the dermatoses themselves (1). The recent discovery of dysbiosis already present on clinically unaffected predilection sites of hidradenitis suppurativa that resembled the microbiota of lesions of hidradenitis suppurativa suggests a primary role of dysbiosis in the initiation of inflammation and lesion formation and argues against secondary dysbiosis (38).

When pathogenic microbes come into contact with the human body through the epithelium, they are detected by pattern recognition receptors (PRRs) on macrophages (39). PRRs include toll-like receptors (TLRs) and NOD-like receptors (NLRs) for the detection of bacterial peptidoglycans and viral and fungal proteins (8). Upon detection of pathogenic microorganisms, PRRs trigger the secretion of first-line pro-inflammatory cytokines, mainly interleukin (IL)-1 and IL-18. IL-1 is a strong inducer of the release of antimicrobial peptides (AMPs) from keratinocytes (40). In addition, microbes can influence the growth of other microbes through the secretion of bacteriocins, auto-induced peptides, and phenol-soluble modulins, and by releasing signaling inhibitory molecules. Some of these bacterial products, for example, reduce the virulence of the pathogen and increase the immune response against it. In addition to the release of bacterial products, commensal microbes prevent the development of dysbiosis with an effect on mucosal-associated invariant T cells (MAITs) (8). Likewise, commensals regulate complement components and can stimulate neutrophil and cytokine production (7). Moreover, microbial metabolites can induce epigenetic modifications (41). AMPs, together with other inflammatory cytokines characteristic of specific inflammatory dermatoses, trigger the differentiation of T lymphocytes, which further stimulate the release of inflammatory mediators that stimulate the formation of chemokines and, last but not least, AMPs, which creates a "vicious cycle" of inflammation (40). Table 2 presents the potential role of excess and deficient microbes in the pathogenesis of autoimmune and inflammatory skin diseases.

Table 1 | **Skin and gut dysbiosis associated with various autoimmune and inflammatory skin diseases.**

	Skin microbiota changes compared to healthy controls			Gut microbiota changes compared to healthy controls		
Skin disease	**Excess microbes**	**Deficient microbes**	**Reduced dysbiosis after treatment**	**Excess microbes**	**Deficient microbes**	**Reduced dysbiosis after treatment**
Psoriasis	*Firmicutes*, *Corynebacterium*, *Staphylococcus*, and *Streptococcus* (16)	*Actinobacteria*, *Cutibacterium* (16)	With NB UVB, cyclosporin A, retinoic acid, fumarates, methotrexate, adalimumab, ustekinumab (17, 18)	*Firmicutes*, *Actinobacteria*, *Verrucomicrobia*, *Faecalibacterium*, *Bacteroides*, *Bifidobacterium*, *Megamonas*, and *Roseburia* (19)	*Bacteroidetes*, *Euryarchaeota*, *Proteobacteria*, *Prevotella*, *Alistipes*, and *Eubacterium* (19)	With secukinumab; no significant change with ustekinumab (20)
Atopic dermatitis	*Staphylococcus aureus* (correlates with intensity of AD), *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*; more diverse non-*Malassezia* spp. (*Aspergillus*, *Candida albicans*, *Cryptococcus diffluens*) (21)	Streptococci, *Cutibacterium*, *Acinetobacter*, *Corynebacterium*, and *Prevotella*; *Malassezia* spp. (21)	With dupilumab, conventional therapy (topical corticosteroids), and dilute bleach baths (21–23)	*Bifidobacterium pseudocatenulatum*, *Faecalibacterium prausnitzii*, *Clostridium*, and *Escherichia coli* (24)	*Akkermansia*, *Bifidobacterium*, *Enterococcus*, *Bacteroides*, and *Ruminococcus* (24)	NA
Hidradenitis suppurativa	Coagulase-negative staphylococci, *Porphyromonas*, *Prevotella*, and *Staphylococcus aureus* (25); in HS tunnels *Corynebacterium* and *Acinetobacter* (26)	NA	NA	Conflicting results (25)		NA
Seborrheic dermatitis / dandruff	*Malassezia*, *Ascomycota*, *Bisidiomycota*, *Mycosphaerella*, *Candida*, *Filobasidium*, *Staphylococcus* and *Streptococcus* (27)	*Cutibacterium* (lower expression in lesions, higher expression in healthy skin of patients), *Ganoderma*, *Exidia*, *Pilatoporus*, and *Engyodontium* (27)	With peroral itraconazole (28)	NA		NA
Acne vulgaris	Difference in the diversity of *Cutibacterium acnes* strains; *Staphylococcus epidermidis* (29)		Increased abundance of antibiotic resistant *Cutibacterium acnes* and other skin commensal bacteria (e.g., *Staphylococcus epidermidis*) after various antibiotic therapies; changes of microbiota following treatment with peroral lymecyclin and sarecycline (29)	*Bacteroidetes* (30)	*Firmicutes*, *Clostridium*, *Clostridiales*, *Lachnospiraceae*, and *Ruminococcaceae* (30)	NA
Rosacea	*Demodex folliculorum*, *Firmicutes*, *Staphylococcus*, *Streptococcus* (31, 32)	*Actinobacteria*, *Cutibacterium* (31)	Topical 1% metronidazole in cream did not affect microbiota change, whereas peroral doxycycline did (33, 34)	*Acidaminococcus* and *Megasphaera* (35)	*Peptococcaceae*, *Methanobrevibacter*, *Slackia*, *Coprobacillus*, *Citrobacter*, and *Desulfovibrio* (35)	NA
Lichen sclerosus	*Porphyromonas*, *Parvimonas*, *Peptoniphilus*, *Prevotella*, *Dialister*, and *Peptostreptococcus* (prepubertal girls) (36); *Fusobacterium* (balanopreputial sac) (37)	*Corynebacterium* (prepubertal girls) (36); *Finegoldia* (balanopreputial sac) (37)	NA	*Dialister*, *Clostridiales*, *Paraprevotella*, and *Escherichia coli* (36)	*Phascolarctobacterium* (36)	NA

AD = atopic dermatitis, HS = hidradenitis suppurativa, IBD = inflammatory bowel disease, NA = not available, NB = narrow band, UV = ultraviolet.

Table 2 | **Potential role of microbes in the pathogenesis of autoimmune and inflammatory skin diseases.**

Microbe(s): disease	Potential role of microbe(s) in pathogenesis of disease (reference)
Staphylococcus aureus: psoriasis	Induction of IL-17-mediated inflammation (42)
Corynebacterium: psoriasis	Negatively regulates interferon signaling (43)
Bacteroides: psoriasis	Produces polysaccharide A, which activates Treg cells (19)
Prevotella: psoriasis	Improves intestinal mucosal integrity, reduces inflammatory markers in cecum (19)
Staphylococcus aureus: AD	Its peptidoglycan induces development of Th2 cells (44)
Cutibacterium acnes: AD	Strong inducer of Th1 immune response (45)
Porphyromonas, *Prevotella*: HS	Increase secretion of AMPs; *Prevotella* also stimulates Th17 and secretion of IL-23 and IL-1 (46, 47)
Acne-associated *Propionibacterium acnes* strains: acne vulgaris	Induce inflammatory responses in keratinocytes, sebocytes, and peripheral blood mononuclear cells (29)
Staphylococcus epidermidis: acne vulgaris	Possibly inhibits *Propionibacterium acnes* through various mechanisms (29)
Clostridium: acne vulgaris	Produces butyrate and inhibits inflammation (30)
Demodex folliculorum: rosacea	Activates TLR2, which then stimulates activity of kallikrein 5 (48)

AD = atopic dermatitis, AMPs = antimicrobial peptides, HS = hidradenitis suppurativa, IL = interleukin, Th = T helper, TLR = toll-like receptors, Treg = regulatory T cells.

Manipulation of dysbiosis as a therapeutic approach in the treatment of skin diseases

Manipulation of the microbiota with the goal of reducing dysbiosis has potential for new therapeutic approaches to the prevention and treatment of autoimmune and inflammatory diseases. Strategies to achieve gut microbiota eubiosis are well known and include the use of probiotics, prebiotics, synbiotics, fecal microbiota transplants, and antimicrobial interventions (49). A systematic review of the effectiveness of probiotics for psoriasis based on randomized controlled trials has shown that probiotics can improve the Psoriasis Area and Severity Index (PASI); however, the difference between patients and a placebo group on meta-analysis was not statistically significant (50). In contrast, a systematic review of randomized controlled trials of supplementation with probiotics in adults with atopic dermatitis has confirmed their beneficial effect on outcomes, both in reducing the severity of the disease and in improving quality of life. A mixture of *Lactobacillus salivarius* (LS01) and *Bifidobacterium* (BR03) appeared to be the best supplement for adult atopic dermatitis (51). Similarly, infants and children with atopic dermatitis treated with oral probiotics have significant differences in SCORing Atopic Dermatitis (SCORAD) compared to controls (52). Interestingly, a meta-analysis has shown that treatment with probiotics during both the prenatal and postnatal periods reduced the incidence of atopic dermatitis in infants and children (53). In contrast to gut microbiota manipulation, methods of human skin microbiota manipulation are developed to a lesser degree and include skin microbiota transplantation, antimicrobial therapy, prebiotics, probiotics, and postbiotics (54). Autologous transplantation of coagulase-negative *Staphylococcus* was tried in a randomized, double-blind, placebo-controlled clinical trial on patients with atopic dermatitis and led to a reduction of skin colonization with *Staphylococcus aureus* as well as to significant clinical improvement as assessed by the local Eczema Area and Severity Index (EASI) score (55).

Conclusions

Skin and gut microbiota are promising for research on the pathogenesis of autoimmune and inflammatory skin diseases. With the development of new molecular methods, there is increasing evidence of a link between dysbiosis and the immune system, and thus indirectly with the development of various diseases. In addition to bacterial dysbiosis, viruses and fungi also show potential for research into the pathogenesis of autoimmune and inflammatory skin diseases. Further research is needed to better understand the dialogue between microbes and the immune system.

Acknowledgement

The authors thank Prof. dr. Maja Rupnik for her advice on writing the manuscript.

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