Skin Microbiota

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Many relatively common chronic inflammatory skin diseases manifest on the face (seborrheic dermatitis, rosacea, acne, perioral/periorificial dermatitis, periocular dermatitis, etc.), thereby significantly imparing patient appearance and quality of life. Given the as yet unexplained pathogenesis and numerous factors involved, these diseases often present therapeutic challenges. Changes in human skin microbiota composition and/or functionality are believed to trigger immune dysregulation and, consequently, an inflammatory response, thereby playing a potentially significant role in the clinical manifestations and treatment of these diseases. Although cultivation methods have traditionally been used in studies of bacterial microbiome species, a large number of bacterial strains cannot be grown in the laboratory. Since standard culture-dependent methods detect fewer than 1% of all bacterial species, a metagenomic approach could be used to detect bacteria that cannot be cultivated. Studies on the possible association between changes in the microbiome and their association with skin diseases have improved understanding of disease development, diagnostics and therapeutics. Identification of the bacterial markers associated with particular inflammatory skin diseases would significantly accelerate the diagnostics and reduce treatment costs. Microbiota research and determination could facilitate the identification of potential causes of skin diseases that cannot be detected by simpler methods, thereby contributing to the design and development more effective therapies.

Keywords: skin microbiota ; skin diseases ; facial skin ; inflammatory skin diseases ; atopic dermatitis ; seborrheic dermatitis ; rosacea ; acne vulgaris ; perioral dermatitis ; periorificial dermatitis ; periocular dermatitis ; psoriasis

1. Current Knowledge of the Characteristics of the Skin Microbiome

The term “microbiome” comprises the totality of microorganisms (microbiota), their genomes, and environmental factors in a particular environment [1]. "Human microbiota", on the other hand, refers to the sum of all the microorganisms living on/in our body and is a source of genetic diversity, a modulator of health and disease, a fundamental component of immunity and an entity that affects metabolism and modulates drug interactions. The purpose of this review is to present the current knowledge on the characteristics of the skin microbiome in inflammatory skin diseases, taking into consideration that therapeutic effects on microbiome imbalance could contribute to disease improvement and sanitation.

The specificity of the microbiome of the epidermis in relation to the microbiome of the dermis is also noted. While the microbiome of the epidermis is strongly influenced by environmental factors, the microbiome of the dermis is more stable and less susceptible to change. Initial research suggests that the microbiome of the dermis is of uniform composition, regardless of body localization [2].The microbiome of the skin of newborns born vaginally is similar to the vaginal microbiome of the mother, whereas the microbiome of children delivered by caesarean section shows similarities to the skin microbiome of the mother [3]. The skin microbiome of premature infants has its own specifics. It is richest in bacteria of the phyla *Firmicutes* (genus *Staphylococcus*) and *Bacteroidetes* (genus *Flavobacterium*). Compared to the skin of term infants, it contains a larger share of bacteria belonging to the *Firmicutes* phylum. Those of the *Proteobacteria* phylum are relatively sparse. Furthermore, the skin of preterm infants (samples collected from the forehead area, cubital fossa and gluteal region) has relatively copious bacteria of the *Staphylococcus*, *Corynebacterium*, and *Prevotella* genera, and sparse *Brevundimonas*, *Flavobacterium,* and *Sphingobacterium* species, compared to term-newborns’ skin [4]. Research has demonstrated that, the predominant phylum found on the skin of healthy infants is the *Firmicutes* phylum (genus *Staphylococcus* and *Streptococcus*), followed by *Actinobacteria*, *Proteobacteria*, and *Bacteroidetes* [3][4][5][6][7].

It is also important to note that the microbiome of the skin, just like the microbiome of other areas, is a dynamic structure that changes, depending on age, gender, environmental factors, and one’s habits, e.g., occupation, use of cosmetics and antibiotics. In normal physiological conditions, the human ecosystem maintains a host–microorganism balance. On the other hand, the interactions between individual microorganisms and those between microorganisms and the host can be a cause of disease. Previous analyses have indicated that the four dominant bacterial phyla living on the skin are: *Actinobacteria*, *Firmicutes*, *Proteobacteria*, and *Bacteroidetes*, with *Corynebacterium*, *Cutibacterium*,

and *Staphylococcus* being the most prevalent among over 40 identified bacteria genera [8].The skin microbiome shows spatial distribution associated with the skin microenvironment (sebaceous, moist and dry areas) [9]. Thus, in sebaceous areas (face, chest, back), the dominant bacteria are the lipophilic species of the genus *Cutibacterium* and *Staphylococcus*. Bacteria that prefer a humid environment, such as those of the *Staphylococcus* and *Corynebacterium* genera are found in abundance in moist areas (elbow, knee and groin folds), whereas the dry areas of the skin (volar surface of the forearm and the hand) are replete with species belonging to the *Proteobacteria* phylum [8][10].

In addition to bacteria, other microorganisms, such as fungi of the *Malassezia* genus and parasites of the *Demodex* genus, are normally found on human skin. Furthermore, a few studies on the viruses that potentially inhabit the skin indicate that the human virome is also dependent on the skin microenvironment [10][11].
The skin microbiome in healthy subjects, as well as the microbiome in inflammatory skin diseases (such as those on the face), has rarely been studied with molecular methods and there is scarce information available. Future research in that area could therefore play an important role in gaining knowledge about the healthy skin microbiome and determining the presence of dysbiosis in patients.

Table 1. Microbiome shifts in most common inflammatory skin diseases.

Atopic dermatitis	↑ ***Staphylococcus spp.*** [1 3 7 8] ↑ ***Staphylococcus aureus*** [1 2 3 4 5 6 8] ↑ ***Staphylococcus epidermidis*** [1 4 7]	↓ ***Streptococcus spp.*** [1] ↓ ***Cutibacterium spp.*** [1 3] ↓ ***Corynebacterium spp.*** [1 3]
Psoriasis	↑ ***Firmicutes*** [9 10] ↑ ***Proteobacteria*** [11 14] ↑ ***Streptococcus spp.*** [9] ↑ ***Prevotella*** [10] ↑ ***Staphylococcus spp.*** [10 13] ↑ ***Staphylococcus aureus*** [11] ↑ ***Staphylococcus pettenkoferi*** [11] ↑ ***Staphylococcus sciuri*** [11]	↓ ***Actinobacteria*** [9 10 11 12] ↓ ***Gordoniaceae*** [11] ↓ ***Proteobacteria*** [9] ↓ ***Staphylococcus epidermidis*** [11] ↓ ***Cutibacterium spp.*** [9 10 14] ↓ ***Staphylococcus spp.*** [14] ↓ ***Cutibacterium acnes*** [11] ↓ ***Cutibacterium granulosum*** [11]
Seborrheic dermatitis	↑ ***Staphylococcus spp.*** [15 16 17 18 19 20 21 22] ↑ ***Staphylococcus epidermidis*** [20] ↑ ***Streptococcus spp.*** [18] ↑ ***Pseudomonas spp.*** [22] ↑ ***Acinetobacter*** [18]	↓ ***Cutibacterium spp.*** [15 16 17 19 20 21]
Acne	↑ ***Firmicutes*** [24 25] ↑ ***Proteobacteria*** [23 24] ↑ ***Staphylococcus spp.*** [24 25]	↓ ***Actinobacteria*** [23 24] ↓ ***Cutibacterium spp.*** [23] ↓ ***Cutibacterium acnes*** [23] ↓ ***Cutibacterium granulosum*** [23]
Rosacea	↑ ***Corynebacterium kropp*** [26] ↑ ***Gordonia*** [27] ↑ ***Geobacillus*** [27]	↓ ***Rosemonas spp.*** [26]

1 Kong et al, 2012, 2 Gonzalez et al, 2016, 3 Shi et al, 2016, 4 Clausen et al, 2017, 5 Baurecht et al, 2018, 6 Callewaert et al, 2020, 7 Seite et al, 2014, 8 Kim et al, 2017, 9 Gao et al, 2008,10 Langan et al, 2019, 11 Chang et al, 2018, 12 Wang et al, 2020, 13 Tett et al, 2017, 14 Fahlén et al 2012, 15 Clavaud et al, 2013, 16 Wang et al, 2015, 17 Xu et al, 2016, 18 Tanaka et al, 2016, 19 Park et al, 2017, 20 Saxena et al, 2018, 21 Grimshaw et al, 2019, 22 Lin et al, 2021, 23 Barnard et al, 2016, 24 Dreno et al, 2017, 25 Kim et al, 2021, 26 Rainer et al, 2020, 27 Zaidi et al, 2018. ↑ higher abundance in lesional than in non-lesional skin; ↓ lower abundance in lesional than in non-lesional skin.

2. The Skin Microbiome in Patients

Atopic dermatitis (AD) is a chronic, recurrent inflammatory skin disease that commonly occurs in children but can also affect In patients with AD, there is a difference in the degree of *Staphylococcus aureus* colonization between the lesional and non-lesional areas of the skin, which indicates that the unaffected areas of the skin are predisposed to increased colonization [10][12][13][14][15][16][17][18]. Studies showed that, excluding *Staphylococcus aureus* species, the skin harbors other species of the genus *Staphylococcus*, especially *Staphylococcus epidermidis*. [12][13][19][20]. The microbiota biodiversity microbiome has its role in supporting the rich immune protective milieu of the skin. Coagulase-negative *staphylococci*, such as *Staphylococcus epidermidis*, play a role in immune modulation. Studies have shown that a defect in the ability of effector T cells to produce cytokines, such as IL-17A and IFN-γ, and their reparation are associated with the presence of this species [21][22]. Patients with chronic AD show deficiency in innate defense against *S. aureus*.

Structural differences in skin bacterial colonization with coagulase-negative Staphylococci strains, in terms of their reduction, result in reduced antimicrobial peptide production and reduced immune functionality of the skin microbiota [23]. Since antimicrobial peptides LL-37, β-defensins, and dermicidin are present at reduced levels in AD skin, it becomes permissive for *S. aureus* colonization. Additionally, metabolites of adult-associated skin commensals can decrease skin pH and enhance antimicrobial activities, thus suppressing the adherence and growth of *S. aureus* in human keratinocytes [24].

Studies of the skin microbiome in patients with seborrheic dermatitis have shown dysbiosis of the affected skin compared to healthy areas, thereby confirming the previously mentioned changes in the microbiome composition in patients with inflammatory skin diseases. Aside from the bacteria, it is believed that yeasts, especially those of the *Malassezia* genus, play a significant role in the etiopathogenesis of seborrheic dermatitis, through their interactions with the skin, bacteria and the host [25][26][27][28][29][30][31]. However, the mechanisms of these interactions remain unclear. All performed studies have shown that the skin lesions of patients with seborrheic dermatitis are richer in bacteria of the genus *Staphylococcus* [25][26][27][28][30][31][32]. In addition, some studies found that the skin of these patients had a greater abundance in the *Streptococcus*, *Acinetobacter*, and *Pseudomonas* genera, while the genus *Cutibacterium* was less abundant. [25][26][27][28][29][30][31][32].

Bacterial microbiome presented a number of decreased KEGG metabolic pathways, including those related to the metabolism and biosynthesis of vitamins, cofactors, and amino acids and antibiotic resistance, which was in negative correlation with the dandruff score and itching. Commensal bacterial species *Cutibacterium spp*. was shown to carry genes for the synthesis of biotin. Since biotin, vitamin-B6, nicotinate, and lysine demonstrated a negative correlation with dandruff-associated parameters, results of this study highlight the possible beneficial role of bacterial scalp microbiome in supplying essential vitamins and amino acids to the host.

The bacterial diversity of the skin affected by rosacea, according to a study by Rainer et al. [33], was higher in comparison to healthy controls, but the difference was not statistically significant. The most abundant species on the skin of patients with rosacea are *Cutibacterium acnes* [33][34][35] and *Staphylococcus epidermidis* [35]. It has been reported that the skin of these patients is richer in certain species of bacteria, such as *Corynebacterium kroppenstedtii*, while the genus *Roseomonas* is reduced [33]. Zaidi et al also did not find a statistically significant change in biodiversity, while a positive and negative correlation was found between the severity of rosacea and abundance of genera *Gordonia* and *Geobacillus* [34]. According to Woo et al., the severity of rosacea increases with age and is associated with a relative decrease in the abundance *of Cutibacterium acnes* and an increase in the prevalence of *Snodgrassella alvi* [35]. Antibiotic treatment reduces the severity of the disease and increases the abundance of *Weissell confus*. The results of studies on bacterial microbiota in other inflammatory skin diseases have stimulated microbiome research in patients with rosacea, but currently only a few studies have been reported, without significant results. Further research is needed.

The skin of patients with acne (i.e., on the surfaces of comedones, papules and pustules) predominantly harbors bacteria of the genera *Firmicutes* and *Staphylococcus*, though mostly *Staphylococcus epidermidis* [36][37] and phylum *Proteobacteria* [36], while the presence of *Actinobacteria* phlyum is reduced [36][38]. Additionally, due to metagenomic shotgun analysis, this study established an important concept of disrupted balance in the metagenomic elements of the microbiota, influencing disease pathogenesis. Among identified operational gene units (OGUs), functional profiles differed between acne patients and healthy individuals. In acne patients, genetic elements involved in cell viability, virulence, and immunity, such as genetic units coding thiopeptide bacteriocin (family of microcins antimicrobial peptides) precursor synthesis and transport, were significantly more abundant. Other genetic elements, like pathogenicity islands previously associated with acne, and locus involved in recombination and chromosome transformation with cluster of streptolysin S-associated genes (sag) involved in the biosynthesis and transport of a bacterial toxin were highly abundant in patients with acne

According to a study by Kelhala et al., the genera *Streptococcus*, *Gamella*, *Fusobacterium*, *Granulicatella*, and *Neisseria* are reduced on the skin of patients with acne, probably due to the relative overgrowth of bacteria of the genus *Cutibacterium*, which limits the growth of other bacteria by competing for the same ecological niche [39]. The genus *Cutibacterium* makes up less than 2% of the bacteria on acne lesions [36]. It has been reported that the amount of *Staphylococcus* genus is in positive correlation with the severity of the disease. Based on these findings, many studies have attempted to identify the *Cutibacteruim acnes* phylotypes associated with this disease. The acne-related phylotype IA1 increases the pathogenic effect of these bacteria due to the it's inflammatory potential, differences in virulence generation and biofilm production [40][41][42]. Recent studies have shown that the most severe stages of the disease are associated with an increase in bacteria belonging to the *Faecalibacterioma*, *Klebsiella*, *Odirobacter,* and *Bacteroides* genera [43]. In conclusion, according to present data,

acne pathogenesis can be related to balance and its disruption in the healthy and acne-affected skin microbiome, including bacterial species and metagenomic elements.

According to data gathered on the epidermal barrier disorder observed in patients with perioral dermatitis, microbiome research could give important conclusions about the microbiome of the perioral region. To date, studies on the skin microbiome of the periorificial region are few. Zheng et al. found that bacteria of the genera *Streptococcus* and *Rothia* predominate on the skin of the perioral region of healthy infants [44].

The microbiome of healthy periocular skin harbors coagulase negative *Staphylococci* (*Staphylococcus epidermidis), Staphylococcus aureus* and *Cutibacterium acnes*, whose presence is not always considered pathological but may play a role in Meibomian gland dysfunction [45][46]. Another common finding on the skin of the periocular region is *Demodex* mite which is observed in healthy individuals but even more common in patients with blepharitis, where it plays a yet insufficiently elucidated role [46]. The skin of the periocular region in healthy individuals is inhabited mostly by bacteria from the phyla *Actinobacteria*, followed by *Firmicutes*, *Proteobacteria*, and *Bacteroidetes*, which corresponds to the findings of other seborrheic skin localizations [47][48].

Studies by Alekseyenko et al., Wang et al. and Langan et al. showed that the biodiversity in psoriatic lesions is reduced compared to healthy skin [49][50][51]. A study by Chang et al. found increased biodiversity in skin affected by psoriasis, while a study by Fahlen et al. found no difference [52][53]. The most abundant bacteria harboring psoriatic lesions are the bacteria of the *Firmicutes* phylum which are present on psoriatic skin in a larger proportion than on the skin of healthy subjects [53][54], whereas the phyla *Actinobacteria* [50][52][55][53][54] and *Proteobacteria* are reduced [54]. Aside from that, studies show an increase in the abundance of *Streptococcus* [54] and *Staphylococcus* genera [56][57], i.e., certain species of *Staphylococcus aureus*, *Staphylococcus pettenkoferi* and *Staphylococcus sciuri*, and the depletion of the genus *Cutibacterium*, *Staphylococcus epidermidis*, *Cutibacterium acnes* and *Cutibacterium granulosum* species [52][54].

Alekseyenko et al. found that the genera *Corynebaterium*, *Cutibacterium*, *Staphylococcus* and *Streptococcus* are more abundant in patients with psoriasis, while the genera *Cupriavidus*, *Methylobacterium* and *Schlegelella* are less abundant [49]. It has also been shown that there are two types of psoriasis, based on the abundance of certain bacteria - type 1, with the predominance of *Proteobacteria* phylum and type 2, with the predominance of *Firmicutes* and *Actinobacteria* phyla. Fahlén et al. analyzed the microbiome using skin bioptates and showed that the phylum *Proteobacteria* was more prevalent on the trunks of patients with psoriasis than on those of healthy subjects, while the genera *Cutibacterium* and *Staphylococcus* were reduced on the affected skin of the limbs [55]

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