Microbiome and Skin Biology

Nonhlanhla Lunjani[1,2], Carol Hlela[2], Liam O'Mahony[1,3]

[1]APC Microbiome Ireland, University College Cork, Cork, Ireland

[2]Department of Dermatology, University of Cape Town, Cape Town, South Africa

[3]Depts of Medicine and Microbiology, University College Cork, Cork, Ireland

Corresponding Author:

Prof. Liam O'Mahony, Office 450, 4th Floor Food Science and Technology Building,

University College Cork, Cork, Ireland.

+353 21 4901316

liam.omahony@ucc.ie

Abstract:

Purpose of review: The skin is home to a diverse milieu of bacteria, fungi, viruses, bacteriophages and archaeal communities. The application of culture independent approaches has revolutionized the characterization of the skin microbiome and have revealed a previously under-appreciated phylogenetic and functional granularity of skin-associated microbes in both health and disease states.

Recent findings: The physiology of a given skin niche drives the site-specific differences in bacterial phyla composition of healthy skin. Changes in the skin microbiome have consistently been associated with atopic dermatitis (AD). In particular, *Staphylococcus aureus* overgrowth with concomitant decline in *S. epidermidis* is a general feature associated with AD and is not restricted to eczematous lesions. Changes in fungal species are now also being described. Changes in the composition and metabolic activity of the gut microbiota are associated with skin health.

Summary: We are now beginning to appreciate the intimate and intricate interactions between microbes and skin health. Multiple studies are currently focussed on the manipulation of the skin or gut microbiome to explore their therapeutic potential in the prevention and treatment of skin inflammation.

Keywords: Microbiome, Atopic dermatitis, *Staphylococcus aureus*, *Malassezia*.

Introduction

An enormous variety of microbes colonize all internal and external body surfaces. These microbes are organized within complex community structures, utilizing nutrients from other microbes, host secretions and the diet. The microbiome is defined as the sum of these microbes, their genomic elements and interactions in a given ecological niche. In addition to bacteria, fungi, viruses and bacteriophages are also considered to be important components of the microbiome. The composition and metabolism of the microbiome is dependent on the specific body site examined, resulting in a series of unique habitats within and between individuals that can change substantially over time [1]. This presents significant challenges to the local immune system, which should tolerate the presence of these microbes to avoid damaging host tissue while retaining the ability to respond appropriately to invasive pathogens. The mechanisms that mediate host-microbe communication are highly sophisticated and need to be constantly coordinated [2]. Indeed, disrupted communication between the microbiome and the host due to altered microbiome composition and/or metabolism is thought to negatively influence immune homeostatic networks and may play a role in immune hypersensitivity to environmental exposures, such as allergens [3, 4, 5].

Relatively recently, epidemiological studies have identified associations between the migration from traditional farming to urban environments, changes in dietary practices, lack of contact with animals, use of antibiotics, lifestyle factors and reduced exposure to biodiverse environments with changes in the composition of the human microbiome and the increased incidence of allergic, inflammatory, metabolic and neuropsychiatric disorders [6*, 7*, 8*, 9*, 10*, 11*]. In particular, early life events have been shown to be significant modifiers of microbial establishment, colonization, development and maturation. These include mode of delivery, breastfeeding, mother's diet and health status, antibiotics and other drug usage in pregnancy and early childhood, early-life environment (i.e. number of siblings,

pets at home, proximity to farm animals and green areas) [12*, 13, 14*, 15*, 16*, 17, 18]. In this review, we will highlight some of the recent advances in our knowledge regarding the influence of the microbiome on skin biology, skin immune reactivity and skin diseases such as atopic dermatitis (AD). In addition, we will discuss the potential translation and challenges associated with microbial-based therapies for the skin.

Skin as a Unique Microbial Habitat

The skin is the most exposed organ, serving as an interface shielding underlying structures against external aggressions. Though open to colonization from the environment, human skin serves as a strong selective filter, largely unsuitable for most microbes to permanently reside [19]. At the forefront is the highly keratinized epidermis, the result of a specialized differentiation process of keratinocytes (the main cell type in the epidermal barrier) interspersed between intercellular lipids, a collection of ceramides, cholesterol and various fatty acids. Recent studies have shown that the uppermost layer of the epidermis, the stratum corneum (SC), harbours a rich diversity of microbes [20*] contributing to the barrier properties of the skin. An aqueous and lipid layer, which is present above the epidermis, also contribute to the ecology of the surface. Below the epidermis are several layers that form part of the skin barrier, profoundly affecting function and also harbouring microbes [21]. A growing body of data suggests that cutaneous microbes can influence the structure and function of healthy skin without penetrating the epidermis [22]. Contributing to the microenvironment is the presence and function of additional skin appendages, including sweat glands, hair follicles, sebaceous glands and the dermal layers which in turn drives the site-specific differences in bacterial phyla composition of healthy skin [21, 23, 24]. Eccrine sweat (water, salt and electrolytes) is secreted directly onto the skin surface, which works to

acidify the skin, creating an environment that plays a major role in limiting the composition of microbes that can survive and proliferate.

Propionibacteria, *Corynebacteria* and *Staphylococci* make up the most abundant bacteria species on the skin. *Staphylococcal* species are found in moist skin niches, and are halotolerant organisms that have evolved to use urea found in sweat as a nitrogen source. Certain *Staphylococcus* species, e.g. *S. aureus*, are able to produce adherens that promote bacterial adherence to skin and produce proteases that release nutrients from the SC [25**]. These sweat glands constitutively express several antimicrobial peptides (AMPs), including cathelicidin and β-defensins. The density of eccrine sweat glands impacts the microbial colonization of the skin [26]. Sebaceous glands are connected to hair follicles, forming the pilosebaceous unit. Sebaceous glands secrete lipid-rich sebum, which lubricates the hair and skin. The breakdown of sebum generates free fatty acids, which work to control microbial colonization, along with sebocyte-derived cathelicidin, β-defensins and antimicrobial histones. However, organisms such as *Propionibacteria acnes*, a facultative anaerobe, are able to flourish in the anoxic sebaceous gland as they can produce proteases and lipases that release amino acids and free fatty acids (that favors bacterial adherence) from skin and sebum respectively and cause acne vulgaris following their over proliferation in this lipid rich environment [25**]. *Corynebacterium* has adapted to survive in moist sites by utilizing SC and sebaceous lipids to generate breakdown products to coats its cell surface.

Current microbial detection techniques have shown that bacteria are not only present on the skin surface but are also found in deeper layers of the epidermis, and even in the dermis and dermal adipose tissue. Recent studies have helped define the skin microbiome landscape, indicating that the skin harbours a diverse population of microbes whose composition is largely determined by site specific physiological factors, such as moisture and sebum content [25**, 27].

Healthy Skin Microbiome

The development and application of culture independent approaches (such as metagenome shotgun sequencing) have revolutionized the characterization of the skin microbiome and have revealed a previously under-appreciated phylogenetic and functional granularity of skin-associated microbes in both health and disease states. Despite the harsh nutrient-poor landscape, healthy human skin is home to a heterogeneous milieu of commensal microorganisms including bacteria, fungi, viruses, bacteriophages and archaeal communities [27]. Multiple factors such as age, gender, ethnicity, climate, UV exposure and lifestyle shape the composition of the healthy skin microbiome. It has also been observed that the adult skin microbiome can remain stable over a period of at least 2 years irrespective of environmental changes [28]. The initial colonization of the newborn baby however depends on many factors, including the delivery mode. With vaginal delivery there is acquisition of maternal vaginal bacterial flora, and with caesarean section acquisition of skin-associated microorganisms. Postnatally, the immature immune system allows microbial colonization in the absence of inflammatory responses. This tolerogenic environment can be attributed to the infiltration of neonatal skin by regulatory T cells. Thereafter different commensals educate distinct aspects of the host immune system in order to respond appropriately to future exposure to pathogens. During puberty, the skin microbiome composition shifts in favor of lipophilic skin organisms [29, 30]. The continuous molecular cross-talk between cutaneous epithelia, tissue resident innate and adaptive immune cells and skin-associated microbes allows the establishment of commensal partners, which have essential roles in protection from invasive pathogens, educating distinct aspects of the host immune system to respond appropriately to future exposure to pathogens, the breakdown of skin-derived lipids and metabolites, and maintenance of immune homeostatic networks [25**]. Interactions between

skin microorganisms may be synergistic or competitive. These interactions may be exploited to identify mechanisms by which commensal microorganisms mediate direct and indirect colonization resistance in the skin.

Whilst skin bacterial microorganisms are the most abundant at the kingdom level, fungi are the least abundant. Within the skin mycobiome, lipophilic *Malassezia* species represent the most predominant fungal flora on the human skin. They are unable to synthesize their own nutrients and therefore produce lipid-utilizing enzymes in order to exploit the lipid-rich environment of the skin. Currently, there are relatively few skin-associated fungal sequenced reference genomes available, which will need to be improved to facilitate future mechanistic assessments on the skin mycobiome. Little is currently known concerning the spectrum of viral and bacteriophage communities present on healthy skin or their interactions with the microbiome and host cells but may be of significant relevance to conditions such as AD complicated by eczema herpeticum and skin cancers associated with oncoviruses.

Microbiome Associated with Skin Disorders

Understanding site-specific differences in microbial composition advances our understanding of diseases such as AD, psoriasis and acne vulgaris. The association between AD and an altered skin microbiome is now well documented. S. *aureus* overgrowth is a common feature of AD and is not restricted to eczematous lesions [31*]. *S. aureus* colonization is evident in 90% of AD cases, associates with AD severity and increased allergen sensitization. AD associated defects in stratum corneum integrity, decreased expression of structural proteins, altered skin lipid composition and skin pH and aberrant cutaneous and systemic immune responses facilitate *S. aureus* overgrowth, whilst *S. aureus*-derived proteases and toxins further damage the skin barrier and induce innate and adaptive

immune responses [32**]. It has also been observed that the *S. aureus* overgrowth is associated with a depletion in commensal Staphylococci such as *S. epidermidis*, and other skin commensal taxa including *Propionibacterium*, *Streptococcus*, *Acinetobacter*, *Corynebacterium*, *Prevotella* and *Proteobacteria*.

While it still needs to be clarified whether *S. aureus* contributes to the initiation of AD or if *S. aureus* blooms as a consequence of the disease, a number of studies do mechanistically link *S. aureus* with skin inflammation. *S. aureus* δ-toxin induces the degranulation of mast cells, which promotes innate and adaptive immune responses [33]. *S. aureus* α-toxin can also induce IL-1β production from monocytes, which may promote Th17 responses, or IL-17 production from CD4+ T cells [34]. Through the defective skin barrier, *S. aureus* may reach the dermis where it interacts with immune cells and trigger cytokine production including IL-4, IL-13, IL-22 and TSLP [35]. The Th2 inflammatory milieu is further deleterious to the epidermal barrier and can additionally impair tissue production of antimicrobial peptides (AMPs) such as human beta defensins (hBD)-2, hBD-3 and cathelicidin LL-37, thus impairing pathogen clearance.

The role for fungi, such as *Malassezia* species, is increasingly being investigated in AD. *Malassezia* DNA has been detected in 90% of AD skin lesions and colonization increases with disease severity [36]. In addition, different *Malassezia* strains were found in AD and healthy individuals suggesting the existence of key pathogenic strains in AD [37]. It has been shown that *Malassezia* could contribute to AD pathogenesis by secreting immunogenic proteins that induce proinflammatory cytokines, upregulate expression of TLR-2 and TLR-4 on keratinocytes, and induction of auto-reactive T cells [38]. Most recently, it was reported that Malassezia-induced Th17 responses are required for antifungal immunity within the skin but might also promote skin inflammation [39**].

S. aureus, via its promotion of Th17 polarising responses, has also been shown to be relevant to psoriasis lesions [40*]. In addition, increased abundance of *Brevibacterium* and *Kocuria palustris* and *Gordonia*, were associated with psoriatic lesions on the back and the elbow, respectively. In the same study, a significantly higher abundance of *Malassezia restricta* was detected on the back, while *Malassezia sympodialis* dominated the elbow mycobiota. In psoriatic elbow skin, there was a significant correlation between the occurrence of *Kocuria*, *Lactobacillus*, and *Streptococcus* with *Saccharomyces*, which was not observed in healthy skin [41*]. Interestingly, successful treatment with balneotherapy or UVB was associated with a significant change in the lesion-associated microbiome [42, 43*].

Role of Gut Microbes in Skin Disorders

Early studies demonstrated that patients with AD have lower levels of *Bifidobacterium* in the gut compared to healthy controls and *Bifidobacterium* levels were inversely correlated with AD disease severity [44]. Several studies have since shown that alterations in gut microbiota composition can precede the development of AD. Early gut colonisation with *C. difficile* was associated with AD development and low gut microbiota diversity and specifically low *Bacteriodetes* diversity at 1 month was associated with AD development at 2 years of age [36, 45]. Reduced colonization of mucin-degrading bacteria (*Akkermansia muciniphila*, *Ruminococcus gnavus* and *Lachnospiraceae*) were more recently shown for AD patients, which were associated with alterations in immune development in the AD group compared with the control group [46**]. In addition to modifying the host gut immune system, certain metabolites produced by microbes within the gut can be absorbed and thereby may directly influence the skin. For example, children with the highest levels of faecal short-chain fatty acids such as butyrate at 1 year of age, have a lower risk of

developing AD by 6 years of age [47*]. Differences in gut taxa and overall gut microbial diversity has also been noted for patients with psoriasis [48*].

Therapeutic Potential of the Microbiome

Multiple studies are currently focussed on the manipulation of the skin microbiome to explore its therapeutic potential. Transplant of *S. hominis* and *S. epidermidis* strains that secrete antimicrobial peptides was effective in controlling *S. aureus* overgrowth [49]. More recently, emollients supplemented with a *Vitreoscilla filiformis* lysate or topical administration of *Rosemonas mucosa* improved clinical severity scores in adults and children with AD [50**].

In addition to topical bacterial treatments, oral administration of probiotics has also been examined. Prenatal and post-natal treatment with certain *Lactobacillus* and *Bifidobacterium* strains can reduce risk of AD development in infants, while a mixture of probiotic strains was recently shown to reduce SCORAD index and topical steroid use in children with AD [51*, 52*]. These beneficial effects in the skin may be associated with changes in T cell-mediated responses [53, 54]. Little has been reported on the clinical effects of probiotic treatment in patients with psoriasis, but administration of a *B. longum* strain to adults with psoriasis resulted in reduced circulating levels of CRP, TNF and IL-17 [55]. Taken together, supplementation with specific probiotic strains may modulate the gut microbiota in a way that attenuates inflammation within the skin.

Conclusions

We are now beginning to appreciate the intimate and intricate interactions between microbes and skin health. Changes in the skin microbiome are associated with damaged or

inflamed skin, but the exact pathological mechanisms or their therapeutic potential remain largely unknown. Indeed, the role of gut microbes in skin health is a fascinating area of study and reaffirms the existence of a gut-skin axis. In the near future, we expect that analysis of the skin microbiome will assist in the clinical management of skin disorders, including the better identification of disease-related microbial communities or "Dermatypes", akin to recently described gut enterotypes. It will afford us the possibility of identifying novel treatment modalities and appropriate microbial reconstitution strategies. However, we still need to better understand the influence of host physiological changes and environmental challenges on the microbiota, describe the nonbacterial members of the skin microbiome, improve the resolution of our assessments to allow strain-level discrimination and most importantly we need better models to elucidate the functional properties of the skin microbiome.

Key points:

- The microenvironment and physiology of a given skin niche drives the site-specific differences in microbiome composition.
- *S. aureus* is consistently associated with atopic dermatitis
- Gut microbes, and their metabolites, influence skin health
- Identification of skin microbiome community patterns, or Dermatypes, will assist in patient stratification
- Microbial reconstitution of the skin community may have significant therapeutic benefits

References

Papers of particular interest, published within the annual period of review, (the last 18 months) have been highlighted as:

* of special interest ** of outstanding interest

1. Huang Y, Marsland B, Bunyavanich S, et al. The microbiome in allergic disease: Current understanding and future opportunities—2017 PRACTALL document of the American Academy of Allergy, Asthma & Immunology and the European Academy of Allergy and Clinical Immunology. J Allergy Clin Immunol 2017; 139:1099-1110.

2. Smolinska S, Groeger D, O'Mahony L. Biology of the Microbiome 1: Interactions with the Host Immune Response. Gastroenterol Clin North Am 2017; 46:19-35.

3. Lan F, Zhang N, Gevaert E, et al. Viruses and bacteria in Th2-biased allergic airway disease. Allergy 2016; 71:1381–1392.

4. Muir AB, Benitez AJ, Dods K, et al. Microbiome and its impact on gastrointestinal atopy. Allergy 2016; 71:1256–1263.

5. Jatzlauk G, Bartel S, Heine H, et al. Influences of environmental bacteria and their metabolites on allergies, asthma, and host microbiota. Allergy 2017;72:1859-1867.

*6. Lunjani N, Satitsuksanoa P, Lukasik Z, et al. Recent developments and highlights in mechanisms of allergic diseases: Microbiome. Allergy 2018; 73:2314-2327.

Review of the microbiome-related mechanisms that contribute to allergy and asthma.

*7. Haahtela T. A biodiversity hypothesis. Allergy 2019; Mar 5.

Review of the biodiversity hypothesis, which states that contact with natural environments enriches the human microbiome, promotes immune balance and protects from allergy and inflammatory disorders.

*8. Federici MJ. Gut microbiome and microbial metabolites: a new system affecting metabolic disorders. Endocrinol Invest 2019; Feb 20.

Review on the role of the microbiome and metabolites in metabolic disorders.

*9. Scriven M, Dinan TG, Cryan JF, Wall M. Neuropsychiatric Disorders: Influence of Gut Microbe to Brain Signalling. Diseases 2018; 6:E78.

Review on the role of the microbiome and metabolites in neuropsychiatric disorders.

*10. Sokolowska M, Frei R, Lunjani N, et al. Microbiome and asthma. Asthma Res Pract 2018; 4:1.

Review on the role of the microbiome and metabolites in allergy and asthma.

*11. Ahmadizar F, Vijverberg SJH, Arets HGM, et al. Early-life antibiotic exposure increases the risk of developing allergic symptoms later in life: A meta-analysis. Allergy 2018; 73:971-986.

This study assessed the relationship between exposure to antibiotics during the first 2 years of life and the risk of allergies/atopies including hay fever, eczema, food allergy, positive skin prick testing, or elevated allergen-specific IgE levels later in life.

*12. Stokholm J, Blaser MJ, Thorsen J, et al. Maturation of the gut microbiome and risk of asthma in childhood. Nat Commun 2018; 9:141.

Delayed maturation of the gut microbiota is associated with a higher risk of asthma in children born to asthmatic mothers.

13. Vuillermin PJ, Macia L, Nanan R, et al. The maternal microbiome during pregnancy and allergic disease in the offspring. Semin Immunopathol 2017; 39:669-675.

*14. Mitre E, Susi A, Kropp LE, et al. Association Between Use of Acid-Suppressive Medications and Antibiotics During Infancy and Allergic Diseases in Early Childhood. JAMA Pediatr 2018; 172:e180315.

This study found associations between the use of acid-suppressive medications and antibiotics during the first 6 months of infancy and subsequent development of allergic disease.

*15. Loewen K, Monchka B, Mahmud SM, et al. Prenatal antibiotic exposure and childhood asthma: a population-based study. Eur Respir J 2018;52.

This study showed that prenatal antibiotic exposure was associated with an increased risk of asthma.

*16. Sitarik AR, Havstad S, Levin AM, et al. Dog introduction alters the home dust microbiota. Indoor Air 2018; 28:539-547.

Dog introduction into the home has both immediate effects and effects that emerge over time on the microbiota composition within the home.

17. Tun HM, Konya T, Takaro TK, et al. Exposure to household furry pets influences the gut microbiota of infant at 3-4 months following various birth scenarios. Microbiome 2017; 5:40.

18. Birzele LT, Depner M, Ege MJ, et al. Environmental and mucosal microbiota and their role in childhood asthma. Allergy 2017; 72:109-119.

19. Vandegrift R, Bateman AC, Siemens KN, et al. Cleanliness in context: reconciling hygiene with a modern microbial perspective. Microbiome 2017; 5:76.

316 *20. Bosko CA. Skin Barrier Insights: From Bricks and Mortar to Molecules and Microbes. J
317 Drugs Dermatol 2019; 18:63-67.

318 This reviews describes the basics of stratum corneum structure and function, and the
319 relationship with the microbiome.

320 21. Nakatsuji T, Chiang HI, Jiang SB, et al. The microbiome extends to subepidermal
321 compartments of normal skin. Nat Commun 2013; 4:1431.

322 22. Prescott SL, Larcombe DL, Logan AC, et al. The skin microbiome: impact of modern
323 environments on skin ecology, barrier integrity, and systemic immune programming. World
324 Allergy Organ J 2017; 10:29.

325 23. Dréno B, Araviiskaia E, Berardesca E, et al. Microbiome in healthy skin, update for
326 dermatologists. J Eur Acad Dermatol Venereol 2016; 30:2038-2047.

327 24. Oh J, Byrd AL, Deming C, et al. Biogeography and individuality shape function in the
328 human skin metagenome. Nature 2014; 514:59-64.

329 **25. Byrd AL, Belkaid Y, Segre JA. The human skin microbiome. Nat Rev Microbiol 2018;
330 16:143-155.

331 This review describes the recent insights into skin microbial communities, including their
332 composition in health and disease.

333 26. Wang E, Qiang X, Li J, et al. The in vitro immune-modulating properties of a sweat
334 gland-derived anti-microbial peptide dermcidin. Shock 2016; 45:28–32.

335 27. Kong HH, Andersson B, Clavel T, et al. Performing Skin Microbiome Research: A
336 Method to the Madness. J Invest Dermatol 2017; 137:561-568.

28. Oh J, Byrd AL, Park M, et al. Temporal stability of the human skin microbiome. Cell 2016; 165:854–866.

29. Jo JH, Deming C, Kennedy EA, et al. Diverse human skin fungal communities in children converge in adulthood. J Invest Dermatol 2016; 136:2356–2363.

30. Jo JH, Kennedy EA, Kong HH. Topographical and physiological differences of the skin mycobiome in health and disease. Virulence 2016; 8:324–333.

*31. Geoghegan JA, Irvine AD, Foster TJ. Staphylococcus aureus and Atopic Dermatitis: A Complex and Evolving Relationship. Trends Microbiol 2018; 26:484-497.

This review describes the role of S. aureus on the skin of AD patients.

**32 Baurecht H, Rühlemann MC, Rodríguez E, et al. Epidermal lipid composition, barrier integrity, and eczematous inflammation are associated with skin microbiome configuration. J Allergy Clin Immunol 2018; 141:1668-1676.

This study clearly demonstrates that epidermal barrier integrity and function affect the skin microbiome composition.

33. Hodille E, Cuerq C, Badiou C, et al. Delta Hemolysin and Phenol-Soluble Modulins, but Not Alpha Hemolysin or Panton-Valentine Leukocidin, Induce Mast Cell Activation. Front Cell Infect Microbiol 2016; 6:180.

34. Nakagawa S, Matsumoto M, Katayama Y, et al. Staphylococcus aureus Virulent PSMα Peptides Induce Keratinocyte Alarmin Release to Orchestrate IL-17-Dependent Skin Inflammation. Cell Host Microbe 2017; 22:667-677.

35. Nakatsuji T, Chen TH, Two AM, et al. Staphylococcus aureus exploits epidermal barrier defects in atopic dermatitis to trigger cytokine expression. J Invest Dermatol 2016; 136:2192–2200.

360 36. Thomas CL, Fernandez-Penas P. The microbiome and atopic eczema: More than skin
361 deep. Australas J Dermatol 2017; 58:18-24.

362 37. Harada K, Saito M, Sugita T, Tsuboi R. Malassezia species and their associated skin
363 diseases. J Dermatol 2015; 42:250-257.

364 38. Glatz M, Bosshard PP, Hoetzenecker W, Schmid-Grendelmeier P. The Role of
365 Malassezia spp. in Atopic Dermatitis. J Clin Med 2015; 4:1217-1228.

366 **39. Sparber F, De Gregorio C, Steckholzer S, et al. The Skin Commensal Yeast Malassezia
367 Triggers a Type 17 Response that Coordinates Anti-fungal Immunity and Exacerbates Skin
368 Inflammation. Cell Host Microbe 2019; 25:389-403.

369 These authors showed that the Malassezia-induced type 17 response is pivotal in
370 orchestrating antifungal immunity and in actively promoting skin inflammation.

371 *40. Chang HW, Yan D, Singh R, et al. Alteration of the cutaneous microbiome in psoriasis
372 and potential role in Th17 polarization. Microbiome 2018; 6:154.

373 This study suggests that the psoriatic skin microbiome has increased diversity and reduced
374 stability compared to the healthy skin microbiome.

375 *41. Stehlikova Z, Kostovcik M, Kostovcikova K, et al. Dysbiosis of Skin Microbiota in
376 Psoriatic Patients: Co-occurrence of Fungal and Bacterial Communities. Front Microbiol
377 2019; 10:438.

378 There is a psoriasis-specific correlation between fungal and bacterial species, suggesting a
379 link between competition for niche occupancy and psoriasis.

380 42. Martin R, Henley JB, Sarrazin P, Seite S. Skin Microbiome in Patients with Psoriasis
381 Before and After Balneotherapy at the Thermal Care Center of La Roche-Posay. J Drugs
382 Dermatol 2015; 14:1400–1405.

*43. Assarsson M, Duvetorp A, Dienus O, et al. Significant Changes in the Skin Microbiome in Patients with Chronic Plaque Psoriasis after Treatment with Narrowband Ultraviolet, B. Acta Dermato Venereol 2018; 98:428–436.

The results of this study suggest that skin microbiome alterations after UVB treatment could be related to treatment and treatment response.

44. Watanabe S, Narisawa Y, Arase S, et al. Differences in fecal microflora between patients with atopic dermatitis and healthy control subjects. J Allergy Clin Immunol 2003; 111:587–591.

45. Abrahamsson TR, Jakobsson HE, Andersson AF, et al. Low diversity of the gut microbiota in infants with atopic eczema. J Allergy Clin Immunol 2012; 129:434–440.

**46. Lee MJ, Kang MJ, Lee SY, et al. Perturbations of gut microbiome genes in infants with atopic dermatitis according to feeding type. J Allergy Clin Immunol 2018; 141:1310-1319.

The reduction in genes for oxidative phosphorylation, phosphatidylinositol 3-kinase-Akt signaling, estrogen signaling, nucleotide-binding domain-like receptor signaling, and antigen processing and presentation induced by reduced colonization of mucin-degrading bacteria was significantly associated with stunted immune development in the AD group.

*47. Roduit C, Frei R, Ferstl R, et al. High levels of butyrate and propionate in early life are associated with protection against atopy. Allergy 2019; 74:799-809.

Children with the highest levels of butyrate and propionate in feces at the age of one year had significantly less atopic sensitization at 6 years.

*48. Hidalgo-Cantabrana C, Gómez J, Delgado S, et al. Gut microbiota dysbiosis in a cohort of psoriasis patients. Br J Dermatol. 2019 Mar 28. doi: 10.1111/bjd.17931.

405 This study showed that the gut microbiota composition of psoriasis patients displayed lower
406 diversity and different relative abundance of certain bacterial taxa compared to healthy
407 individuals.

408 49. Nakatsuji T, Chen TH, Narala S, et al. Antimicrobials from human skin commensal
409 bacteria protect against Staphylococcus aureus and are deficient in atopic dermatitis. Sci
410 Transl Med 2017; 9:378.

411 **50. Myles IA, Earland NJ, Anderson ED, et al. First-in-human topical microbiome
412 transplantation with Roseomonas mucosa for atopic dermatitis. JCI Insight 2018; 3:e120608.

413 Treatment with *R. mucosa* was associated with significant decreases in measures of disease
414 severity, topical steroid requirement, and *S. aureus* burden.

415 *51. Navarro-López V, Ramírez-Boscá A, Ramón-Vidal D, et al. Effect of Oral
416 Administration of a Mixture of Probiotic Strains on SCORAD Index and Use of Topical
417 Steroids in Young Patients With Moderate Atopic Dermatitis: A Randomized Clinical Trial.
418 JAMA Dermatol 2018; 154:37-43.

419 This mixture of probiotics was effective in reducing SCORAD index and reducing the use of
420 topical steroids in patients with moderate AD.

421 *52. Li L, Han Z, Niu X, et al. Probiotic Supplementation for Prevention of Atopic
422 Dermatitis in Infants and Children: A Systematic Review and Meta-analysis. Am J Clin
423 Dermatol 2018 Nov 21.

424 This meta-analysis suggests that supplementation with certain probiotics during both the
425 prenatal and the postnatal period reduced the incidence of AD in infants and children.

426 53. Rø ADB, Simpson MR, Rø TB, et al. Reduced Th22 cell proportion and prevention of
427 atopic dermatitis in infants following maternal probiotic supplementation. Clin Exp Allergy
428 2017; 47:1014-1021.

429 54. Konieczna P, Groeger D, Ziegler M, et al. Bifidobacterium infantis 35624 administration
430 induces Foxp3 T regulatory cells in human peripheral blood: potential role for myeloid and
431 plasmacytoid dendritic cells. Gut 2012; 61:354-366.

432 55. Groeger D, O'Mahony L, Murphy EF, et al. Bifidobacterium infantis 35624 modulates
433 host inflammatory processes beyond the gut. Gut Microbes 2013; 4:325-339.

434