

Title	Microbiome and skin biology
Authors	Lunjani, Nonhlanhla;Hlela, Carol;O'Mahony, Liam
Publication date	2019-08-01
Original Citation	Lunjani, N., Hlela, C. and O'Mahony, L. (2019) 'Microbiome and skin biology', Current Opinion in Allergy and Clinical Immunology, 19(4), pp. 328-333. doi: 10.1097/aci.0000000000000542
Type of publication	Article (peer-reviewed)
Link to publisher's version	<a href="https://journals.lww.com/co-allergy/Fulltext/2019/08000/Microbiome_and_skin_biology.10.aspx">https://journals.lww.com/co-allergy/Fulltext/2019/08000/Microbiome_and_skin_biology.10.aspx</a> - 10.1097/aci.0000000000000542
Rights	© 2019, Wolters Kluwer Health, Inc. All rights reserved. This document is the Accepted Manuscript version of a Published Work that appeared in final form in Current Opinion in Allergy and Clinical Immunology. To access the final edited and published work see: <a href="https://doi.org/10.1097/aci.0000000000000542">https://doi.org/10.1097/aci.0000000000000542</a>
Download date	2024-06-22 11:10:36
Item downloaded from	<a href="https://hdl.handle.net/10468/8293">https://hdl.handle.net/10468/8293</a>

1 Microbiome and Skin Biology

2 Nonhlanhla Lunjani<sup>1,2</sup>, Carol Hlela<sup>2</sup>, Liam O'Mahony<sup>1,3</sup>

3

4 <sup>1</sup>APC Microbiome Ireland, University College Cork, Cork, Ireland

5 <sup>2</sup>Department of Dermatology, University of Cape Town, Cape Town, South Africa

6 <sup>3</sup>Depts of Medicine and Microbiology, University College Cork, Cork, Ireland

7

8 Corresponding Author:

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

10 University College Cork, Cork, Ireland.

11 +353 21 4901316

12 [liam.omahony@ucc.ie](mailto:liam.omahony@ucc.ie)

13 **Abstract:**

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

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

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

30

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

## 32 **Introduction**

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

48 Relatively recently, epidemiological studies have identified associations between the  
49 migration from traditional farming to urban environments, changes in dietary practices, lack  
50 of contact with animals, use of antibiotics, lifestyle factors and reduced exposure to  
51 biodiverse environments with changes in the composition of the human microbiome and the  
52 increased incidence of allergic, inflammatory, metabolic and neuropsychiatric disorders [6\*,  
53 7\*, 8\*, 9\*, 10\*, 11\*]. In particular, early life events have been shown to be significant  
54 modifiers of microbial establishment, colonization, development and maturation. These  
55 include mode of delivery, breastfeeding, mother's diet and health status, antibiotics and other  
56 drug usage in pregnancy and early childhood, early-life environment (i.e. number of siblings,

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

62

### 63 **Skin as a Unique Microbial Habitat**

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

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

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

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

106

## 107 **Healthy Skin Microbiome**

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

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

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

144

#### 145 **Microbiome Associated with Skin Disorders**

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



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

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

170         The role for fungi, such as *Malassezia* species, is increasingly being investigated in  
171 AD. *Malassezia* DNA has been detected in 90% of AD skin lesions and colonization  
172 increases with disease severity [36]. In addition, different *Malassezia* strains were found in  
173 AD and healthy individuals suggesting the existence of key pathogenic strains in AD [37]. It  
174 has been shown that *Malassezia* could contribute to AD pathogenesis by secreting  
175 immunogenic proteins that induce proinflammatory cytokines, upregulate expression of TLR-  
176 2 and TLR-4 on keratinocytes, and induction of auto-reactive T cells [38]. Most recently, it  
177 was reported that *Malassezia*-induced Th17 responses are required for antifungal immunity  
178 within the skin but might also promote skin inflammation [39\*\*].

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

188

### 189 **Role of Gut Microbes in Skin Disorders**

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

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

205

## 206 **Therapeutic Potential of the Microbiome**

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

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

223

## 224 **Conclusions**

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

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

239

240 **Key points:**

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

249

250

251 **References**

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

254 \* of special interest \*\* of outstanding interest

255

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

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

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

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

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

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

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

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

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

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

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

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

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

281 \*10. Sokolowska M, Frei R, Lunjani N, et al. Microbiome and asthma. *Asthma Res Pract*  
282 2018; 4:1.

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

284 \*11. Ahmadizar F, Vijverberg SJH, Arets HGM, et al. Early-life antibiotic exposure increases  
285 the risk of developing allergic symptoms later in life: A meta-analysis. *Allergy* 2018; 73:971-  
286 986.

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

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

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

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

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

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

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

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

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

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

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

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

314 19. Vandegrift R, Bateman AC, Siemens KN, et al. Cleanliness in context: reconciling  
315 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.



337 28. Oh J, Byrd AL, Park M, et al. Temporal stability of the human skin microbiome. *Cell*  
338 2016; 165:854–866.

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

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

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

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

346 \*\*32 Baurecht H, Rühlemann MC, Rodríguez E, et al. Epidermal lipid composition, barrier  
347 integrity, and eczematous inflammation are associated with skin microbiome configuration. *J*  
348 *Allergy Clin Immunol* 2018; 141:1668-1676.

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

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

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

357 35. Nakatsuji T, Chen TH, Two AM, et al. *Staphylococcus aureus* exploits epidermal barrier  
358 defects in atopic dermatitis to trigger cytokine expression. *J Invest Dermatol* 2016;  
359 136:2192–2200.

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.

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

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

388 44. Watanabe S, Narisawa Y, Arase S, et al. Differences in fecal microflora between patients  
389 with atopic dermatitis and healthy control subjects. *J Allergy Clin Immunol* 2003; 111:587–  
390 591.

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

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

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

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

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

403 \*48. Hidalgo-Cantabrana C, Gómez J, Delgado S, et al. Gut microbiota dysbiosis in a cohort  
404 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