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1 Microbiome and Skin Biology

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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 β -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, β -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* δ -toxin induces the
162 degranulation of mast cells, which promotes innate and adaptive immune responses [33]. *S.*
163 *aureus* α -toxin can also induce IL-1 β 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

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