



# Microbiome and skin diseases

Patrick L.J.M. Zeeuwen<sup>a</sup>, Michiel Kleerebezem<sup>b</sup>, Harro M. Timmerman<sup>c</sup>, and Joost Schalkwijk<sup>a</sup>

## Purpose of review

This article reviews recent findings on the skin microbiome. It provides an update on the current understanding of the role of microbiota in healthy skin and in inflammatory and allergic skin diseases.

## Recent findings

Advances in computing and high-throughput sequencing technology have enabled in-depth analysis of microbiota composition and functionality of human skin. Most data generated to date are related to the skin microbiome of healthy volunteers, but recent studies have also addressed the dynamics of the microbiome in diseased and injured skin. Currently, reports are emerging that evaluate the strategies to manipulate the skin microbiome, intending to modulate diseases and/or their symptoms.

## Summary

The microbiome of normal human skin was found to have a high diversity and high interpersonal variation. Microbiota compositions of diseased lesional skin (in atopic dermatitis and psoriasis) showed distinct differences compared with healthy skin. The function of microbial colonization in establishing immune system homeostasis has been reported, whereas host–microbe interactions and genetically determined variation of stratum corneum properties might be linked to skin dysbiosis. Both are relevant for cutaneous disorders with aberrant immune responses and/or disturbed skin barrier function. Modulation of skin microbiota composition to restore host–microbiota homeostasis could be future strategies to treat or prevent disease.

## Keywords

atopic dermatitis, host–microbe interactions, microbiome, psoriasis, skin barrier

## INTRODUCTION

Skin is our largest organ and plays an important protective role against infection and penetration of toxic agents, as it is a major interface between the body and its environment. *In utero*, the skin is sterile, but after birth environmental microbes rapidly start to colonize the stratum corneum eventually developing into a complex microbial ecosystem that is in homeostasis with its host [1,2]. It is estimated that over 100 distinct species making up a total of 1 million microorganisms colonize each square centimetre of our skin [3]. The total microbial community that lives in association with the human body is collectively known as the human microbiota, and the human skin microbiota includes all microbial members found in a particular cutaneous body site habitat [4]. The diversity of human microbiota is determined by various factors such as transmission of nonresident microbes, genetic predisposition, lifestyle, and host demographic and environmental characteristics [5,6]. Until recently, most of our knowledge of bacteria that reside on skin came from conventional culture-based approaches.

However, these approaches have significant limitations, which are due to the fact that only a minority of the bacteria are readily culturable in the laboratory. Moreover, many slow growing organisms from a complex microbial community are overcrowded by bacteria that are better adapted to the in-vitro growth conditions applied. Therefore, culture-dependent microbiota analyses lead to underestimation of diversity and artificial skewing of relative abundances of certain bacterial groups. Advances in DNA sequencing technologies have allowed comprehensive examination of microbial communities using

<sup>a</sup>Department of Dermatology, Radboud University Nijmegen Medical Centre, Nijmegen, <sup>b</sup>Host-Microbe Interactomics Group, Wageningen University, Wageningen and <sup>c</sup>NIZO Food Research B.V., Ede, The Netherlands

Correspondence to Dr Joost Schalkwijk, Department of Dermatology, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmegen, The Netherlands. Tel: +31 24 3614094; e-mail: j.schalkwijk@derma.umcn.nl

**Curr Opin Allergy Clin Immunol** 2013, 13:514–520

DOI:10.1097/ACI.0b013e328364ebeb

## KEY POINTS

- The microbiome of normal human skin was found to have a high diversity and high interpersonal variation.
- Normal skin microbiota supports and modulates the innate immune host response.
- Genetically determined epidermal dysfunction and the disturbance of the symbiosis and interactions between the host and present microbes might be driving factors in inflammatory skin diseases.
- Maintaining a normal and healthy skin microbiome is beneficial for our health.
- Selective modulation of skin microbiota composition by topical therapeutics to restore or optimize the pathogenic-commensal and host–microbe interactions might be future strategies to achieve beneficial effects in patients.

culture-independent methods [7<sup>•</sup>]. These new molecular approaches enable analysis of genetic material derived from complete microbial communities harvested from their natural environment. Comprehensive large-scale projects such as the Human Microbiome Project (HMP) [8<sup>••</sup>], the Metagenomics of the Human Intestinal Tract (MetaHIT) consortium [9], and the project Microbes in Allergy and Autoimmunity Related to the Skin (MAARS) [10<sup>•</sup>], have revealed the extent of variation in the human microbiota, including the microbiota that resides on the skin.

## THE HUMAN SKIN MICROBIOME

The microbiota present on the skin can be transient or resident; the latter are considered to be members of the ‘normal’ commensal skin microbiota that is in homeostasis with the host, whereas the former are microbes from the environment that temporarily live on the skin [11]. The diversity of these transient and permanent microbes on our skin is dependent on the topographical regions of the body that have distinctive characteristics (pH, moisture, salinity, and sebum content), and may also vary due to intrinsic factors (e.g. genotype, age, and sex) and extrinsic individual-dependent factors such as occupation, lifestyle, geographical location, and use of antibiotics, or cosmetics [12]. The human skin microbiota controls colonization by potentially pathogenic microorganisms [13,14<sup>•</sup>], can modulate the cutaneous immune system [15,16,17<sup>•</sup>], and is necessary for optimal skin immune fitness [18<sup>••</sup>]. Altogether, this indicates that maintaining our skin microbiota is beneficial for our health [19].

Recent culture-independent studies of the cutaneous microbiota revealed a considerably greater diversity of organisms than presumed from culture-based methods [20]. These studies [21,22] showed that bacterial diversity largely depends on the topographical location on the body, and that it remains relatively stable over time. These large-scale studies of the composition of microbial communities in healthy volunteers have revealed that most of the resident skin bacteria are categorized into four different phyla: Actinobacteria, Firmicutes, Proteobacteria, and Bacteroidetes. Furthermore, it was demonstrated that specific bacteria were associated with moist, dry, and sebaceous microenvironments, respectively. For example, *Staphylococcus* spp. and *Corynebacterium* spp. are organisms that abundantly colonize moist areas such as the armpit, the inner elbow, and behind the knee, whereas *Propionibacterium* spp. are found in large quantities in sebaceous areas such as the forehead, the back, and behind the ear [21,22]. The dry areas of the skin, such as the forearm, buttock, and parts of the hand, are colonized by a microbiota of the highest diversity, but lowest absolute numbers. In general, the human skin microbiome has a high degree of variation between persons. Within subjects, site-specific differences exist (e.g. moist versus dry regions); the variability of the skin microbiota within a subject was lower, however, when comparing symmetrical sites (e.g. left and right antecubital creases) [8<sup>••</sup>,21,22]. Importantly, all these studies were performed under nonchallenged, static conditions in healthy volunteers. Recently, the dynamics of recolonization of skin microbiota was investigated following skin barrier disruption by tapestripping as a model for superficial injury [23<sup>•</sup>]. It was shown that bacteria are not uniformly distributed in the stratum corneum. The highest bacterial density is, not surprisingly, found in the surface layers, whereas the stratum corneum adjacent to the stratum granulosum (the first living cell layer) contains very few bacteria. A recent publication showed that the microbiome may even extend to the dermal compartment [24<sup>••</sup>]. The developing neo-microbiome at 2 weeks after skin barrier disruption was more similar to the deeper stratum corneum layers than to the initial surface microbiome, which suggested that the bacteria found in the deeper layers of the stratum corneum predominate during the recolonization process of injured skin [23<sup>•</sup>]. In addition, considerable inter-individual variation in epidermal antimicrobial protein expression following superficial injury was observed. The individual-specific levels of constitutive and induced expression of innate immunity functions are likely to account for the host-specific

microbiota present on normal and challenged or wounded skin.

## MICROBIOTA AND SKIN DISEASES

The 'hygiene hypothesis', which was adduced in 1989 for the first time, postulated that declining family size, improvements in household facilities, and higher standards of personal cleanliness has resulted in more widespread clinical expression of atopic diseases [25]. It is nowadays more and more accepted that the recent increase in allergic and (chronic) inflammatory diseases is a result of our modern western lifestyle, and that this is also associated with changes in the human microbiome [26]. Furthermore, the recently proposed 'biodiversity hypothesis' implies that limited exposure to various environmental microbiota leads to aberrant development of our immune system [27], and that environmental biodiversity is linked to microbiota diversity and human health. It was shown that atopic individuals, compared with healthy controls, have lower skin microbiota diversity of Gammaproteobacteria, which correlated with lower environmental biodiversity in the surroundings of their homes [10<sup>¶</sup>]. The disturbance of homeostatic relations between the host and its microbiota might also be a driving factor in inflammatory skin diseases such as atopic dermatitis and psoriasis [28] (Fig. 1). Recently, it was reported that mutations in the epidermal expressed filaggrin (*FLG*) gene are associated with atopic dermatitis and other allergic diseases [29,30], and that copy number variation of epidermis-expressed genes such as  $\beta$ -defensins and LCE3B/C predispose to psoriasis [31,32]. These observations strongly suggest that variation of the skin barrier and consequent cutaneous sensitization by penetration of microbes or pathogen-associated molecular patterns plays an important role in these two most common inflammatory skin diseases. To understand the role of microbes in inflammatory and allergic skin diseases, a few groups have recently analysed the skin microbiome of diseased and injured skin.

The presence of *Staphylococcus aureus*, which is found on the skin in more than 90% of atopic dermatitis patients, is thought to play an important role in the pathogenesis of this disease [33], as some treatments to reduce *S. aureus* colonization proved to decrease severity of atopic dermatitis [34]. However, it is unlikely that a single species causes atopic dermatitis. In a recent study [35<sup>¶¶</sup>], the microbiota composition of lesional skin of moderate-to-severe paediatric atopic dermatitis patients was analysed at baseline, during disease flare, and posttreatment,

revealing that temporal shifts in skin microbiota composition were associated with disease flares and treatment. More specifically, the relative abundance of *S. aureus* and, surprisingly, also the skin commensal *Staphylococcus epidermidis* was increased with clinical disease activity, whereas species of the genera *Streptococcus*, *Propionibacterium*, and *Corynebacterium* were increased following therapy. One could speculate that the increased abundance of *S. epidermidis* in lesional atopic dermatitis skin reflects a microbial response to overgrowth of *S. aureus*, as *S. epidermidis* is able to selectively inhibit *S. aureus* [13]. Overall, the atopic dermatitis skin of the inner elbow and the back of the knee, two areas that are commonly affected in atopic dermatitis patients, showed a much lower microbiota diversity relative to the same skin area of healthy controls [35<sup>¶¶</sup>] (Supplemental Table 1, <http://links.lww.com/COAI/A3>). This suggests that the changing milieu of lesional atopic dermatitis skin might be a perfect microenvironment and substrate for specific (staphylococcal) species.

The pathogenesis of psoriasis has also been associated with changes in the skin microbiota [36]. The first microbiota study [37] in patients with psoriasis revealed that the bacterial composition of the lesional skin was much more diverse than that observed in skin from healthy individuals or non-lesional skin from psoriatic patients. Firmicutes was the most abundant and diverse phylum populating the psoriatic lesions, whereas the genus *Propionibacterium* was significantly underrepresented compared with nonlesional skin samples from psoriasis patients, or healthy controls. However, these results appear to be contradicted by a subsequent study [38<sup>¶</sup>] that analysed the skin microbiota of whole skin biopsies. It was shown that the microbiota diversity in psoriatic lesions was reduced relative to normal skin. In addition, also the genera that were present at discriminating abundance levels were different. These apparent contradictions may be because of different sampling techniques, wherein the first study determines the microbiota composition using swab samples, whereas the subsequent study analysed the microbiota from the complete epidermis and dermis. As recent studies [23<sup>¶</sup>,24<sup>¶¶</sup>] have shown that bacteria are also present in deeper parts of the skin, one could imagine that the microbiota of the superficial layer is just a part of the total host indigenous skin microbiota. However, it remains unclear whether disease-associated changes in the microbiota composition have a causal role in disease development or are merely the result of abnormal skin biology, which may depend primarily on host-specific genetic determinants and skin immune-system variation that are

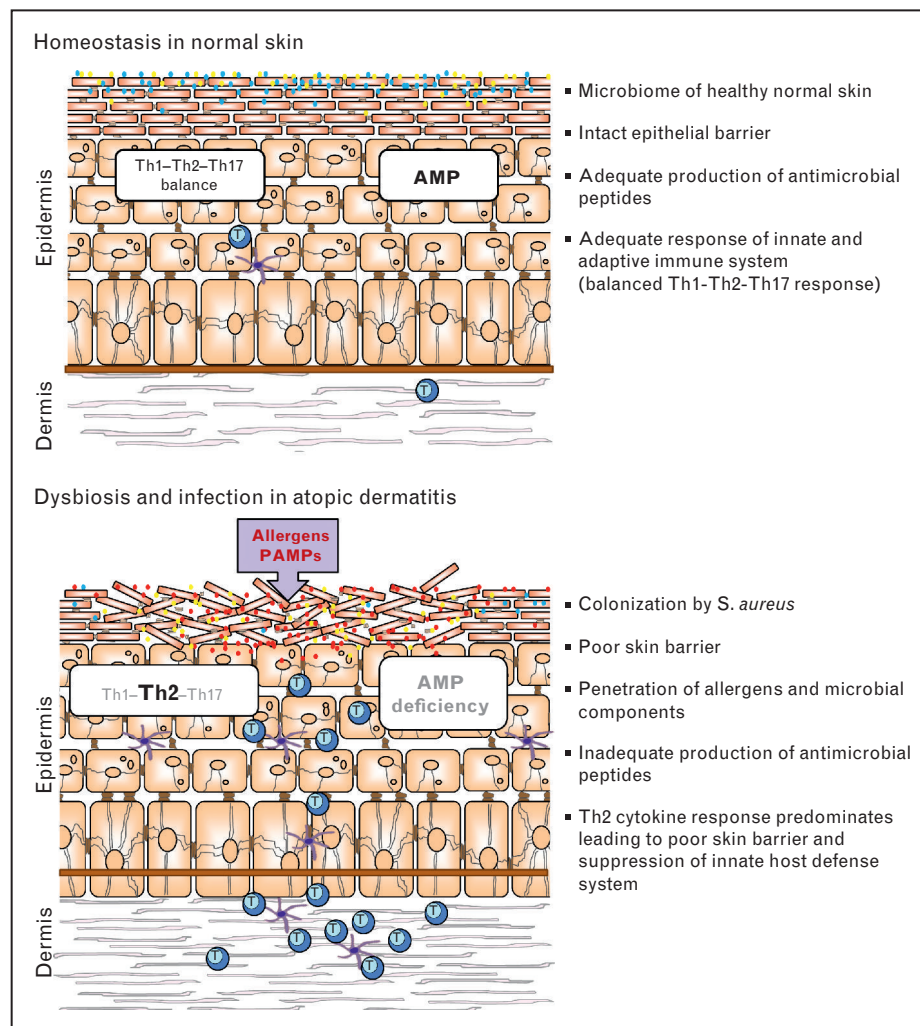


**FIGURE 1.** Model for homeostasis and dysbiosis in normal skin and atopic dermatitis skin. The microbiota composition of normal healthy skin consists largely of bacteria that belong to Firmicutes (mainly *Staphylococcus* spp. like *Staphylococcus epidermidis*, depicted in yellow) and Actinobacteria (*Propionibacterium* and *Corynebacterium*, depicted in blue). In atopic dermatitis, the skin is often colonized by *Staphylococcus aureus* (depicted in red), whereas the abundance of other bacteria is decreased. See also Supplemental Table 2, <http://links.lww.com/COAI/A3> for more specific microbe–microbe or host–microbe interactions related to skin immune function and skin barrier function. AMP, antimicrobial protein; PAMP, pathogen-associated molecular pattern.

highly prevalent in inflammatory skin diseases like atopic dermatitis and psoriasis [29–32,39,40].

### SKIN MICROBIOME RESEARCH IN THE OMICS ERA

The most commonly applied high-throughput technologies for microbiota composition profiling target the highly conserved 16S rRNA gene sequence. The continuously expanding and improving bioinformatic tools, which allow the effective assessment of microbial diversity and taxonomic composition (genus or OTU), places this field within reach of clinical investigators. The microbiota data generated by these methods are very well suited for

multivariate statistical modelling to assess the impact of environmental and external variables on microbiota composition, enabling the selective identification of microbial biomarkers of disease, which may allow the assessment of disease status in individuals, or the tracing of therapy efficacy. Apart from addressing bacterial populations, molecular methods can also be adapted to characterize yeast, fungal, and viral communities associated with skin [41,42,43]. Moreover, upcoming advances in sequencing technology will increase throughput (more samples), sequencing depth (more reads per sample), and phylogenetic resolution (longer reads). Nevertheless, rRNA targeting methodologies are restricted to assessment of

ecosystem composition, and do not provide direct information of the functionality of the microbiota. Metagenomic approaches, in which the total DNA of an ecosystem is sequenced, offer great potential for the generation of untargeted inventories of ecosystem inhabitants and provide direct access to the functional composition of the skin microbiome. A major hurdle in these approaches is that they require a substantial quantity of DNA, which is currently limiting the applicability of metagenomics in (dry) skin sites that are colonized by low-density communities. Nevertheless, the potential of this technology has been illustrated recently for two skin sites, namely, the anterior nares (moist) and retroauricular crease (sebaceous) sites, revealing that these ecosystems are more similar in terms of functional composition as compared with their phylogenetic composition [8<sup>■</sup>]. A compelling advantage of metagenomic function profiling is the high phylogenetic resolution that goes beyond the species level. Importantly, functional adaptations of the microbiome were associated with changes at the strain level, which was reflected in host-specific structural variant enrichment that illustrates the genomic plasticity of a microbial community in response to its environmental conditions. The potential power of metagenomic technologies in unravelling the functional adaptations of the skin microbiome to the diseased skin still has to be evaluated, but strain level analyses of the major skin commensal *Propionibacterium acnes* found in both acne and healthy skin provided insight into specific phylogenetic lineages typically associated with acne and unhealthy skin versus healthy skin controls [44<sup>■</sup>,45]. Moreover, the potential role of acne-associated lineages in the pathophysiology was further addressed by whole genome comparison of representative strains, enabling the identification of genes with a role in adherence, virulence, and pathogenic immune response in *P. acnes* lineages derived from unhealthy skin [46<sup>■</sup>]. Apart from these genetic differences, several studies [47,48] also addressed the functional differences of *P. acnes* communities in the skin of healthy and acne patients, demonstrating that the anaerobic compartment of the sebaceous follicles of acne-skin biopsies was more frequently colonized with *P. acnes*, which were mostly present as microbial biofilms. It remains unknown how this relates to lineage or strain-specific genetics of the *S. aureus* genus representatives that are found to dominate the atopic dermatitis-affected skin microbiota, but comparative genomics in cutaneous infections already revealed specific phylotypes to be associated with distinct clinical properties [49<sup>■</sup>]. Increasing our understanding of the compartmentalized behaviour

of skin microorganisms in relation to skin diseases might be a crucial step towards unravelling their role in pathophysiology.

The determination of the collective pool of messenger RNAs that are expressed *in situ*, a technology known as metatranscriptomics, enables the characterization of the activity of specific metabolic functions. These approaches also have the capacity to reveal functions expressed at high level by low-abundance members of the skin microbiota. High resolution functional activity profiles of the skin microbiota in relation to clinical entities of the skin such as inflammation, infection, and disease hold great promises to refine our understanding of the molecular interplay between the skin and the microbial community it hosts. Metatranscriptome approaches have not yet been reported for the skin, most likely because of the limited amount of sample material that can be collected. However, emerging advances in sample preparation, material enrichment, RNA amplification, or sequencing technologies may solve these problems in the future [50].

Overall, skin microbiome research will be able to harness the emerging technological possibilities that are being developed for other microbial communities that inhabit human niches such as the oral and gastrointestinal tract. The combination of different omics-based technologies and their integration will enable the deciphering of microbiome functionalities related to pathophysiologic host–microbe interactions, which may open avenues for novel prophylactic or therapeutic approaches for skin diseases, which may include microbiome manipulation strategies.

## PERSPECTIVES AND FUTURE DIRECTIONS

Meta'omics studies are on the verge of revolutionizing our perspective on the skin microbiome and its interactions with the host skin barrier and defence systems. Apart from increasing our basic knowledge on the involvement of the microbiome in skin diseases, the implications for health will be two-fold. First, investigation of microbiota composition and functionality in longitudinal cohorts of well characterized disease phenotypes will facilitate the identification of markers related to disease onset, progression, and outcome. Early shifts in microbiota composition, like in atopic dermatitis patients with *S. aureus* overgrowth, can identify patients at risk of relapsing disease and be employed for noninvasive guidance of therapy regimes. In addition, investigation of skin microbiome dynamics during the course of currently applied disease treatment strategies could allow the recognition of microbiota features that distinguish responders from

nonresponders, thereby potentially fuelling the development of combinatorial drug administration regimes that aim at controlling both host inflammation and skin microbiome dysbiosis. Second, skin microbiome explorations can uncover potential leads for the development of novel therapeutics that are specifically targeted to inhibit skin pathogens or restore natural commensal population structures. To date, encouraging observations have been made for direct and indirect protection against skin pathogens (Supplemental Table 2, <http://links.lww.com/COAI/A3>).

## CONCLUSION

In this review, we have summarized recent work on the human skin microbiome and highlighted the involvement of microorganisms in skin diseases and the possibilities to develop new treatment strategies. Although these lines of research are still in their infancy and ground-breaking research is needed for the development and validation of such conceptually new topical treatments, it is increasingly apparent that we are at the start of an exciting era for basic biological discovery and translational research in dermatology.

## Acknowledgements

None.

## Conflicts of interest

The authors are funded by a grant from the Dutch Ministry of Economic Affairs (PID082025) and by a TOP grant from ZonMw (91211052).

There are no conflicts of interest for any of the authors in relation to this publication.

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 581).

1. Dominguez-Bello MG, Costello EK, Contreras M, *et al.* Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci U S A* 2010; 107:11971–11975.
2. Capone KA, Dowd SE, Stamatas GN, Nikolovski J. Diversity of the human skin microbiome early in life. *J Invest Dermatol* 2011; 131:2026–2032.
3. Grice EA, Kong HH, Renaud G, *et al.* A diversity profile of the human skin microbiota. *Genome Res* 2008; 18:1043–1050.
4. Cho I, Blaser MJ. The human microbiome: at the interface of health and disease. *Nat Rev Genet* 2012; 13:260–270.
5. Ursell LK, Clemente JC, Rideout JR, *et al.* The interpersonal and intrapersonal diversity of human-associated microbiota in key body sites. *J Allergy Clin Immunol* 2012; 129:1204–1208.
6. Rosenthal M, Goldberg D, Aiello A, *et al.* Skin microbiota: microbial community structure and its potential association with health and disease. *Infect Genet Evol* 2011; 11:839–848.
7. Kuczynski J, Lauber CL, Walters WA, *et al.* Experimental and analytical tools ■ for studying the human microbiome. *Nat Rev Genet* 2012; 13:47–58. Comprehensive review on the tools and strategies for microbiome studies.
8. Consortium THMP. Structure, function and diversity of the healthy human microbiome. *Nature* 2012; 486:207–214.
- In this paper, the HMP Consortium reports the first results of their analysis of microbiomes from distinct, clinically relevant body habitats in a human cohort.
9. Qin J, Li R, Raes J, *et al.* A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* 2010; 464:59–65.
10. Hanski I, von Hertzen L, Fyhrquist N, *et al.* Environmental biodiversity, human microbiota, and allergy are interrelated. *Proc Natl Acad Sci U S A* 2012; 109:8334–8339.
- This study demonstrates that environmental biodiversity in the surroundings of peoples' homes influences the bacterial composition on their skin, and that this is strongly associated with allergic conditions.
11. Chiller K, Selkin BA, Murakawa GJ. Skin microflora and bacterial infections of the skin. *J Invest Dermatol Symp Proc* 2001; 6:170–174.
12. Fierer N, Lauber CL, Zhou N, *et al.* Forensic identification using skin bacterial communities. *Proc Natl Acad Sci U S A* 2010; 107:6477–6481.
13. Iwase T, Uehara Y, Shinji H, *et al.* *Staphylococcus epidermidis* Esp inhibits *Staphylococcus aureus* biofilm formation and nasal colonization. *Nature* 2010; 465:346–349.
14. Shu M, Wang Y, Yu J, *et al.* Fermentation of *Propionibacterium acnes*, a ■ commensal bacterium in the human skin microbiome, as skin probiotics against methicillin-resistant *Staphylococcus aureus*. *PLoS One* 2013; 8:e53380.
- This study demonstrates that fermentation of glycerol by *P. acnes* can inhibit skin colonization of methicillin-resistant *S. aureus*.
15. Lai Y, Di NA, Nakatsuji T, *et al.* Commensal bacteria regulate Toll-like receptor 3-dependent inflammation after skin injury. *Nat Med* 2009; 15:1377–1382.
16. Wanke I, Steffen H, Christ C, *et al.* Skin commensals amplify the innate immune response to pathogens by activation of distinct signaling pathways. *J Invest Dermatol* 2011; 131:382–390.
17. Li D, Lei H, Li Z, *et al.* A novel lipopeptide from skin commensal activates ■ TLR2/CD36-p38 MAPK signaling to increase antibacterial defense against bacterial infection. *PLoS One* 2013; 8:e58288.
- This study shows that a novel lipopeptide derived from *S. epidermidis* increases hBD2 and hBD3 expression via activation of the TLR2/CD36-p38 MAPK signaling pathway.
18. Naik S, Bouladoux N, Wilhelm C, *et al.* Compartmentalized control of skin ■ immunity by resident commensals. *Science* 2012; 337:1115–1119.
- This important study reported the requirement of commensal bacteria for optimal immune fitness in a manner dependent on signalling downstream of IL-1R.
19. Blaser M. Antibiotic overuse: stop the killing of beneficial bacteria. *Nature* 2011; 476:393–394.
20. Grice EA, Segre JA. The skin microbiome. *Nat Rev Microbiol* 2011; 9:244–253.
21. Costello EK, Lauber CL, Hamady M, *et al.* Bacterial community variation in human body habitats across space and time. *Science* 2009; 326:1694–1697.
22. Grice EA, Kong HH, Conlan S, *et al.* Topographical and temporal diversity of the human skin microbiome. *Science* 2009; 324:1190–1192.
23. Zeeuwen PL, Boekhorst J, van den Bogaard EH, *et al.* Microbiome dynamics ■ of human epidermis following skin barrier disruption. *Genome Biol* 2012; 13:R101.
- Our study describes the analysis of the microbiota of the surface and deeper layers of skin, and how it changes following skin barrier disruption.
24. Nakatsuji T, Chiang HI, Jiang SB, *et al.* The microbiome extends to sub- ■ epidermal compartments of normal skin. *Nat Commun* 2013; 4:1431.
- This study reported that a partial skin microbiome is present in subcutaneous regions of our skin and is, therefore, directly located to influence host behaviour.
25. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989; 299:1259–1260.
26. Ehlers S, Kaufmann SH. Infection, inflammation, and chronic diseases: consequences of a modern lifestyle. *Trends Immunol* 2010; 31:184–190.
27. von Hertzen L, Hanski I, Haahela T. Natural immunity. Biodiversity loss and inflammatory diseases are two global megatrends that might be related. *EMBO Rep* 2011; 12:1089–1093.
28. Kuo IH, Yoshida T, De Benedetto A, Beck LA. The cutaneous innate immune response in patients with atopic dermatitis. *J Allergy Clin Immunol* 2013; 131:266–278.
29. McAleer MA, Irvine AD. The multifunctional role of filaggrin in allergic skin disease. *J Allergy Clin Immunol* 2013; 131:280–291.
30. Palmer CN, Irvine AD, Terron-Kwiatkowski A, *et al.* Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; 38:441–446.
31. Hollox EJ, Huffmeier U, Zeeuwen PL, *et al.* Psoriasis is associated with increased beta-defensin genomic copy number. *Nat Genet* 2008; 40:23–25.
32. de Cid R, Riveira-Munoz E, Zeeuwen PL, *et al.* Deletion of the late cornified envelope LCE3B and LCE3C genes as a susceptibility factor for psoriasis. *Nat Genet* 2009; 41:211–215.
33. Boguniewicz M, Leung DY. Atopic dermatitis: a disease of altered skin barrier and immune dysregulation. *Immunol Rev* 2011; 242:233–246.
34. Huang JT, Abrams M, Tloughan B, *et al.* Treatment of *Staphylococcus aureus* colonization in atopic dermatitis decreases disease severity. *Pediatrics* 2009; 123:e808–e814.

35. Kong HH, Oh J, Deming C, *et al*. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res* 2012; 22:850–859.

The first study that describes microbiome analysis of atopic dermatitis skin during disease flares and treatment.

36. Fry L, Baker BS. Triggering psoriasis: the role of infections and medications. *Clin Dermatol* 2007; 25:606–615.
37. Gao Z, Tseng CH, Strober BE, *et al*. Substantial alterations of the cutaneous bacterial biota in psoriatic lesions. *PLoS One* 2008; 3:e2719.
38. Fahlen A, Engstrand L, Baker BS, *et al*. Comparison of bacterial microbiota in skin biopsies from normal and psoriatic skin. *Arch Dermatol Res* 2012; 304:15–22.

This study used skin biopsies instead of superficial skin swabs to study the microbiota composition of normal and psoriatic skin.

39. Zeeuwen PL, de Jongh GJ, Rodijk-Olthuis D, *et al*. Genetically programmed differences in epidermal host defense between psoriasis and atopic dermatitis patients. *PLoS One* 2008; 3:e2301.
40. Brauweiler AM, Bin L, Kim BE, *et al*. Filaggrin-dependent secretion of sphingomyelinase protects against staphylococcal alpha-toxin-induced keratinocyte death. *J Allergy Clin Immunol* 2013; 131:e421–e422.

This study shows that a filaggrin-dependent secretion of sphingomyelinase protects against *S. aureus*  $\alpha$ -toxin-induced death of keratinocytes. As filaggrin deficiency is the primary feature of atopic dermatitis, the authors suggested that their study provides a mechanism to explain the increased tendency for *S. aureus*-mediated exacerbation of atopic dermatitis.

41. Park HK, Ha MH, Park SG, *et al*. Characterization of the fungal microbiota (mycobiome) in healthy and dandruff-afflicted human scalps. *PLoS One* 2012; 7:e32847.

A study reporting on the distribution of fungal communities associated with dandruff.

42. Paulino LC, Tseng CH, Strober BE, Blaser MJ. Molecular analysis of fungal microbiota in samples from healthy human skin and psoriatic lesions. *J Clin Microbiol* 2006; 44:2933–2941.

43. Foulongne V, Sauvage V, Hebert C, *et al*. Human skin microbiota: high diversity of DNA viruses identified on the human skin by high throughput sequencing. *PLoS One* 2012; 7:e38499.

44. McDowell A, Barnard E, Nagy I, *et al*. An expanded multilocus sequence typing scheme for *Propionibacterium acnes*: investigation of 'pathogenic', 'commensal' and antibiotic resistant strains. *PLoS One* 2012; 7:e41480.

The data in this study lend support to the view that pathogenic versus truly commensal lineages of *P. acnes* may exist.

45. Lomholt HB, Kilian M. Population genetic analysis of *Propionibacterium acnes* identifies a subpopulation and epidemic clones associated with acne. *PLoS One* 2010; 5:e12277.

46. Fitz-Gibbon S, Tomida S, Chiu BH, *et al*. *Propionibacterium acnes* strain populations in the human skin microbiome associated with acne. *J Invest Dermatol* 2013; doi: 10.1038/jid.2013.21. [Epub ahead of print]

This study presents the skin microbiome at the strain level and genome level of *P. acnes* between acne patients and healthy individuals by sampling the pilosebaceous units on their noses.

47. Alexeyev OA, Lundskog B, Ganceviciene R, *et al*. Pattern of tissue invasion by *Propionibacterium acnes* in acne vulgaris. *J Dermatol Sci* 2012; 67: 63–66.

48. Jahns AC, Lundskog B, Ganceviciene R, *et al*. An increased incidence of *Propionibacterium acnes* biofilms in acne vulgaris: a case-control study. *Br J Dermatol* 2012; 167:50–58.

49. Kurt K, Rasigade JP, Laurent F, *et al*. Subpopulations of *Staphylococcus aureus* clonal complex 121 are associated with distinct clinical entities. *PLoS One* 2013; 8:e58155.

This study demonstrates that phylogenetic lineages with distinct clinical properties exist within a *S. aureus* clonal complex, and that SNPs serve as powerful discriminatory markers, which are able to identify these lineages.

50. Fredrich E, Barzanthy H, Brune I, Tauch A. Daily battle against body odor: towards the activity of the axillary microbiota. *Trends Microbiol* 2013; 21:305–312.