CrossMark

Microbial Ecology of the Human Skin

Anthony M. Cundell[1]

Abstract This review article on the skin microbiota was written in response to recent advances that transitioned from culture methods to PCR amplification and sequencing of bacterial and fungal genes as a result of the Human Microbiome Project. This transition enables the investigation of the full diversity of microorganisms inhabiting human skin. The skin provides a range of habitats with different microbiota associated with the three major regions of the skin, namely the moist axilla, perineum, and toe webs; oily or sebaceous head, neck, and trunk; and dry forearms and legs. These new culture-independent tools are revealing the diversity of the human skin microbiota in the different locations of the body and with skin depth. These tools should lead to a better understanding of the state of homeostasis between the microbiota and the host and the overall functionality of that microbiota.

Introduction

Why would a review article on skin microbiology be published in the journal *Microbial Ecology*? Microbial ecology can be broadly defined as the ecology of microorganisms and their relationships with one another and their environment. The central themes of microbial ecology have been the recycling of elements especially carbon, nitrogen, and phosphorus in water, soil, and sediments; the structure of microbiological communities; interactions between microorganisms and animals and plants; and the environmental effects on the growth and activities of microorganisms. Applied fields that are of interest to microbial ecology range from bioremediation, soil fertility, the digestive tract and the rumen, biofilms, aerobiology, plant pathology to microbial engineering. This breadth supports that skin microbiology, usually associated with clinical microbiology, is a topic that can be viewed in the context of the field of microbial ecology and should interest the readership of this issue of *Microbial Ecology*. Furthermore, the broader field of the human microbiome was the topic of a popular exhibit *The Secret World Inside You* at the American Museum of Natural History in New York City.

This article celebrates the contributions to the field of microbial ecology of Dr. Ralph Mitchell, Gordon McKay Professor Emeritus of Applied Biology at Harvard University in Cambridge, MA, founder of the journal some 50 years ago, and my post-doctoral mentor and friend. Congratulations, Ralph.

Human Skin as a Habitat

The research on the microbiology of human skin has been extended beyond the traditional concerns of the role of microorganisms in wound infection and skin diseases and their survival after disinfection prior to surgery to the implications of the human microbiota to our well-being. The human skin is the boundary between the body and the external environment

✉ Anthony M. Cundell
  tonycundell@gmail.com

1 Microbiological Consulting, LLC, 105 Lee Ave.,
  Scarsdale, NY 10583, USA

that provides structure and flexibility protecting the underlying muscles, bones, ligaments, and internal organs and prevents the excessive loss of moisture and the entry of microorganisms and toxic materials into the body. For an average adult, the skin has a surface area of 1.5 to 2.0 m^2 and is between 2 and 3 mm thick [1]. Other major functions of the skin include insulation; acting as a water shield; temperature regulation; generating sensations of touch, heat, and cold; and synthesis of Vitamin D when the skin is exposed to sunlight. A clinical function of the human skin microbiota is by occupying various habitats; it blocks the colonization of the skin by opportunistic or pathogenic microorganisms [2]. The skin provides a diversity of habitats for bacteria, yeast, and mold with different microbiota associated with the three major regions of the skin: (1) moist axilla, perineum, and toe webs; (2) oily or sebaceous head, neck, and trunk; and (3) dry forearms and legs. In geographical terms, the axilla can be likened to a tropical rain forest and the lower forearm to a desert [3, 4]. Of the total surface area, the legs provide 18 % each, arms 9 % each, head 9 %, and the trunk the remaining 37 %. Specialized areas with a rich microbiota such as the perineal region and axillae account for less than 2 % of the area [1].

The surface of the skin is slightly cooler than the core body temperature (37 ° C), it is slightly acid (pH around 5.6), and squames are constantly being shed from the skin surface due to terminal differentiation [5]. The normal microbial counts using culture methods typically range from 10^3 to 10^4 organisms per square centimeter with counts reaching a high of 10^6 per square centimeter in the most humid areas such as the groin and axilla. Washing the body with soap and water temporarily reduces the microbial count by an order of magnitude and removes transient microorganisms that may be potential pathogens from the skin surface. Based on traditional culture methods, the predominant bacteria are *Propionibacterium acnes* and *Staphylococcus* spp. in oily sites, *Corynebacterium* spp. and *Staphylococcus* spp. in moist sites, and a significant presence of members of the phyla *beta-Proteobacteria* and *Flavobacteriales* in the dry sites [1].

In addition to the different longitudinal regions of the skin, the epidermis is vertically stratified where keratinocytes undergo differentiation from mitotically active basal cells to transcriptionally active spinous cells to enucleated granular cells and finally differentiated squames in the stratum corneum that are continuously shed from the skin surface as microscopic particles in healthy individuals [6]. Furthermore, numerous pores of sweat glands and hair follicles, giving the skin additional structural complexity, penetrate the epidermis. Skin cells turnover around every 4 weeks, differentiating from stem cells deep within the epidermis and hair follicles and eventually sloughing off from the upper layer as cornified, enucleated, and dead cells [7]. The published skin shedding rates are up between 500 and 3000 cells per square centimeter per hour with around 10 % of the cells bearing bacteria [1, 7, 8]. This shedding will result in the persons occupying a room having a unique impact of the microbiota in that room. The size of a shedding skin cell is about 15–20 μm, so they will vertically fall through the air alighting on horizontal surfaces. The number of bacteria in microcolonies on shedded skin cells is reportedly small ranging from 2 to over 1000, predominantly in the low end of the range, and is relatively sparse in distribution considering the total skin area [8]. Using scanning electron microscopy, earlier researchers [9] confirmed that bacteria were widely distributed in small colonies usually containing less than 10 on the skin surface with larger colonies within the stratum corneum usually associated with sweat glands or the underside of furrows in the skin surface.

Factors determining the overall numbers and composition of the skin microbiota include the following: (1) region of the skin on the human body; (2) chemical attributes of the skin, i.e., pH, fatty acid composition, and moisture level; (3) gender; (4) geographical location and ethnicity; (5) depth within the epidermis; (6) antibiotic treatment; (7) use of cosmetics; (8) age of the individual; and (9) health status of the individual. These factors will be explored in more detail later in this review article.

Origin of the Bacterial Diversity

The skin microbiota is established immediately after birth with the mode of delivery influencing the initial infant microbiota [10, 11]. Vaginal delivery leads to skin colonization predominantly with vaginal bacteria, i.e., *Lactobacillus*, *Prevotella*, and *Sneathia* spp., while Cesarean section leads to colonization of bacteria associated with maternal skin, i.e., *Propionibacterium*, *Staphylococcus*, and *Corynebacterium* spp. As an infant ages, the diversity of their skin microbiota increases, as does the location specificity. At puberty, in response to hormone-stimulated sebaceous gland secretion, the lipophilic taxa *Corynebacterium* and *Propionibacterium* become more prominent on the skin. Disruptions in the skin microbiota, in terms of loss of diversity and more prominence of specific strains of bacterial species, e.g., *Staphylococcus aureus* and *P. acnes*, are associated with many dermatological diseases [2]. In general, trends in human microbiota diversity vary with disease and body location with more examples from other body locations than the skin. For example, diversity is reduced in the gut microbiome with obesity [12], whereas the diversity is increased in vaginal microbiome with vaginitis [13]. More research on the diversity of skin microorganisms with factors such as lifestyle, disease state, and age would be very useful.

Landmark Publications

For those of us who are historically minded, two landmark books on the microbiology of the skin that developed many concepts in use today are the 1965 publication of the Professor Mary J. Marples, University of Otago, New Zealand, seminal book *The Ecology of the Human Skin* [14] and the 1981 book of William C. Noble, St. John's Hospital for Diseases of the Skin, London, UK, entitled *Microbiology of Human Skin* [1]. In the former book, Molly Marples first promoted the idea that the skin is an ecosystem supporting a diversity of microorganisms in habitats such as the desert of the forearm, the cool woodlands of the scalp, and the tropical rain forest of the armpit and differentiated between resident and transition microbial populations, themes that she further developed in her general audience 1969 Scientific American article entitled *Life on the Human Skin* [14]. Bill Noble's book is divided into three sections discussing skin as a habitat, microbial inhabitants of the skin, and the ecology of the skin [1]. These pioneers deserve remembering as they first established the field of skin microbiology, advanced an ecological viewpoint, and anticipated many of the broad findings of more recent studies using modern non-cultural methods.

Human Microbiome Project

In 2007, the US National Institutes of Health (NIH) funded the Human Microbiome Project (HMP) with 5-year funding of $150 million opportunistically using four large-scale sequencing centers at Baylor College of Medicine, Broad Institute, J. Craig Venter Institute, and Washington University School of Medicine developed during the Human Genome Project. The NIH-sponsored HMP has examined the microbial populations within and across body habitats of the oral, skin, distal gut, and vaginal body regions using multiple individuals over a time sequence [12, 15]. This was achieved using pyrosequencing-based profiling of 16S ribosomal RNA (rRNA) gene sequencing. As we now recognize, traditional culture methods do not identify many significant taxa and significantly underestimate the diversity of the bacterial communities. It has been estimated, in the general literature, that there are at least ten times as many bacteria as human cells in the body (approximately 10^{14} bacterial cells versus 10^{13} somatic cells). The majority of those bacteria are found in the gastro-intestinal tract and not the skin (10^{12} per g of fecal matter versus up to 10^6 per cm^2 of skin) [16]. Furthermore, there are 1,000,000+ genes in the microbiome versus the 23,000 gene human genomes [17]. The taxonomic and genetic diversity was found to be greatest in the tooth surface and stool samples, intermediate in the skin and inside surface of

the cheek, and lowest in the vaginal samples. The researchers reported that each habitat is characterized by a small number of highly abundant taxa, i.e., predominant organisms, but these taxa vary widely between individuals. High-abundance taxa are accompanied by low abundance taxa of the same genus, suggesting some community niche specialization.

Until very recently, the composition of the skin microbiota was determined by culture-based methods that selected bacteria that more readily grew on microbiological media with short incubation times using swabbing of the skin surface and not gene sequencing [17, 18]. These limitations would not capture the full diversity of the skin microbiota. However, it has been suggested that up to 80 % of the species associated with the skin are recoverable by culture methods, which is much higher than other sites like the gut [18]. Furthermore, characterization of the human microbiome using culture-independent, high-throughput 16S rRNA gene sequencing has revealed the diversity and differences in the human microbiota in the different locations of the body and skin depth. For example, it estimated that there are, in descending order, an estimated 4000 bacterial species in the human intestine with the genera *Bacteroides*, *Prevotella*, and *Lactobacillus* predominant; 1200 bacterial species on the skin with the genera *Propionibacterium*, *Staphylococcus*, and *Corynebacterium* predominant; 800 bacterial species in the oral cavity with the genus *Streptococcus* predominant; and 300 bacterial species in the vagina with the genus *Lactobacillus* predominant [17]. Of the 1200 species from around 20 phyla associated with the human, the majority (>90 %) across all skin sites are from only four phyla [17]. They are as follows: *Actinobacteria* (52 %) represented by the genera *Micrococcus*, *Corynebacteria*, and *Propionibacteria*; *Firmicutes* (24 %) represented by the genera *Lactobacillus*, *Staphylococcus*, and *Streptococcus*; *Proteobacteria* (16 %) that includes the genera *Paracoccus*, *Haematobacter*, and *Sphingomonas*; and *Bacteriodetes* (5 %) represented by Gram-negative, non-spore-forming anaerobic, rod-shaped bacteria including the genera *Prevotella*, *Porphyromonas*, and *Flavobacterium*. As in other microbial ecosystems, highly abundant genera in the human microbiota are widely prevalent in a higher percentage of subjects sampled while low abundant genera were more restricted in their distribution [19].

The diversity of the human microbiota at both the species and strain levels and its association with human well-being and disease were largely unknown, but these issues are being addressed in ongoing research [17, 20]. It is widely understood that many infectious diseases may be strain-related and not solely species-related. Well-known examples from clinical and food microbiology would include methicillin-resistant *S. aureus* and *Escherichia coli*

O157: H7 [21]. As acne is one of the most common skin diseases, with prevalence up to 85 % in teens and 11 % in adults, it has received attention in terms of number of bacteria on the skin and their strain type. The marked increase in *P. acnes* on the skin around puberty corresponding to the increase in sebaceous secretions is generally considered evidence of the role of this bacterium in acne. Topical and systemic antibiotic treatment has long been used to control acne with the efficacy attributed to decreased *P. acnes* colonization and or activity [22]. Recent genomic analysis found that the relative abundances of *P. acnes* did not differ between skin conditions, whereas the relative abundances of different strains did differ [23]. More follow-up studies by skin microbiologist are expected in this area before there is complete understanding of the causes of acne.

It should not be overlooked that the human skin bears lower numbers of fungi, with less diversity than bacterial populations. In a 2013 study by the National Cancer Institute, dermatologist Heidi Kong and her colleagues sequenced the fungal microbiota from 14 different sites of ten healthy adults and found fungal communities, with the exception of the feet that have a greater fungal diversity, dominated by the genus *Malassezia* [24].

Other researchers used quantitative PCR to enumerate the total bacterial and fungal populations using 16S rRNA gene and internal transcribed spacer (ITS) region primers and probes, respectively, as well as the most common bacteria genera, i.e., *Propionibacterium*, *Staphylococcus*, *Corynebacterium*, and *Streptococcus*, and the fungal genus *Malassezia* using bacterial and fungal genus-specific probes, in six skin habitats in eight healthy human subjects instead of culture-based methods that determine colony-forming units [25]. The results reported as $\log_{10}$ copies per microliter of extraction sample were corrected for human DNA contamination, using the housekeeping glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene, which are summarized in Table 1. These results generally confirm patterns seen with earlier culture-based methods [1, 14] and emphasize the presence of both bacteria and fungi in the skin microbiota.

Factors Affecting the Skin Microbiota

The following factors may influence the numbers and diversity of the skin microbiota (see "Human Skin as a Habitat" section):

1. Region of the skin

A study determined the relative abundance of different bacterial taxa across the major skin regions, i.e., sebaceous, moist, and dry sites [3]. The results are summarized in Table 2(A, B, and C). Another key finding over and above diversity was that the longitudinal stability was related to the skin location, with sebaceous sites being the most stable and the dry sites such as the palm and forearm being the most variable over time. The location variability is greater than the temporal variability amongst individuals. However, the skin microbiota for an individual exhibits a greater diversity compared with the gut or oral microbiota due to the difference in various skin locations [2]. A study using 16S rRNA gene sequencing of the palm of 51 normal individuals isolated 4742 operational taxonomic units (OTC) with 32 % of the sequences *Propionibacterium*, 17 % *Streptococcus*, and 8 % *Staphylococcus*; only 17 % identity between the left and right hands; 13 % identity between individuals; and a greater overall diversity with female hands [26]. The implications of these finding are under discussion amongst skin microbiologists.

1. Chemical attributes of the skin

The pH, fatty acid composition, water retention, and sun damage all influence the skin microbiota. The functional barrier of the skin is largely derived from a patterned lipid lamellae and protein filaments between the enucleated keratinocytes in stratum corneum [27]. Chemical analysis of the solvent-extracted lipid from the stratum corneum reveals an unusual composition of near equimolar mixtures of ceramides (45–50 % by weight), cholesterol (25 %), free fatty acids (10–15 %), and other lipids including cholesterol sulfate (less than 5 %). These structure and lipid composition provide the water-

Table 1 Composition of the human skin microflora from six locations (mean $\log_{10}$ copies/µL ± SEM)

Body location	Sample number	All bacteria	Corynebacterium	Streptococcus	Staphylococcus	Propionibacterium	All fungi	Malassezia	Human GAPDH
Forehead	8	4.2 ± 0.3	0.8 ± 0.5	3.3 ± 0.2	2.6 ± 0.2	2.7 ± 0.2	2.8 ± 0.2	2.7 ± 0.3	1.6 ± 0.2
Forearm	16	3.0 ± 0.2	0.1 ± 0.1	2.0 ± 0.1	1.8 ± 0.3	1.9 ± 0.2	1.7 ± 0.1	1.3 ± 0.2	0.1 ± 0.1
Behind ear	16	4.6 ± 0.1	0.1 ± 0.1	3.8 ± 0.2	3.6 ± 0.1	3.6 ± 0.1	2.8 ± 0.1	2.7 ± 0.1	2.1 ± 0.2
Inner elbow	16	2.9 ± 0.2	0.6 ± 0.3	1.9 ± 0.2	1.9 ± 0.3	1.8 ± 0.3	1.6 ± 0.1	1.2 ± 0.2	0.3 ± 0.1
Foreleg	16	3.0 ± 0.1	0.4 ± 0.1	2.0 ± 0.1	2.1 ± 0.2	2.0 ± 0.2	1.5 ± 0.1	1.1 ± 0.1	0.5 ± 0.1
Armpit	10	5.0 ± 0.1	3.0 ± 0.7	4.2 ± 0.2	4.1 ± 0.1	4.0 ± 0.1	2.2 ± 0.2	2.1 ± 0.3	0.6 ± 0.1

Subtracting the human GAPDH copies for the site from the 16S rRNA can normalize the reported results. ITS region and genus-specific rRNA copies

SEM standard error of the measurement

Table 2 Relative abundance of bacterial groups ($N = 10$ healthy individuals)

Bacterial taxa	Percentage of the microbiota as 16S gene sequences	Cumulative percentage
A. Sebaceous or oily sites (glabella, alar crease, external auditory canal, occiput, manubrium, and back)		
Propionibacterium	46	46
Staphylococcus	16	62
Corynebacterium	10	72
Beta-Proteobacteria	9	81
Other	5	86
Unclassified *Actinomycetales*	4	90
Flavobacteriales	4	94
Lactobacillales	3	97
Clostridiales	1	98
Gamma-Proteobacteria	1	99
Alpha-Proteobacteria	<1	>99
Bacteroidales	<1	>99
B. Moist sites (nare, axillary vault, antecubital fossa, interdigital web space, inguinal crease, gluteal crease, popliteal fossa, plantar heel, and umbilicus)		
Corynebacterium	28	28
Beta-Proteobacteria	21	49
Staphylococcus	21	70
Flavobacteriales	9	79
Propionibacterium	7	86
Other	5	91
Gamma-Proteobacteria	3	93
Lactobacillales	2	95
Clostridiales	2	97
Alpha-Proteobacteria	2	99
Unclassified *Actinomycetales*	1	100
Bacteroidales	<1	100
C. Dry sites (volar forearm, hypothenar palm, and buttock)		
Beta-Proteobacteria	32	32
Corynebacterium	15	47
Flavobacteriales	14	61
Propionibacterium	13	74
Gamma-Proteobacteria	7	81
Staphylococcus	5	86
Other	5	91
Lactobacillales	4	95
Clostridiales	3	98
Alpha-Proteobacteria	2	100
Bacteroidales	<1	100
Unclassified *Actinomycetales*	<1	100

repellant and retention properties of the skin. The free fatty acids are undoubtedly the basis of the slightly acid pH and the inherent antibacterial activity of the skin to invading microorganisms. New tools are available to study the human skin. For example, metabolomic investigations of paired sun-protected and sun-damaged skin samples have shown that out of 122 metabolites analyzed, 46 were lower and 76 higher in sun damaged skin. [28]. It is inferred that oxidative stress due to sun damage leads to changes in the purine, methionine-glutathione, and nicotinamide metabolic pathways in the skin. Future microbiological research will likely demonstrate how the physiology of healthy and damaged skin affects the microbiota on the skin [28, 29].

2. Gender

According to pioneering skin microbiologist Bill Noble, healthy adult males carry higher populations of bacteria on the skin, generally because the micro-colony size is larger in males than in females [1]. This has been supported by more recent studies. Physiological gender differences that influence skin properties include hormone production, sweating rate, sebum production, surface pH, and skin thickness and hair growth. Recent studies have shown that women have lower numbers but show a significant higher bacterial diversity than men, after controlling hand washing [26]. This reinforces the stereotype that women pay more attention to personal hygiene than men. Men and women were found to harbor different bacterial communities on their hands. Taxa shared by both sexes but were more abundant on one sex over the other were *Propionibacterium* (37 % more abundant on men), *Corynebacterium* (80 % more abundant on men), *Enterobacteriales* (400 % more abundant on women), *Moraxellaceae* (180 % more abundant on women), *Lactobacillaceae* (340 % more abundant on women), and *Pseudomonadaceae* (180 % more abundant on women). At this time, the reason for these differences is not clear, but the authors of the study suggest that the lower pH of the male skin, greater sweating by men, and more frequent female hand washing may play a role in the gender differences.

3. Geographical location and ethnicity

A study comparing the Amazonian Indians and US residents suggests that the diversity of the skin microbiota between individuals may be influenced by ethnicity, lifestyle, and geographic location [30]. Additional studies will be needed to further develop the effects of these influences.

4. Depth within the epidermis

Recent evidence suggests that the bacterial cell numbers increase as you go deeper into the epidermis. Grice and her co-workers [15] estimated the bacterial numbers assessing the sample collection method and used a quantitative PCR method based on a small amplicon of the 16S rRNA gene. This

study generated a standard curve using *E. coli* DNA and demonstrated that a background of human DNA did not alter the amplification measured by the threshold cycle (Ct) for the *E. coli* DNA. The values based on the molecular weight of an average bacterial genome for punch biopsies from the lower epidermal layers, scrapes from the intermediate layers, and swabs from the surface were 1,000,000; 50,000; and 10,000 bacteria per square centimeter, respectively. These results were unexpected but clearly are related to the higher moisture and nutrient levels in the lower layers of the skin.

5.   Antibiotic treatment and vaccination

Perturbation of the human microbiota by aggressive broad-spectrum antibiotic administration, more directed antibacterial vaccination, or even probiotic treatment is known to be pronounced and may be exploited for future medical treatments [31]. A vaccine may stimulate the immune system to remove or prevent the growth of a single species or single or multiple strains of a species from the human microbiota. This may change the numbers and composition of the human microbiota. Two well-known examples, unrelated to the skin but revealing, are inoculation with conjugated vaccines against *Haemophilus* type b and *Streptococcus pneumoniae* that protect against pulmonary infection or prevent colonization of the respiratory tract. The vaccines eliminate the most virulent strains of *Haemophilus influenzae* and *S. pneumoniae* from the pharyngeal microbiota, but they are inevitably replaced by less virulent, non-vaccine serotypes. Vaccines against skin pathogens like *P. acnes* and *S. aureus*, if available, may play a similar role eliminating pathogenic strains.

Antibiotics, which can be viewed as a miracle of modern medicine, profoundly reduce the numbers and diversity of the human microbiota, thus providing the opportunity for the overgrowth of a pathogen in different body sites. For example, the antibiotic minocycline, which is widely used to control acne, may disrupt the skin microbiota as well as reduce the number of *P. acnes*. Secondary infections associated with antibiotic use are *Clostridium difficile*-associated diarrhea and vaginal candidiasis, although not directly related to the skin, they highlight this trend [32, 33]. With persistent *C. difficile*-associated diarrhea that is unresponsive to vancomycin treatment, fecal matter transplant from healthy donors has been shown to be highly effective in treating recurrent *C. difficile* infections. These finding are revolutionary suggesting a new role for probiotics in disease treatment that may eventually be extended from the intestine to other sites on the human body, thus as the skin [34].

In the skin, it has been suggested that bacteriophage communities, as well as changing the bacterial composition of the skin microbiota, may act as mediators of antibiotic resistance gene transfer between bacteria [35]. This area needs further study to fully understand the role of these viruses in human health.

6.   Use of cosmetics

The resident skin microbiota may be beneficial in that they occupy many habitats in the skin and make it harder for transient pathogens to survive and grow on the skin. The application of cosmetics may adversely impact the skin, if they reduce microbial numbers and diversity [36]. Cosmetics that are formulated to reduce microbial abundance such as deodorants or germicidal soaps may differ in their impact on the numbers and diversity of the skin microbiota by site of application, whereas moisturizers that help retain the water content may support the skin microbiota and reduce skin cell shedding. A more complete understanding of the interaction of cosmetics with the microbiota may improve skin care.

7.   Age of the individual

As noted earlier in the review article, the bacterial colonization of newborn infants reflects their mode of delivery. Studies have shown that the mouth, skin, and first bowel movements of vaginally delivered babies were populated by vaginal *Lactobacillus*, *Prevotella*, and *Sneathia* species, while those babies born by Cesarean section were populated by skin *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* species [10]. During the first few months of life, the skin microbiota of Cesarean-sectioned and vaginally delivered babies began to converge [30]. Another notable change in microbiota composition is the appearance of *P. acnes* at puberty that hydrolyzes triglycerides in response to increased sebum secretion. The effect of aging on the composition of the skin microbiota may be a future area of research.

8.   Health status of the individual

Dysbiosis of the skin microbiota undoubtedly plays a significant role in common skin diseases such as atopic dermatitis, psoriasis, acne, and even dandruff [37]. *S. aureus*, a major cause of skin and soft tissue infections that colonize the nares of over 20 % of the population, is associated with atopic dermatitis. Kong and her co-workers [38] demonstrated that flares of this skin disease are associated with decreased microbial diversity and increased relative abundance of *S. aureus*.

A recent review article emphasized the role of the microbiome in immune development [39]. Germ-free mice, with no skin microbiota, in studies have abnormal cytokine production and improper T cell differentiation that appeared following *Staphylococcus epidermidis* colonization. Healthy skin employs a barrier that uses both immune surveillance and epidermal keratinocytes, which produce antimicrobial peptides (AMP) that contribute to the innate immunity of the skin.

AMP expression is upregulated by the presence of *Propionibacterium* species. This suggests that skin microbiota directly contribute to the innate immunity. For example, sebum triacylglycerides are hydrolyzed by *P. acnes* and *S. epidermidis* and peptides called pheno-soluble modulins (PSM) are produced by some strains of *S. epidermidis* and have selective activity against *S. aureus*, group A *Streptococcus*, and *E. coli* but not other *S. epidermidis* strains [39].

Other recent publications have emphasized the application of ecological theory toward the understanding of the human microbiome exploring development in infants (assembly of the microbiota in previously unoccupied habitat), recovery from antibiotics (re-assembly after a disturbance), and invasion of pathogens (role of the microbiota in stasis) [40] and the role of the skin microbiota in modulating immunity [20]. For example, Stanley Spinola and his colleagues at Indiana University found evidence that the composition of the skin microbiota played a role in the ability of individuals to clear abscesses on the shoulder caused by the inoculation of the bacterium *Haemophilus ducreyi* that causes sexually transmitted genital ulcers termed chancre endemic in parts of Africa and Asia and implicated in yaws and chronic skin ulcers in children in topical Africa and the South Pacific Islands. By characterizing the skin microbiome before, during, and after experimental inoculation with *H. ducreyi*, the researchers found that distinct community structure, especially the prevalence of *P. acnes*, strongly influenced if the individuals were so-called pustule formers or resolvers [41].

Impact of Skin Bacteria on Blood Collection and the Injection of Drug Products into People

As a pharmaceutical microbiologist, the author is interested in the entry of microorganisms into the human body with injection. When the skin is penetrated with needle for blood collection or the administration of injectable drugs, bacteria may contaminate the donation or be transferred into the surrounding tissue ultimately reaching the blood stream. Transfusion-transmitted bacterial infections (TTBI) have been a serious complication of transfusion since the introduction of blood banking at the beginning of the twentieth century. The introduction of donor-arm disinfection and sterile materials and anticlotting agents followed by closed systems for blood collection, component preparation, and storage resulted in significant TTBI rate reductions. Improved donor selection and blood testing significantly decrease the risk of hepatitis and HIV/AIDS infection; however, TTBI infection especially associated with platelet concentrate transfusion represented up to 10 % of blood transfusion-associated deaths annually [42]. Undoubtedly, room temperature storage of platelet concentrates for up to 5 days before transfusion contributes to the infection rates.

The major source of bacterial contamination of blood products is the donor arm followed by a much lesser extent by donor bacteremia, contaminated collection equipment, contamination during processing, and, lastly, transfusion. Reports show that skin-derived bacteria (both resident and transient) account for 90 % of the platelet concentrate-associated and 70 % of the red cell concentrate bacterial transmissions. The effectiveness of the disinfection of the skin may result in less contamination during skin penetration during venipuncture during blood collection and during intramuscular or intravenous injection. A single-step swabbing of the entry point with a 70 % isopropyl alcohol/2 % chlorhexidine preparation is widely used due to its relative effectiveness and short waiting time [42].

Conclusions

Tools are now available to fully characterize the human microbiome using culture-independent, high-throughput 16S rRNA sequencing. These tools are revealing the diversity and differences in the human skin microbiota in the different locations of the body and with skin depth and should lead to a better understanding of the state of homeostasis between the microbiota and the host and functionality of the microbiota. The role of the skin microbiota in the host well-being, prevention of infection, and their relationship to common skin diseases should become more apparent with further study.

References

1. Noble WC (1981) Microbiology of human skin, 2nd edn. Lloyd-Luke, London, p 443
2. Hannigan GD, Grice EA (2013) Microbial ecology of skin in the era of metagenomics and molecular microbiology. Cold Spring Harb Perspect Med 3:a015362
3. Grice EA et al (2009) Topographical and temporal diversity of the human skin microbiome. Science 324:1190–1192
4. Grice EA, Segre JA (2011) The skin microbiota. Nat Res Microbiol 9:244–253
5. Fuchs E, Raghaven S (2002) Getting under the skin of epidermal morphogenesis. Nat Rev Genet 3(3):199–209
6. Segre JA (2006) Epidermal barrier formulation and recovery in skin disorders. J Clin Invest 116:1150–1158
7. Blanpain C, Horsley V, Fuchs E (2007) Epithelial stem cells: turning over new leaves. Cell 128:445–458
8. Somerville DA, Noble WC (1973) Micro-colony size of microbes on human skin. J Med Microbiol 6:323
9. Malcolm SA, Hughes TC (1980) The demonstration of bacteria on and within the stratum corneum using scanning electron microscopy. Br J Dermatol 192(3):267–275

10. Dominguez-Bello MG et al (2010) Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci U S A 107:11971–119775

11. Mueller NT et al (2015) The infant microbiome development: mom matters. Trends Mol Med 21(2):109–117

12. Turnbaugh PJ et al (2009) The Human Microbiome Project. Nature 449:804–810

13. Fredricks DN et al (2005) Molecular identification of bacteria associated with bacterial vaginosis. N Engl J Med 353:1899–1911

14. Marples MJ (1965) The ecology of the human skin. Springfield, Illinois Thomas

15. Marples MJ (1969) Life on the human skin. Sci Am 220:108–115

16. Savage DC (1977) Microbial ecology of the intestinal tract. Ann Rev Microbiol 31:107–133

17. Grice EA et al (2008) A diversity profile of the human skin microbiota. Genom Res 18:1043–1050

18. Gao Z et al (2007) Molecular analysis of the human forearm superficial skin bacterial biota. Proc Natl Acad Sci U S A 104(8):2927–2932

19. Zhou YJ et al (2013) Biogeography of the ecosystems of the healthy human body. Genom Biol 14:R1

20. Belkaid Y, Segre JA (2014) Dialogue between skin microbiota and immunity. Science 346(6212):954–959

21. Findley K, Grice EA (2014) The skin microbiome: a focus on pathogens and their association with skin disease. Plos Pathogens 10(11):31004436

22. Tan HH (2003) Antibacterial therapy for acne. Am J Clin Dermatol 4(5):307–314

23. Fitz-Gibbon S et al (2013) *Propionibacterium acnes* strain populations in the human skin microbiome associated with acne. J Invest Dermatol 133(9):2153–2160

24. Findley K et al (2013) Human skin fungal diversity. Nature 498(7454):367–370

25. Gao Z et al (2010) Quantification of major human cutaneous bacterial and fungal populations. J Clin Microbiol 48(10):3575–3581

26. Fierer N et al (2008) The influence of sex. handedness, and washing on the diversity of hand surface bacteria. Proc Natl Acad Sci U S A 105:17994–17999

27. Madison KC (2003) Barrier function of the skin: la raison d'être of the epidermis. J Invest Dermatol 121:231–241

28. Randhawa M et al (2014) Metabolic signature of sun-exposed skin suggests catabolic pathway overweighs anabolic pathway. Plos One 9(3):e90367

29. Zeeuwen P et al (2012) Microbiome dynamics of human epidermis following skin barrier disruption. Gen Bio 13(R101):1–18

30. Blaser MJ (2014) Missing microbes: how the overuse of antibiotics is fueling our modern plagues. Henry Holt, New York, p 273

31. Lemon KP et al (2012) Microbiota—target therapies: an ecological perspective. Sci Transl Med 4(137):1–8

32. Spinillo A et al (1999) Effect of antibiotic use on the prevalence of symptomatic vulvovaginal candidiasis. Am J Obstet Gynecol 180:14–17

33. Kelly CP, LaMont JT (2008) *Clostridium difficile*—more difficult than ever. N Engl J Med 358:1932–1940

34. Van Nood E et al (2013) Duodenal infusion of donor feces for recurrent *Clostridium difficile*. N Engl J Med 368(5):407–415

35. Varga M et al (2012) Efficient transfer of antibiotic resistance plasmids by transduction within methicillin-resistant *Staphylococcus aureus* USA300 clone. FEMS Microbiol Lett 332:146–152

36. Holland KT, Bojar RA (2002) Cosmetics: what is their influence on the skin microflora. Am J Clin Dermatol 3:445–449

37. Kong HH, Segre JA (2012) Skin microbiome: looking back to move forward. J Invest Dermatol 132(3):933–939

38. Kong HH et al (2012) Temporal shifts in the skin microbiome with disease flares and treatment in children with atopic dermatitis. Genome Res 22:850–859

39. Chen YE, Tsao H (2013) The skin microbiome: current perspectives and future challenges. J Am Acad Dermatol 69(1):143–155

40. Costello EK et al (2012) The application of ecological theory towards an understanding of the human microbiome. Science 336(6086):1255–1262

41. van Rensburg JJ, Lin H et al (2015) The human skin microbiome associates with the outcome of and is influenced by bacterial infection. mBio 6(5):e01315-15

42. Korte D, Marcelis JH (2014) Platelet concentrates: reducing the risk of transfusion-transmitted bacterial infections. Intern J Clin Trans Med 2:29–37