ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Characterization of the Human Skin Microbiome.

Christopher W Cefalu*

Louisiana State University

ABSTRACT

Bacteria have developed an inveterate relationship with humans and play a vital role in homeostasis, given their high occupancy within numerous habitats in the human body. The interactions between bacteria and humans are profound and the effects are noted for both. An area of significant interest when discussing bacterial-human interaction pertains to the bacterial ecology of the human skin. Yet, there remains a number of questions regarding the skin microbiome in regards to human health and disease progression. This mini-review will synthesize data regarding this diversity, and will discuss factors affecting the variegation of bacterial populations and their colonization efforts on the skin.

Keywords: skin, microbiome, bacteria

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Bacteria have developed an inveterate relationship with humans and play a vital role in homeostasis, given their high occupancy within numerous habitats in the human body. The interactions between bacteria and humans are profound and the effects are noted for both. An area of significant interest when discussing bacterial-human interaction pertains to the bacterial ecology of the human skin. Skin serves as the largest organ in the human body, and functions as a dynamic and complex and environment for various populations of bacteria [15]. Investigative efforts have taken place for years in an attempt to qualify the bacteria present on the surface of the skin. In this regard, an appreciation of the structure of the skin is of principal importance in understanding how it affects the structure of bacterial communities, as well as how the structure of those communities subsequently affects the health of the host.

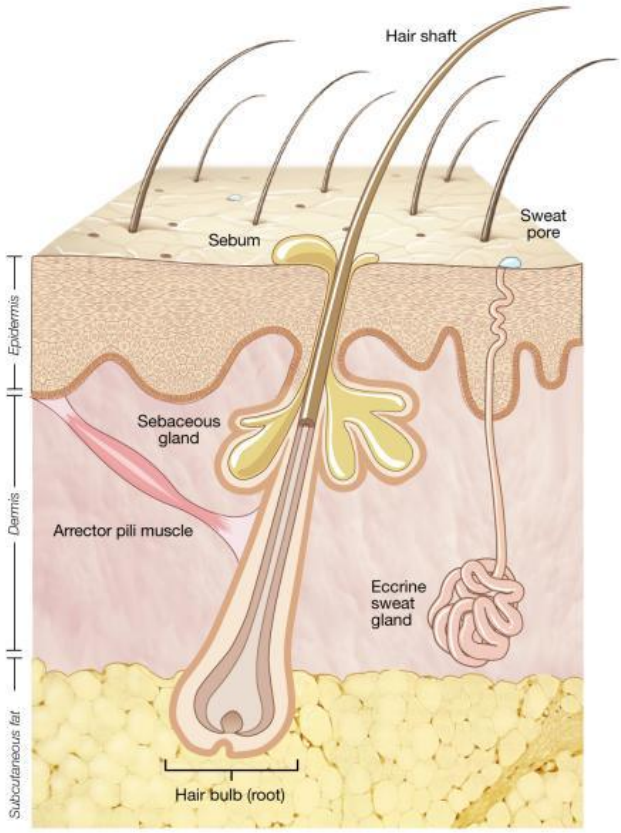

Figure 1: Anatomical cross section of the human skin. As demonstrated, there are two main layers of the skin that may be involved with interaction with microbes. The lower layer of the skin is the dermis, while the outermost layer comprises the epidermis. As shown, the dermis contains the network of vasculature required to deliver nutrient rich blood to the outermost epidermal layer of the skin. The epidermis is the outermost layer and principally comprises cells denoted as keratinocytes. During the process of desquamation, the cells are then shed from the outermost epidermal layer, which is referred to as the stratum corneum [Figure obtained from Kong *et al* (7)].

As described, the skin is a complex organ with a unique anatomy, and functions to provide protection to the host while concurrently serving as a dynamic ecosystem for bacterial

colonization (Figure 1). The lower layer of the skin is the dermis, while the outermost layer comprises the epidermis [7]. The dermis contains the network of vasculature that is required to deliver nutrient rich blood to the outermost epidermal layer of the skin. The epidermis principally comprises cells denoted as keratinocytes, which develop in the basal layer of the epidermis and migrate towards the surface over a 12 day period [12]. During the process of desquamation, the cells are then shed from the outermost epidermal layer, which is referred to as the stratum corneum.

As proposed, an understanding of the diversity and range of bacteria present on the skin, as well as their community structure and distribution, will indubitably provide vital information that has important health implications to the host. To date, culturing techniques have provided modest insight into this potential diversity, while more recent molecular techniques have offered more comprehensive information. Specifically, new data from molecular techniques have opened a window into the population diversity of the skin microbiota, which will certainly assist with such qualification efforts. Yet, there is much to discover regarding the structure of bacterial communities on the skin. How much variegation exists in the bacterial diversity of the skin between and within individuals? What factors affect population formation, and how does bacterial community structure affect the health of the host? Such questions serve as the impetus for contemporary research efforts. This review will synthesize data regarding this diversity, and will discuss factors affecting the variegation of bacterial populations and their colonization efforts on the skin.

Distribution of Bacterial Populations

Observations from early life indicate that the biogeography of bacterial communities on the human skin may be a function of the age of the individual. For example, the skin of a healthy fetus is bacterially sterile until slightly before birth [15]. Disruption to the amniotic sac can promote infection, and the placenta does not possesses the capacity to allow the migration of bacteria to the fetus [12]. Even in the hours following the birth of a newborn, the bacterial community structure on the surface of the infant differs drastically from the structure typically seen in adults [12]. Such differences may be attributable to the vernixcaseosa, a fatty coating formed from the degradation of epidermal cells. This coating envelops the skin of newborns, and its disappearance is associated with more acidic skin levels [1]. The skin of a newborn is also thinner and produces fewer sweat secretions than the skin of the adult. Both intrinsic and extrinsic factors (as discussed below) alter the physiology of the skin and therefore the distribution of bacterial populations in the early days of life [15].

Additional studies have demonstrated the diminished ability of various bacteria to colonize the skin during the incipient days of life. In a study comparing the ability of *S.aureus* to bind to nasal mucosal cells in newborns, it was found that in the first four days of life, the ability of *S. aureus*to bind to such cells was greatly reduced [14]. With each subsequent day from birth, a slightly higher percentage of *S.aureus* was able to adhere to the nasal cells. However, on the fifth day of life, almost 100% of *S. aureus* was found to have the ability to adhere to the nasal cells [14]. Although the mechanism for this observation is not specifically known, immature

ISSN: 0975-8585

receptor sites have been posited as potential explanations of this trend, as well as other physical differences in the structure of the skin of infants [12]. Regardless of the mechanism, the bacterial community structure of newborns is certainly different from that of adults, and intrinsic physiological factors in the skin of newborns appear play a role in creating this difference. After 6 weeks, the bacterial community structure on the skin of a newborn is more similar to that of an adult [16].

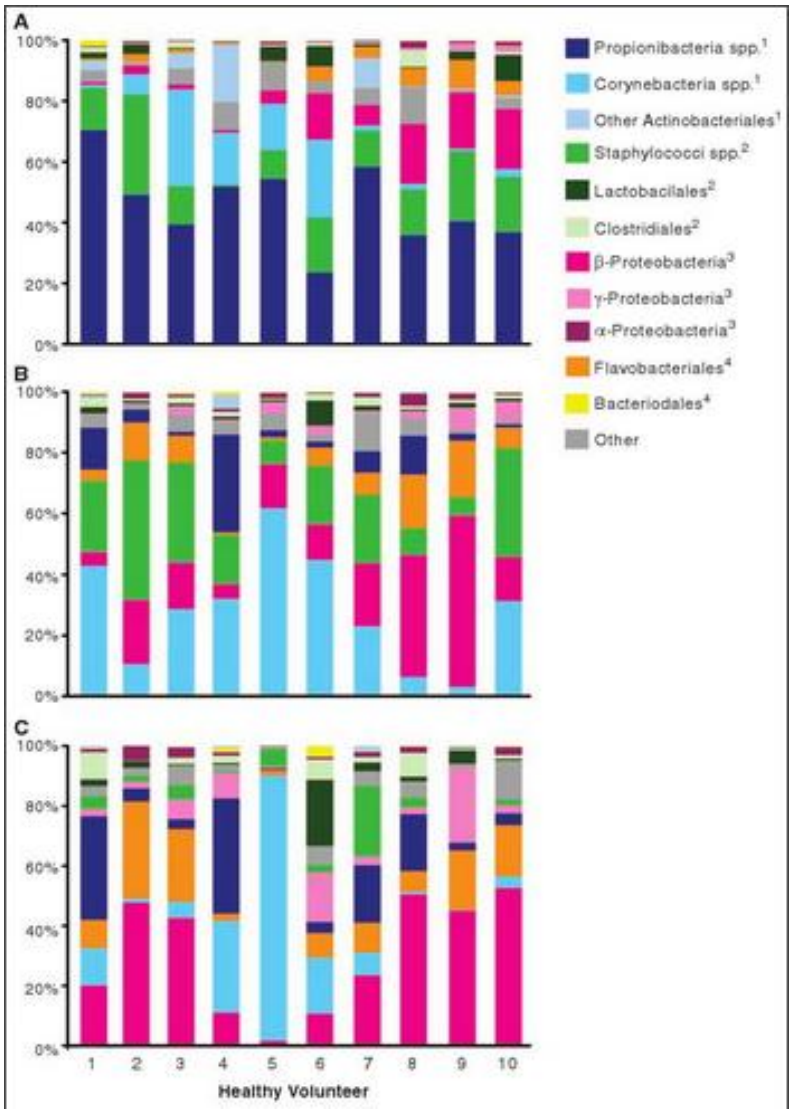

Figure 2: The 20 skin sites and associated microbiotaare representative of three microenvironments: (A**) sebaceous, (**B**) moist, and (**C**) dry. Each bar represents the various phyla and genera observed to be present from each site. The figure demonstrates the heterogeneity of bacterial populations in the skin as a function of specific sites[Figure obtained from Grice *et al* (5)].**

Recent molecular studies have investigated the bacterial diversity present on the skin, as well as the spatial distribution of such populations. A studyby Grice *et al* [5] assessed bacteria from 20 sites on the skin from 10 healthy human subjects (Figure 2). Sequencing of the

16S rRNA gene was employed to assess this diversity. A total of nineteen bacterial phyla were detected [5]. However, 99% of the sequences were assigned to just 4 phyla: Actinobacteria (51.8%), Firmicutes (24.4%), Proteobacteria (16.5%), and Bacteriodetes (6.3%). Two hundred and five genera were represented as having at least 5 sequences, yet more than 62% of the sequences were associated with the following genera: *Corynebacteria*(22.8%), *Propionibacteria* (23%), and *Staphylococci* (16.8%) [5]. Analysis of the 16S rRNA gene also revealed far greater species diversity than culture based modalities.

Niche occupation and spatial distribution of bacteria across the skin were also assessed. Each of the 20 sites from which samples were obtained fell into one of three distinct physiological categories classified as sebaceous, moist, and dry [5]. *Propionibacteria* and *Staphylococci* were more present in sebaceous sites, such as the ear canals and area between the eyebrows. *Corynebacteria* and *Staphylococci* species were present in greater populations in moist sites [5]. Dry sites, such as the forearm, displayed more variation in the bacterial populations present, although Proteobacteria and Flavobacteriales appeared with slightly more prevalence [5].

Sequences were then clustered into species level operational taxonomic units (OTU) in an effort to assess the relative evenness and distribution of species via the Shannon Diversity Index. The index not only accounts for the richness or abundance of a single species, but also factors in the relative amounts of species present in a given site. Species were defined as having 99% sequence similarity via the furthest-neighbor method [5]. In general, it was found that moist sites, such as the pits of the elbow and knee, were more even with respect to species composition, while sebaceous sites, such as the back and toe webbings, displayed the least parity in terms of species distribution [5].

In addition to differences in the spatial distribution of bacterial populations, community structure was found to differ temporally as well. In the study by Grice *et* al [5], samples from the same test subjects were re-obtained ~5 months after the initial study to assess site specific temporal variation in bacterial populations. The most invariable sites in terms of community structure were the ear canal, nare, and area behind the nostril, while sites with the most demonstrable variation included the forearm, buttocks, and the pit of the knee [5]. Temporal variation was therefore site specific, as no temporal consistency in community structure was found among the three distinct microenvironments (sebaceous, dry, and moist).

Additional genomic studies of the bacterial communities of the skin have produced similar data. Costello *et al* [2] reported on data obtained from volunteers for skin samples from 18 sites. The V2 region of the bacterial 16S rRNA gene was amplified via PCR techniques to generate a collection of sequences [2]. Assessment of phyla diversity revealed 22 total bacterial phyla, with 92.3% corresponding to four phyla: Actinobacteria (36.6%), Firmicutes (34.3%) Proteobacteria (11.9%), and Bacteriodetes (9.5%). Such findings are congruous with the study performed by Grice *et al* [5]. Topographical distribution of bacteria also mirrored findings from the study by Grice *et al* [5], as *Propionibacteria* were more prevalent in sebaceous sites, such as the forehead and ear canals, and less prevalent in drier sites, such as the forearm [2].

Diversity within specific sites on the skin was also assessed by Costello *et al* [2], and the data follows the trend established study by Grice *et al*(5). Generally, moist sites such as the pits of the knees, elbows, and soles of the feet were found to contain higher levels of bacterial diversity, while sebaceous sites, such as the forehead, contained less overall diversity [2].

Site specific temporal diversity in the structure of bacterial communities was also observed [2]. In all body habitats, including the skin, interpersonal variation in the structure of bacterial communities was less in 24 hours than over the course of 3 months, suggesting a high level of temporal variation in numerous sites [2]. However, the intrapersonal temporal variation in bacterial populations was found to be less than the interpersonal variations in bacterial populations on a given day. Specific skin sites, such has the hair and nostril, were found to exhibit more intrapersonal diversity than any other organ in the body [2].

The data from these studies reveal two important factors regarding the distribution of bacterial communities on the skin. The first apparent trend is that bacterial populations at specific skin sites appear to vary temporally. Second, the change in community structure within the same individual at the same site over time is less than the bacterial diversity at the same site within different individuals. Therefore, while the biogeography of bacterial communities on the human skin displays general consistency across most individuals, there is high variation not only among different sites on the skin, but among different individuals as well. Numerous factors have been hypothesized to affect this variation, including bacterial interactions, local environmental factors, as well as the unique behavioral patterns of a given individual.

Bacterial Interactions Affecting Community Structure

Interactions among various bacterial species on the surface of the skin can have a profound influence on the composition of communities. Generally, four primary types of interactions among different species can occur on the skin: 1) interference, which is unilateral or reciprocal antagonism between species; 2) satellitism, which involves unilateral enhancement of another species; 3) synergism or symbiosis, which is reciprocal enhancement between species; and 4) neutral interactions, in which organisms do not directly affect the fitness of each other [12].

While most documented interactions among various skin bacteria involve antagonistic relationships, more contemporary data has revealed how community compositioncan play a role in the synergistic effects of *S. aureus* and *Propionibacterium acnes*. *P. acnes*isa spatially diverse commensal found in numerous locations throughout the body, but is primarily concentrated on the skin of the face [11]. A study by Lo *et al* [11]revealed that the virulence of *S. aureus*in the induction of facial lesions is enhanced by the presence of the *P. acnes* [11]. The synergistic effects between the two bacteria therefore result in more severe lesions than *S. aureus* could have elicited if it were operating solitarily [15]. Thus, alterations in the compositional structure of bacterial communities could have important health implications for the host individual.

ISSN: 0975-8585

Antagonistic effects among bacteria can result in substantially profound alterations in the community composition in the skin. Many bacteria produce bacteriocins, which are proteins that function in a similar manner to antibiotics in that they inhibit the growth of species that are closely related to the producer [12]. *Lactococcus* produces a bacteriocin that inhibits the growth of various pathogenic, skin-inflammatory bacteria, such as *S. aureus, S. pyogenes, and P. acnes* [13]. The antagonistic effects of *Lactococcus* can therefore have substantial effects on the structure of the bacterial community of the skin, and thus has important health implications. In addition to bacteriocins, bacteriolytic enzymes have also been implicated as a produced compound that can alter community structure. *Staphylococci*, for example, have been found to lyse cells of pathogenic bacteria by employing such enzymes [17].

Environmental Factors Affecting Bacterial Colonization

The structure of bacterial communities on the skin is not only affected by interactions with other microbes, but by an interplay between various intrinsic and extrinsic factors [Figure 3 [15]]. Intrinsic factors affecting bacterial distribution on the skinhave been reported to include the pH of the skin, moisture content, as well as oxygen and CO_2availability [15]. Various extrinsic factors can also result in the differential colonization of various bacteria, such as different wavelengths of light and the temperature of the air.

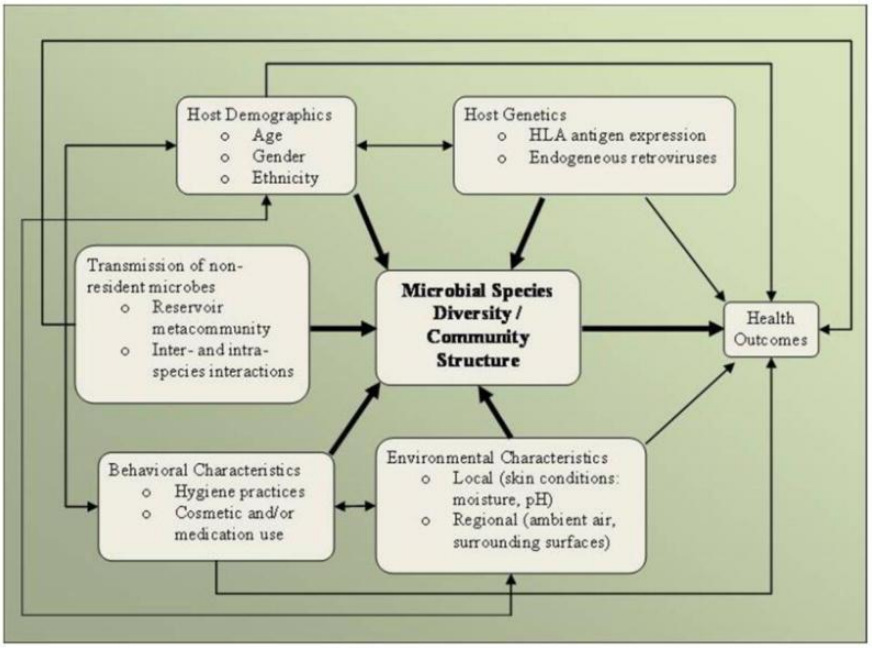

Figure 3: Driving forces behind the variations in the structure of bacterial communities on the skin. As shown, many intrinsic and extrinsic factors can modulate the bacterial populations of the skin. It is proposed that alterations in these bacterial populations will ultimately have an effect on human health outcomes [Figure obtained from Rosenthal *et al* (15)].

As mentioned, the average pH of the skin in newborns is approximately neutral (pH 7.4), although within weeks it is altered to values between 4 and 8, depending on the specific site on

the skin [12]. It has been found that the average systemic pH of the skin is approximately 4.7 (10). Eccrine sweat glands are the primary contributor to the acidic pH of the skin, which are more prevalent on the palms of the hands, feet, forehead, and armpit [12]. While this relatively acidic pH is unsuitable for non-residential bacteria, it has been demonstrated that residential bacterial flora require such a pH for adhesion to the skin, whereas a more basic pH between 8 and 9 results in the disassociation of such organisms from the skin [10].

The partial pressures of oxygen andCO_2in the tissues can also have profound effects on the growth and survival of many bacteria [12]. Many bacteria colonize the epidermal layers of the skin, and the partial pressure of CO_2(pCO_2)in the epidermis correlates with the pCO_2in the arterial blood. However, the $pO_2$of oxygen in the blood is far higher than the pO_2in the epidermal layers (12). The physiological mechanisms regulating the differential concentrations of these two compounds is vital, as various bacteria have differing oxygen and CO_2 requirements. *Propionibacterium*species are anaerobic, while various *Staphylococci* and *Corynebacteria*are facultative. It has been shown that a lower pO_2can actually enhance the growth of many residential bacteria. A study by Knighton*et al*(6) found that improving tissue oxygenation matched the efficacy of antibiotics in reducing certain bacterial populations, while the combination of both antibiotics and increased tissue oxygenation had additive effects [6].

Various extrinsic environmental factors can also drive alterations in bacterial community structure on the skin. Certain wavelengths of light have been demonstrated to have a detrimental effect on the survivability of certain bacteria on the skin. A study by Dotterud*et al* [3] demonstrated that UVB light can reduce populations of *S. aureus*in individuals with atopic dermatitis [3]. UVB has wavelengths between 290 nm and 320 nm, and induces the formation of sunburns in many individuals. Prolonged exposure to UVB could therefore have effects on the community structure of bacterial populations on the skin.

Moisture content of the skin is of principal importance in regulating communities of bacteria on the skin, and the hydration level of the skin can be regulated by both intrinsic and extrinsic factors. Physiological regulation of the skin is accomplished by increased sweat production and transepidermal water loss [12]. Environmental factors, such as temperature and humidity, can also affect the moisture levels of the skin. Generally, increased hydration of the skin is associated with increased growth of bacterial populations. This was observed in the molecular studies performed by Grice *et al*(5), which showed greater OTU diversity and species richness in moist sites of the skin, such as the pits of the elbow, knee, and arm [5].

Behavioral and Demographic Factors Affecting Bacterial Community Structure

While environmental factors and local interactions among bacteria have profound effects on the structure of bacterial communities of the skin, there are various other factors which also appear to differentially affect bacterial populations on the skin. A study by Fierer*et al* [4] evaluated bilateral palmar samples from approximately 85 individuals, and the authors sequenced the 16S rRNA gene via PCR amplification. The structure of bacterial communities on the palms of the individuals varied based on numerous factors.

Interestingly, hand dominance appeared to affect bacterial community composition, as the composition of the bacterial community on the dominant hand differed significantly from the composition of the bacterial community on the non-dominant hand, despite similar levels of overall diversity [4]. On average, the communities between the two hands shared just 17% of the same phylotypes [4]. It is posited that differential contact with surfaces may be responsible for the alterations in community composition between the two hands of an individual.

Gender also appears to play a role in the formation of bacterial communities. In the same study, it was found that males possessed a higher abundance of Actinobacteria on the surface of the hands, while women possessed a higher abundance of bacteria from the phyla Firmicutes and Proteobacteria [4]. Additionally, it was found that the palms of women also contained significantly higher levels of overall bacterial diversity than the palms of males. There are numerous hypotheses as to why such differences in bacterial community structure exists between the genders, although it is posited that the application of topical moisturizers and cosmetics, as well as differential levels in circulating hormones, may have an effect.

The frequency with which one bathes can also have pronounced effects on bacterial community composition. It was demonstrated that bacteria in the *Propionibacteria*and *Neisseriaceae* taxa experienced population increases in the time since the last hand washing, while bacteria belonging to *Staphylococcaceae*and *Lactobacillaceae*were more abundant directly after a hand washing event [4]. While hand washing was found to alter the overall composition of bacterial communities, levels of overall diversity remained relatively unchanged.

Alterations in bacterial community structure and the development of disease

The various mechanisms by which the structure of bacterial communities on the skin is altered holds significant implications for the health of the host. Recent molecular studies by Kong *et al* [9] report that individuals with atopic dermatitis display atypical alterations in the structure of bacterial communities on their skin (Table 1). Additional observations by Kong *et al* [8] have reported that individuals with psoriasis have highly altered bacterial community structures on their skin when compared with healthy controls (Table 1). Thus, while interpersonal diversity in the structure of bacterial communities can vary,alterations to the standard population ecology of a given individual is correlated with the development of disease.

The bacterial communities of the skin are exceptionally diverse, and show incredible variation not only between individuals, but among different sites within the same individual. Culturing techniques have provided a generalized map of the bacterial skin flora, while more recent molecular techniques have begun to elucidate specific bacteria and their preferred ecological niches within the skin. While these molecular studies have assisted in providing additional details regarding the biogeography of bacterial populations on the skin, much is still unknown regarding this distribution. Advances in high throughput sequencing will certainly enhance the celerity and efficiency with which such studies take place. Additionally, while

certain hypotheses have been made regarding the factors that influence this distribution, there are many questions that have yet to be answered regarding the specific factors that result in such compositional diversity.

Table 1: Displays alterations in bacterial community structure in the context of disease states. As demonstrated are specific examples of certain diseases of the skin which are reported to be associated with either decreases or increases in specific microbial populations x[Data from table obtained from Kong *et al* (8) and Kong *et al* (9)].

Disease	Increased Populations	Decreased Populations
Atopic Dermatitis	*Staphylococcus Aureus, Staphyloccocusepidermidis*	*Streptococcus, Propionibacterium, Corynebcaterium*
Psoriasis	*Streptococcus*	*P. acnes*

In review of this topic, one can readily appreciate that the composition and structure of bacterial communities on the skin can have important health implications for the host. Skin disease states are not rendered by a single organism, but rather by atypical vicissitudes within the compositional structure of bacterial communities. Thus, continued research efforts are imperative in revealing additional details regarding the intricacies of bacterial populations on the skin. Future studies must continue to discern the differential characteristics of bacterial populations in varying locations of the skin, and should evaluate the effects of bacterial community structure on the development of disease and the maintenance of health within the host. Indeed, much has been identified regarding the community structure of bacteria on the skin. However, a more profound understanding of this exquisite microbiome, as well as the implications it holds for the health of humans, will undoubtedly provide immense benefits for future generations.

REFERENCES

[1] Aly R, C Shirley, B Cunico, HI Maibach. J Invest Dermatol 1978; 71(6): 378-381.
[2] Costello E, C Lauber, M Hamady, N Fierer, JI Gordon and R Knight. Sci 2009; 326: 1694-1697.
[3] Dotterud LK, T Wilsgaard, LH Vorland, ES Falk. Int J Circumpolar Health. 2008; 67(2-3): 254-260.
[4] Fierer N, M Hamady, CL Lauber, R Knight. Proc Natl Acad Sci USA. 2008; 105 (46): 17994-17999.
[5] Grice E, H Kong, S Conlan, C Deming, J Davis and A Young. Sci 324: 1190-1192.
[6] Knighton DR, B Halliday, TK Hunt. Arch Surg 1986; 121 (2): 191-195.
[7] Kong HH. 2011; 17(6): 320-328.
[8] Kong HH, J Segre. J Inv Dermatol 2012; 132: 933-939.
[9] Kong HH, J Oh, et al. Genome Res 2012; 22 (5): 850-859.
[10] Lambers H, S Piessens, A Bloem, H Pronk, P Finkel. Int J Cosmet Sci 2006; 28 (5): 359-370.
[11] Lo CW, YK Lai, YT Liu, RL Gallo and CM Huang. J Invest Dermatol. 2011; 131(2):401-409.

[12] Noble WC. The Skin Microflora and Microbial Skin Disease. Cambridge University Press, Cambridge, UK 1993.
[13] Oh S, SH Kim, Y Ko, JH Sim, KS Kim, SH Lee, S Park, YJ Kim. Food Chem Toxicol 2006; 44(8): 1184-1190.
[14] Raz A, H Shinefield and H Maibach. Am J Dis Child 1980; 134 (5): 522-523.
[15] Rosenthal M, D Goldberg, A Aiello, E Larson, B Foxman. Infect Genet Evol 2011; 11(5): 839-848.
[16] Somerville DA. British J Dermatol 1969; 81(4): 248 – 258.
[17] Woodroffe RCS, DA Shaw. Natural control and ecology of microbial populations on skin and hair. In: Skinner FA, Carr JA, Eds. The normal microbial flora of man. London: Academic Press 1974; 13-34.