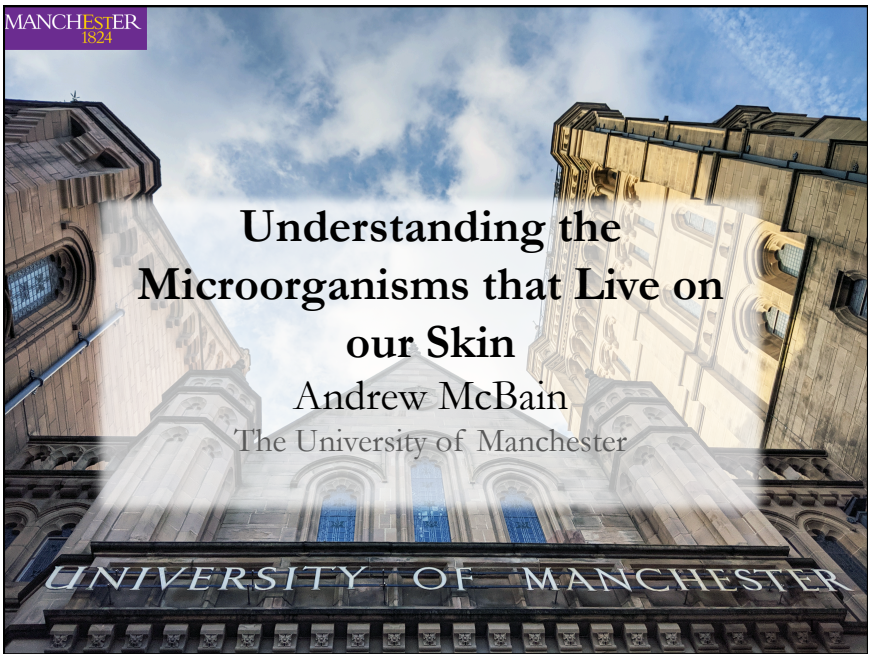

The Microbial World

- 10^{29} microbial cells on earth
- 10^{19} insects on earth
- 10^{14*} microbial cells per human
- 10^{13} human cells per human
- 10^{12} stars in our galaxy
- 10^{10*} humans on the planet
- 10^{10} bacteria *per gram* of faeces
- 10^{6} bacterial per ml of saliva
- $>10^{3}$ bacteria per cm^2 of skin
- *c* 10^{3} bacteria per ml of tap water

2

The Human Microbiome

Many (if not most) bacteria that associate with mammals do so as (mostly) sessile microbial communities

- Oral
- Nasal
- **Skin**
- Genitourinary
- Intestinal

Micro*flora* / Microbiota / Microbiome

3

The microbiota- traditional view

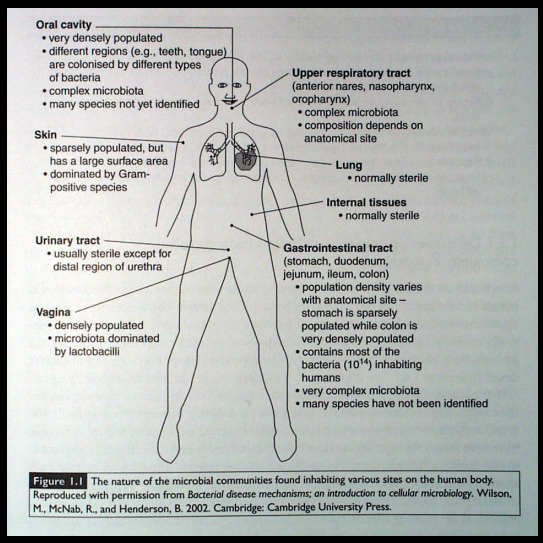

Figure 1.1 The nature of the microbial communities found inhabiting various sites on the human body. Reproduced with permission from *Bacterial disease mechanisms; an introduction to cellular microbiology*. Wilson, M., McNab, R., and Henderson, B. 2002. Cambridge: Cambridge University Press.

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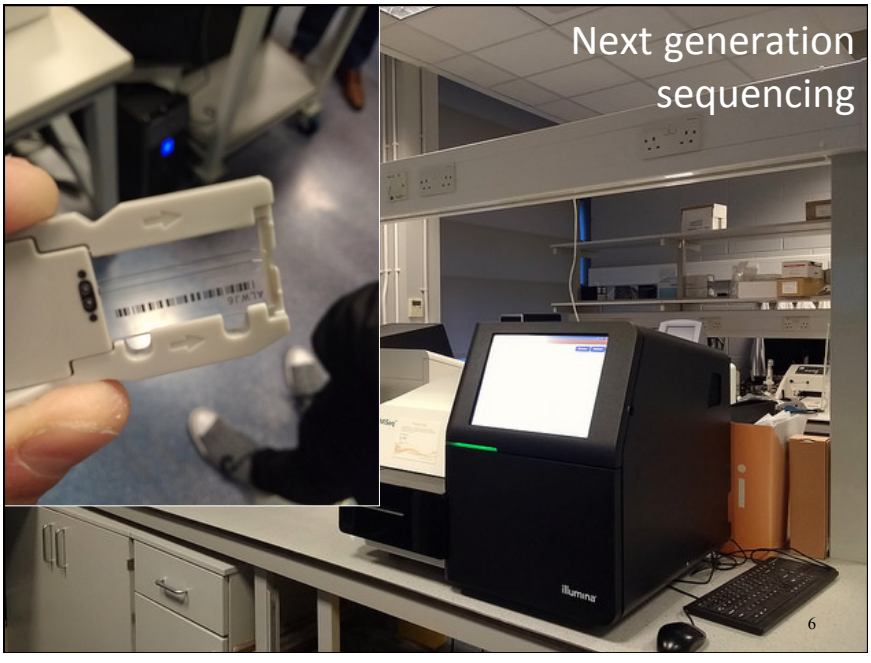
Microbial inhabitants of humans. Michael Wilson Cambridge University Press, 2005.



The microbiome- current view

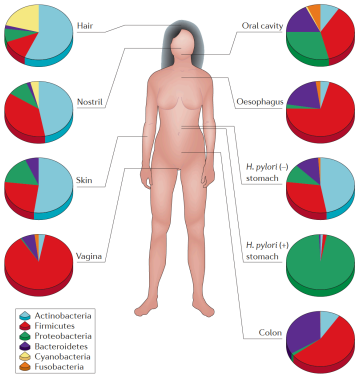


Figure 1 | **Compositional differences in the microbiome by anatomical site.** High-throughput sequencing has revealed substantial intra-individual microbiome variation at different anatomical sites, and inter-individual variation at the same anatomical sites[4,5,25,52,99,93]. However, higher-level (for example, at the level of phyla) taxonomic features display temporal (longitudinal) stability in individuals at specific anatomical sites. Such site-specific differences and the observed conservation between human hosts provide an important framework to determine the biological and pathological significance of a particular microbiome composition. The figure indicates the relative proportion of sequences determined at the taxonomic phylum level at eight anatomical sites. Certain features, such as the presence (+) or absence (–) of *Helicobacter pylori*, can lead to permanent and marked perturbations in community composition[93].

- The composition of the microbiome varies by anatomical site
- The primary determinant of community composition is anatomical location:
- Interpersonal variation is substantial and is higher than the temporal variability seen at most sites in a single individual.
- Minor perturbations such as dietary changes can rapidly cause substantial intestinal metagenomic changes
  - Nasopharyngeal microbiota in children varies seasonally
  - Vaginal microbiota varies with menses
  - Oral microbiota varies with hygiene/diet
- Microbiota composition is extensively conserved at high taxonomic levels
- Variation increases at lower taxonomic levels
- 85% of the sequences obtained from the distal gut of the mouse represent genera that are not detected in humans

Cho and Blaser (2012) The Human Microbiome: at the interface of health and disease. Nat Rev Genet 13(4): 260–270

7

APPLICATIONS OF NEXT-GENERATION SEQUENCING

The human microbiome: at the interface of health and disease

Ilseung Cho[1,2] and Martin J. Blaser[1,2,3,4]

Abstract | Interest in the role of the microbiome in human health has burgeoned over the past decade with the advent of new technologies for interrogating complex microbial communities. The large-scale dynamics of the microbiome can be described by many of the tools and observations used in the study of population ecology. Deciphering the metagenome and its aggregate genetic information can also be used to understand the functional properties of the microbial community. Both the microbiome and metagenome probably have important functions in health and disease; their exploration is a frontier in human genetics.

Microbiota
The microbial organisms that constitute the microbiome. The composition of the microbiota in a community can vary substantially between environmental sites, among host niches and between health and disease.

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[3]*Department of Microbiology,*

Until recently, the properties of the microbiota of humans (formerly called 'the normal flora') were largely a black box. Cultivation *in vitro*, which has been the cornerstone of microbiology since the nineteenth century, cannot be applied to many of the most densely populated microbial communities[1]. However, DNA-based analyses have expanded our horizon by generating enormous new data sets that can be mined for information on the composition and functional properties of vastly greater numbers of microbial communities. For example, the Human Microbiome Project (HMP)[2] by the US National Institutes of Health has produced a 2.3 terabyte 16S ribosomal RNA metagenomic data set of over 35 billion reads taken from 690 samples from 300 US subjects, across 15 body sites. Large-scale endeavours (for example, the HMP and also the European project, MetaHIT[3]) are already providing a preliminary understanding of the biology and medical significance of the human microbiome and its collective genes (the metagenome).

The aim of these projects, particularly the HMP, is to characterize the compositional range of the 'normal' microbiome of healthy individuals. Important questions concerning the commonalities and differences systems with strong phenotypes is essential for making progress in this field of applied genetics. Although a focus on bacteria is important, inquiries aimed at archaea, viruses and retroviruses are also needed.

The purpose of this Review is to develop the theoretical basis for investigating how microbiome composition and function affect human health. We provide examples of applying this knowledge to better understand human health, and we discuss how microbiome changes could alter host–microbiome interactions to mitigate disease. We also consider the next steps in the development of this field, particularly regarding the need to focus on the inheritance of the microbiome and on its involvement in modulating complex traits.

Characterizing the microbiome

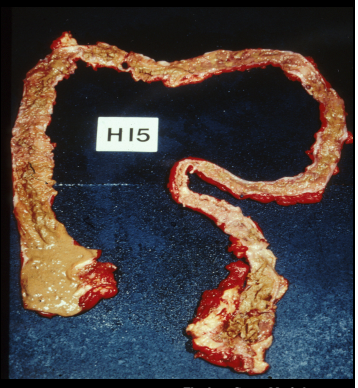
Animals have had residential microbes carrying out metabolic functions for at least 500 million years, at a conservative estimate[6,7]. Extensive congruent phylogenies of animal hosts and their microbiota, involving both individual organisms and whole microbial populations[1,8,9], suggest the existence of specific selection based on co-adaptation. Cooperative interactions between microbes

8

The colonic microbiota- *very* heavily studied

What is known about gut microbiota?

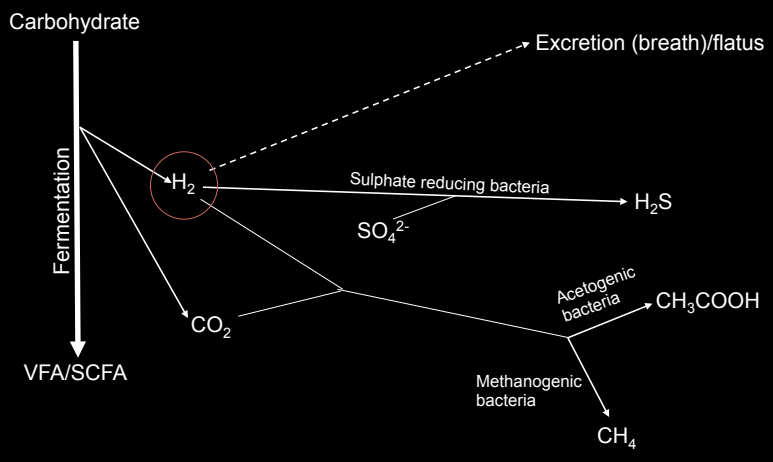
- Ancient origins of symbiosis
- ***c*** **10^{14}** bacteria in the human gut
  i.e. 100,000000,000000
- Colonisation begins at birth
- Stable dominant biota
- Chemotherapeutic agents disrupt balance of biota
- Microbiota involved in drug metabolism
- A metabolic organ



Thanks to George Macfarlane

9

Microbial gas metabolism in the colon



10

Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites

William R. Wikoff[a], Andrew T. Anfora[b], Jun Liu[b], Peter G. Schultz[b,1], Scott A. Lesley[b], Eric C. Peters[b], and Gary Siuzdak[a,1]

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Communicated by Steve A. Kay, University of California at San Diego, La Jolla, CA, December 19, 2008 (received for review December 12, 2008)

Although it has long been recognized that the enteric community of bacteria that inhabit the human distal intestinal track broadly impacts human health, the biochemical details that underlie these effects remain largely undefined. Here, we report a broad MS-based metabolomics study that demonstrates a surprisingly large effect of the gut "microbiome" on mammalian blood metabolites. Plasma extracts from germ-free mice were compared with samples from conventional (conv) animals by using various MS-based methods. Hundreds of features were detected in only 1 sample set, with the majority of these being unique to the conv animals, whereas ≈10% of all features observed in both sample sets showed significant changes in their relative signal intensity. Amino acid metabolites were particularly affected. For example, the bacterial-mediated production of bioactive indole-containing metabolites derived from tryptophan such as indoxyl sulfate and the antioxidant indole-3-propionic acid (IPA) was impacted. Production of IPA was shown to be completely dependent on the presence of gut microflora and could be established by colonization with the bacterium *Clostridium sporogenes*. Multiple organic acids containing phenyl groups were also greatly increased in the presence of gut microbes. A broad, drug-like phase II metabolic response of the host to metabolites generated by the microbiome was observed, suggesting that the gut microflora has a direct impact on the drug metabolism capacity of the host. Together, these results suggest a significant interplay between bacterial and mammalian metabolism.

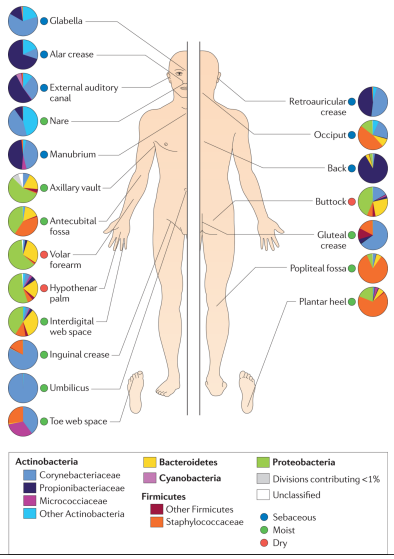
The human body is colonized by hundreds of trillions of microbes, which collectively possess hundreds of times as many found to extract energy from their food more efficiently compared with lean counterparts due to alterations in the composition of their gut microflora that resulted in an increased complement of genes for polysaccharide metabolism (10). It has also been observed that bile salt hydrolase encoding genes are enriched in the gut microbiome, and that enteric bacteria carry out a wide range of bile acid modifications (6, 14). These metagenomic studies suggest that the metabolites derived from this diverse microbial community can have a direct role in human health and disease. To date, metabolomics-based investigations of aspects of the impact of the microbiome on mammalian biochemistry have detailed changes in the levels of well-documented metabolites based primarily on NMR-based analysis and subsequent multivariate statistics of unfractionated samples, such as urine, gut tissue, or cecum extracts (15–17). Recently, this same group reported the multicompartmental effects of the microbiome on murine metabolism by using NMR-based analysis of urine and tissue extracts from both conventional (conv) and germ-free (GF) mice (18). Although extremely powerful, these studies provide only limited opportunity for the discovery of differences in unexpected or lower level metabolites.

Here, we demonstrate the large effect of the microbiome on mammalian plasma biochemistry. Specifically, a broad, untargeted, mass spectrometry-based profiling of serum from GF and conv mice demonstrates that a significantly large number of chemical species found in systemic circulation arise because of the presence of the microbiome, whereas at least 10% of all detectable endogenous circulating serum metabolites vary in concentration by at least 50% between the 2 mouse lines. Several microbiome-affected

Bacteria living on the skin

The Skin Microbiome

Topographical distribution of bacteria on skin sites



Grice and Segre, 2011

PLOS | BIOLOGY

ESSAY

Revised Estimates for the Number of Human and Bacteria Cells in the Body

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OPEN ACCESS

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Abstract

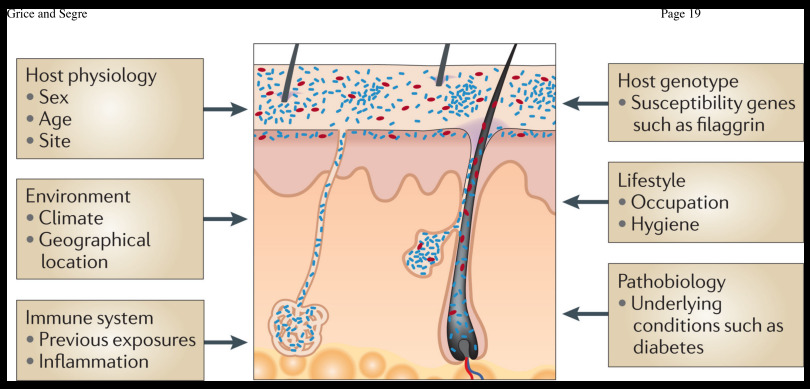
Reported values in the literature on the number of cells in the body differ by orders of magnitude and are very seldom supported by any measurements or calculations. Here, we integrate the most up-to-date information on the number of human and bacterial cells in the body. We estimate the total number of bacteria in the 70 kg "reference man" to be $3.8 \cdot 10^{13}$. For human cells, we identify the dominant role of the hematopoietic lineage to the total count (≈90%) and revise past estimates to $3.0 \cdot 10^{13}$ human cells. Our analysis also updates the widely-cited 10:1 ratio, showing that the number of bacteria in the body is actually of the same order as the number of human cells, and their total mass is about 0.2 kg.

Introduction

How many cells are there in the human body? Beyond order of magnitude statements that give no primary reference or uncertainty estimates, very few detailed estimates have been performed (the one exception [1] is discussed below). Similarly, the ubiquitous statements regarding 10^{14}–10^{15} bacteria residing in our body trace back to an old back-of-the-envelope calculation [2–4].

The aim of this study is to critically revisit former estimates for the number of human and bacterial cells in the human body. We give up-to-date detailed estimates where the calculation logic and sources are fully documented and uncertainty ranges are derived. By updating the

Factors contributing to variation in the skin microbiome

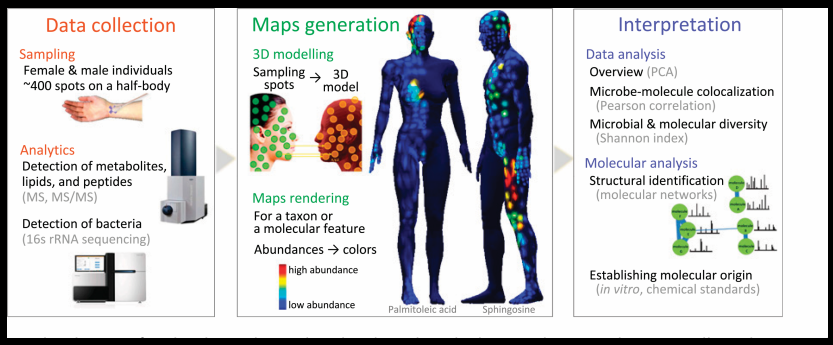


Grice and Segre, 2011

Functions

Positive	Negative
Colonisation resistance	Infection
Immune modulation	Implicated in a range of skin diseases
Metabolism	Metabolism
Protection	
Barrier augmentation	

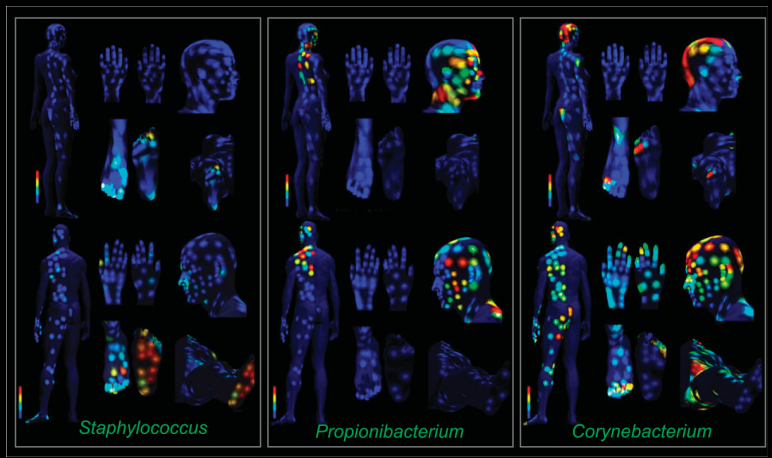
Mapping the skin




Molecular cartography of the human skin surface in 3D

Bouslimani et al., 2014

Mapping the skin



Bouslimani et al., 2014

What about aging?

Human microbiome aging clocks based on deep learning and tandem of permutation feature importance and accumulated local effects

Fedor Galkin[1], Aleksandr Aliper[1], Evgeny Putin[1], Igor Kuznetsov[1], Vadim N. Gladyshev[2], Alex Zhavoronkov[1,3,4]

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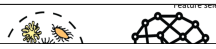
Here, we developed a method of predicting biological age of the host based on the microbiological profiles of **gut microbiota** using a curated dataset of 1,165 healthy individuals (3,663 microbiome samples). Our predictive model, a human microbiome clock, has an architecture of a deep neural network and achieves the accuracy of 3.94 years mean absolute error in cross-validation



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RESEARCH ARTICLE
Host-Microbe Biology

New Insights into the Intrinsic and Extrinsic Factors That Shape the Human Skin Microbiome

Pedro A. Dimitriu,[a,b] Brandon Iker,[c] Kausar Malik,[c] Hilary Leung,[a] W. W. Mohn,[a,b] Greg G. Hillebrand[c]

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[c]Amway Corporation, Ada, Michigan, USA

ABSTRACT Despite recognition that biogeography and individuality shape the function and composition of the human skin microbiome, we know little about how extrinsic and intrinsic host factors influence its composition. To explore the contributions of these factors to skin microbiome variation, we profiled the bacterial microbiomes of 495 North American subjects (ages, 9 to 78 years) at four skin surfaces plus the oral epithelium using 16S rRNA gene amplicon sequencing. We collected subject metadata, including host physiological parameters, through standardized questionnaires and noninvasive biophysical methods. Using a combination of statistical modeling tools, we found that demographic, lifestyle, and physiological factors collectively explained 12 to 20% of the variability in microbiome composition. The influence of health factors was strongest on the oral microbiome. Associations between host factors and the skin microbiome were generally dominated by operational taxonomic units (OTUs) affiliated with the *Clostridiales* and *Prevotella*. A subset of the correlations between microbial features and host attributes were site specific. To further explore the relationship between age and the skin microbiome of the forehead, we trained a Random Forest regression model to predict chronological age from microbial features. Age was associated mostly with two mutually coexcluding *Corynebacterium* OTUs. Furthermore, skin aging variables (wrinkles and hyperpigmented spots) were independently correlated to these taxa.

IMPORTANCE Many studies have highlighted the importance of body site and individuality in shaping the composition of the human skin microbiome, but we still have a poor understanding of how extrinsic (e.g., lifestyle) and intrinsic (e.g., age) factors influence its composition. We characterized the bacterial microbiomes of North American volunteers at four skin sites and the mouth. We also collected extensive subject metadata and measured several host physiological parameters. Integration of host and microbial features showed that the skin microbiome was predominantly associated with demographic, lifestyle, and physiological factors. Furthermore, we uncovered reproducible associations between chronological age, skin aging, and members of the genus *Corynebacterium*. Our work provides new understanding of the role of host selection and lifestyle in shaping skin microbiome composition. It also contributes to a more comprehensive appreciation of the factors that drive interindividual skin microbiome variation.

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Editor David S. Guttman, University of Toronto

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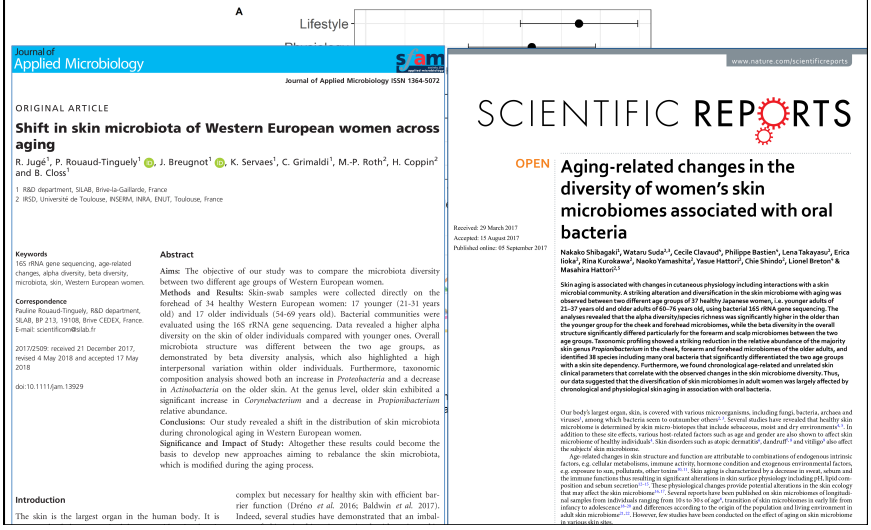
Aging and the skin microbiome



A

Lifestyle

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ORIGINAL ARTICLE

Shift in skin microbiota of Western European women across aging

R. Jugé[1], P. Rouaud-Tinguely[1], J. Breugnot[1], K. Servaes[1], C. Grimaldi[1], M.-P. Roth[2], H. Coppin[2] and B. Closs[1]

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Keywords
16S rRNA gene sequencing, age-related changes, alpha diversity, beta diversity, microbiota, skin, Western European women.

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doi:10.1111/jam.13929

Abstract

Aims: The objective of our study was to compare the microbiota diversity between two different age groups of Western European women.

Methods and Results: Skin-swab samples were collected directly on the forehead of 34 healthy Western European women: 17 younger (21-31 years old) and 17 older individuals (54-69 years old). Bacterial communities were evaluated using the 16S rRNA gene sequencing. Data revealed a higher alpha diversity on the skin of older individuals compared with younger ones. Overall microbiota structure was different between the two age groups, as demonstrated by beta diversity analysis, which also highlighted a high interpersonal variation within older individuals. Furthermore, taxonomic composition analysis showed both an increase in *Proteobacteria* and a decrease in *Actinobacteria* on the older skin. At the genus level, older skin exhibited a significant increase in *Corynebacterium* and a decrease in *Propionibacterium* relative abundance.

Conclusions: Our study revealed a shift in the distribution of skin microbiota during chronological aging in Western European women.

Significance and Impact of Study: Altogether these results could become the basis to develop new approaches aiming to rebalance the skin microbiota, which is modified during the aging process.

Introduction

The skin is the largest organ in the human body. It is complex but necessary for healthy skin with efficient barrier function (Dréno *et al.* 2016; Baldwin *et al.* 2017). Indeed, several studies have demonstrated that an imbal-

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Aging-related changes in the diversity of women's skin microbiomes associated with oral bacteria

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Nakako Shibagaki[1], Wataru Suda[2,3], Cecile Clavaud[4], Philippe Bastien[4], Lena Takayasu[2], Erica Iioka[1], Rina Kurokawa[2], Naoko Yamashita[2], Yasue Hattori[1], Chie Shindo[1], Lionel Breton[4] & Masahira Hattori[2,3]

Skin aging is associated with changes in cutaneous physiology including interactions with a skin microbial community. A striking alteration and diversification in the skin microbiome with aging was observed between two different age groups of 37 healthy Japanese women, i.e. younger adults of 21–37 years old and older adults of 60–76 years old, using bacterial 16S rRNA gene sequencing. The analyses revealed that the alpha diversity/species richness was significantly higher in the older than the younger group for the cheek and forehead microbiomes, while the beta diversity in the overall structure significantly differed particularly for the forearm and scalp microbiomes between the two age groups. Taxonomic profiling showed a striking reduction in the relative abundance of the majority skin genus *Propionibacterium* in the cheek, forearm and forehead microbiomes of the older adults, and identified 38 species including many oral bacteria that significantly differentiated the two age groups with a skin site dependency. Furthermore, we found chronological age-related and unrelated skin clinical parameters that correlate with the observed changes in the skin microbiome diversity. Thus, our data suggested that the diversification of skin microbiomes in adult women was largely affected by chronological and physiological skin aging in association with oral bacteria.

Our body's largest organ, skin, is covered with various microorganisms, including fungi, bacteria, archaea and viruses[1], among which bacteria seem to outnumber others[2–5]. Several studies have revealed that healthy skin microbiome is determined by skin micro-biotopes that include sebaceous, moist and dry environments[3–5]. In addition to these site-effects, various host-related factors such as age and gender are also shown to affect skin microbiome of healthy individuals[6]. Skin disorders such as atopic dermatitis[6], dandruff[7,8] and vitiligo[9] also affect the subjects' skin microbiome.

Age-related changes in skin structure and function are attributable to combinations of endogenous intrinsic factors, e.g. cellular metabolisms, immune activity, hormone condition and exogenous environmental factors, e.g. exposure to sun, pollutants, other toxins[10–13]. Skin aging is characterized by a decrease in sweat, sebum and the immune functions thus resulting in significant alterations in skin surface physiology including pH, lipid composition and sebum secretion[10–13]. These physiological changes provide potential alterations in the skin ecology that may affect the skin microbiome[14–17]. Several reports have been published on skin microbiomes of longitudinal samples from individuals ranging from 18 s to 30 s of age[6], transition of skin microbiomes in early life from infancy to adolescence[18–20] and differences according to the origin of the population and living environment in adult skin microbiome[21,22]. However, few studies have been conducted on the effect of aging on skin microbiome in various skin sites.

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Lactobacillus reuteri Protects Epidermal Keratinocytes from *Staphylococcus aureus*-Induced Cell Death by Competitive Exclusion

Tessa Prince,[a] Andrew J. McBain,[b] and Catherine A. O'Neill[a]

Schools of Medicine[a] and Pharmacy and Pharmaceutical Sciences,[b] The University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom

Recent studies have suggested that the topical application of probiotic bacteria can improve skin health or combat disease. We have utilized a primary human keratinocyte culture model to investigate whether probiotic bacteria can inhibit *Staphylococcus aureus* infection. Evaluation of the candidate probiotics *Lactobacillus reuteri* ATCC 55730, *Lactobacillus rhamnosus* AC413, and *Lactobacillus salivarius* UCC118 demonstrated that both *L. reuteri* and *L. rhamnosus*, but not *L. salivarius*, reduced *S. aureus*-induced keratinocyte cell death in both undifferentiated and differentiated keratinocytes. Keratinocyte survival was significantly higher if the probiotic was applied prior to ($P < 0.01$) or simultaneously with ($P < 0.01$) infection with *S. aureus* but not when added after infection had commenced ($P > 0.05$). The protective effect of *L. reuteri* was not dependent on the elaboration of inhibitory substances such as lactic acid. *L. reuteri* inhibited adherence of *S. aureus* to keratinocytes by competitive exclusion ($P = 0.026$). *L. salivarius* UCC118, however, did not inhibit *S. aureus* from adhering to keratinocytes ($P > 0.05$) and did not protect keratinocyte viability. *S. aureus* utilizes the α5β1 integrin to adhere to keratinocytes, and blocking of this integrin resulted in a protective effect similar to that observed with probiotics ($P = 0.03$). This suggests that the protective mechanism for *L. reuteri*-mediated protection of keratinocytes was by competitive exclusion of the pathogen from its binding sites on the cells. Our results suggest that use of a topical probiotic prophylactically could inhibit the colonization of skin by *S. aureus* and thus aid in the prevention of infection.

Humans live in constant contact with a multitude of microorganisms. The gut is by far the most heavily colonized environment of the human body, and the gut microbiota play multiple roles in normal physiology, including nutrient sequestration (2) and development of normal immune responses (20).

Among the normal gut microbiota are the so-called probiotic bacteria. Ingestion of these has been claimed to prevent or treat gastrointestinal disorders such as antibiotic-associated diarrhea (45) and inflammatory bowel disease (40). The mechanisms underlying these effects are largely unknown. However, studies have suggested that probiotics can inhibit colonization of the gut by pathogens. *In vitro* work has suggested that probiotics use various mechanisms to inhibit pathogens, including direct competition for binding sites on epithelial cells (10) and competition with pathogenic bacteria for nutrients. Probiotic organisms are also able to produce inhibitory substances such as bacteriocins (11) and organic acids (23) that can kill or limit the growth of pathogens. Selected probiotics, such as *Lactobacillus plantarum* 299v, have been shown to upregulate mucin production by epithelial cells, thereby preventing pathogen attachment (31). Probiotics may also produce biosurfactants that allow attachment of the probiotic while inhibiting attachment of pathogenic bacteria to cells (41).

under certain circumstances (14). By contrast, probiotics are generally regarded as safe (GRAS) and therefore could potentially be used topically if they have therapeutic value (15). So far, the limited amount of research in this area suggests that conventional probiotic bacteria may be of significant value when used on the skin. For example, topical application of a *Bifidobacterium longum* reuter lysate has been shown to induce clinical improvement of "reactive skin." This is skin that is more sensitive to physical changes such as atmospheric temperature and to chemical changes such as seen with topically applied products (18). Application of the *B. longum* lysate to the skin of volunteers decreased sensitivity and transepidermal water loss (TEWL) after tape stripping. Additionally, application of the lysate to skin *ex vivo* reportedly decreased signs of inflammation such as vasodilation, edema, and tumor necrosis factor alpha (TNF-α) release (18). Topical application of *Lactobacillus plantarum* has also been demonstrated to improve tissue repair in a burned mouse model and to prevent infection in chronic leg ulcers and burns in humans (38, 39, 44). However, in general, the mechanisms underlying these effects are unknown.

Staphylococcus aureus is a transient colonizer of skin predominantly in the moist, warm regions of the body such as the groin, axilla, and anterior nares (26). Up to 60% of people are intermit-

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Strain-Dependent Augmentation of Tight-Junction Barrier Function in Human Primary Epidermal Keratinocytes by *Lactobacillus* and *Bifidobacterium* Lysates

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In this study, we investigated whether probiotic lysates can modify the tight-junction function of human primary keratinocytes. The keratinocytes were grown on cell culture inserts and treated with lysates from *Bifidobacterium longum*, *Lactobacillus plantarum*, *Lactobacillus reuteri*, *Lactobacillus fermentum*, or *Lactobacillus rhamnosus* GG. With the exception of *L. fermentum* (which decreased cell viability), all strains markedly enhanced tight-junction barrier function within 24 h, as assessed by measurements of transepithelial electrical resistance (TEER). However, *B. longum* and *L. rhamnosus* GG were the most efficacious, producing dose-dependent increases in resistance that were maintained for 4 days. These increases in TEER correlated with elevated expression of tight-junction protein components. Neutralization of Toll-like receptor 2 abolished both the increase in TEER and expression of tight-junction proteins induced by *B. longum*, but not *L. rhamnosus* GG. These data suggest that some bacterial strains increase tight-junction function via modulation of protein components but the different pathways involved may vary depending on the bacterial strain.

The concept of using "probiotic" bacteria to benefit human health is well established. Ingestion of probiotic bacteria has been claimed to prevent or treat a variety of disorders of the gut, ranging from travelers' diarrhea to the chronic relapsing inflammatory condition Crohn's disease (1, 2) through mechanisms that are incompletely understood. However, evidence suggests that one mechanism may be via protection or augmentation of gut epithelial barrier function (3, 4, 5). This is provided for in the most part by tight junctions (TJs), which are multiprotein complexes sealing the paracellular space between adjacent epithelial cells and limiting transport through this pathway to small, hydrophilic molecules and ions (reviewed in reference 6). The importance of the TJ seal is demonstrated under conditions where the gut barrier is compromised. For example, elevated gut permeability has been observed in inflammatory bowel disease, apparently due to aberrant expression of essential TJ proteins such as claudin isoforms, occludin, or ZO-1 (7, 8). Although direct evidence in humans is still lacking, defects in TJs could allow greater ingress of antigens leading to the inflammatory responses associated with this condition.

Probiotic bacteria, particularly members of the genus *Lactobacillus*, enhance or protect epithelial barrier function *in vitro* and in animal models, via modulation of TJs. In this respect, studies using the enterocyte cell line Caco-2 demonstrated that certain probiotic strains inhibited cytokine and hydrogen peroxide-mediated disturbances of transepithelial electrical resistance (TEER), a measure of gut permeability in humans; a recent clinical study demonstrated that a strain of *L. plantarum* affected relocation of ZO-1 and occludin in duodenal cells within 6 h of administration (12). Thus, probiotics may have utility as therapeutic interventions by increasing TJ function under conditions where gut barrier function is aberrant.

Recently, investigations into the utility of probiotics to benefit health have moved beyond the gut, and in particular, the use of lactobacilli and bifidobacteria as topical therapies for skin has received attention (13–16). The skin and the gut have much in common; they both support taxonomically diverse microbiotas, act as a barrier between internal and external environments, and are subject to breaches in that barrier. Investigations have suggested that probiotics may be of value as treatments for skin: *L. plantarum* improved tissue repair in a burned mouse model and prevented infections in burns and chronic leg ulcers (13–15). Application of *B. longum* to healthy human skin reduced water loss (16), and we previously demonstrated that specific lactobacilli can inhibit adherence of the skin pathogen *Staphylococcus aureus* to primary human keratinocytes (17). Thus, the limited amount of work in this area suggests that probiotic bacteria may be of considerable use as agents to protect/enhance the skin's barrier function, but in general, the mechanisms underlying these effects are unexplored.

Until recently, the skin barrier was thought to function entirely through the tough, waterproof outer layer of the epidermis, the

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REVIEW

Consumer Safety Considerations of Skin and Oral Microbiome Perturbation

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Microbiome challenges and opportunities

- Over-interpretation of data
- Linking composition to function (e.g. what is dysbiosis?)
- Understanding disease
- Understanding health*
- Manipulation for health benefits

25