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MICROBIOLOGY
Editorial

Human Microbiome of the Skin: Advances in Metagenomics

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Received: June 11, 2015; **Published:** June 15, 2015

Summary

The microbiology of human health and disease has moved forwards significantly in the past decade, with the Human Microbiome Project findings being pivotal. Such is the depth and complexity of the findings that the results continue to be examined. In relation to human skin, the variation in microbial types and how they relate to different 'ecological niches' is both fascinating and important for understanding health and disease; the treatment of those diseases; and with human contamination risks. The research is thus important to both clinical and pharmaceutical microbiology.

Introduction

The Human Microbiome Project (HMP) was a United States National Institutes of Health initiative, launched in 2008. The project was set the goal of identifying and characterizing the microorganisms which are found in association with both healthy and diseased humans (the Human microbiome).

A microbiome is "the ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space [1]." It is well established that the human body contains over 10 times more microbial cells than human cells, although the entire microbiome only weighs about 200 grams [2]; however, the full extent of the microbiome and the full-species richness were hitherto unrealized.

The key goals of the project included [3]:

1. To develop a reference set of microbial genome sequences and to perform preliminary characterization of the human microbiome.
2. To explore the relationship between disease and changes in the human microbiome.
3. To develop new technologies and tools for computational analysis.
4. To establish a resource repository.
5. To study the ethical, legal, and social implications of human microbiome research.

From an array of different samples, the project consisted of various culture-independent methods of microbial community characterization, such as metagenomics (which provides a broad genetic perspective on a single microbial community). In metagenomic sequencing, DNA is recovered directly from environmental samples in an untargeted manner with the goal of obtaining an unbiased sample from all genes of all members of the community [4].

Other techniques include extensive whole genome sequencing (which provides a "deep" genetic perspective on certain aspects of a given microbial community, i.e. of individual bacterial species).Whole genome sequencing is a laboratory process that determines the complete DNA sequence of an organism's genome at a single time. This entails sequencing an organism's entire chromosomal DNA [5].

The project also included deep sequencing of bacterial 16S rRNA sequences amplified by polymerase chain reaction from human subjects. The 16S rRNA gene is used as the standard for classification and identification of microorganisms because it is highly conserved.

Samples were drawn from volunteer subjects. With this analysis, the microbiology of five body sites was emphasized: oral, skin, vaginal, gut, and nasal/lung. What is of interest in this article is the human microbiome of the skin.

Understanding the microbial community of the skin is important in relation to understanding disease; with the development of antimicrobial compounds; and in understanding the risk that personnel pose under conditions designed to maintain asepsis through the shedding of desquamated skin cells and subsequent re-suspension (as with the preparation of pharmaceutical products within clean rooms) [6].

Key Findings

Skin plays a key role in health and disease. Functions of skin include:

1. Protecting the body from pathogens,
2. Preventing loss of moisture,
3. Regulation of body temperature.

The skin also presents a risk to aseptic operations through personnel shedding.

Our understanding of the skin microbial community has been advanced through the Human Microbiome Project. Here it is more fully understood that the skin is a complex ecosystem and the skin supports a range of microbial communities that live in distinct niches [7]. Here analysis has shown that there is a high population and a considerable diversity of microbial species across, the outer layer of the skin (there are around 1000 species upon human skin from 19 phyla) [8,9]. This diversity is not, however, evenly distributed [10].

The distribution of microorganisms varies by topography, with different types of microorganisms resident in different locations. There are three main ecological areas of the skin: sebaceous, moist, and dry. Examples of microbial divergence are: *Propionibacteria* and *Staphylococci* species being the main species found in sebaceous areas; with dry areas, Gram-positive cocci (primarily the *Micrococcaceae*) are found on the arms and legs and Gram-positive rods are found in high numbers on the torso; and with moist areas, *Staphylococci* are found together with some Gram-negative bacteria [11]. Ecologically, sebaceous areas have a greater species richness compared with the moist and dry regions.

The reasons for the topographical variations relate to the physicochemical properties of the skin [12]. The pH of the skin, for example, varies between neutral and alkali. Another important variation is with temperature, for the skin temperature ranges between 25-37°C. A further variation relates to the level of humidity. Here the dampest places are the groin region, the armpits and between the toe webs. In these relatively moist areas proportionately higher numbers of Gram-negative rods are found, with *Acinetobacter* the dominant genus [13]. There is also a variation with oxygen levels. The lower oxygen regions across the forehead and within hair follicles provide environments for anaerobic bacteria to colonize. With fungi, the area of greatest richness is the foot, with the heel the most diverse area.

Variation is not only across different body locations, there is also some variation between individuals, with men carrying more microorganisms than women [14]. A further complication to understanding the skin microbiota is that the human skin microbiome may not be stable and may change over time as a person ages [15].

Implications

To advance understanding of health and disease of the skin, the Human Microbiome Project has coupled together the in-depth characterization of the skin microbiota with the way that the microbial community interacts with the host. These complex interactions provide insights into infections and treatments. For example, the results reveal how different skin diseases are associated with specific

microorganisms and how some skin disorders can be triggered by different microorganisms or microorganisms in specific communities. Here, not only understanding the role of pathogens is important, for sometimes seemingly innocuous bacteria that are transient or residential to the skin can become disease-causing.

The research findings also assist with the treatment of skin specific microbial diseases. For example, knowing that seborrhoeic dermatitis is caused by fungi of the *Malassezia* genus allows for more specific targeting with anti-fungicides and emphasizes that anti-bacterial agents will be ineffective. To draw on a second example, insights to the way that *Propionibacterium acnes* causes acne, which now seems to result from tissue damage to the pilosebaceous unit of the skin, suggests new target pathways for treatment [16]. Here it is also of interest that those with acne have types of *P. acnes* that are very closely related to each other, suggesting that them arosevia a common ancestral strain. Some current research, based on the microbiome findings, is looking at conditions like atopic dermatitis and psoriasis, to determine the role of microbial infection.

A further implication relates to the assessment of pharmaceutical cleanrooms. The species richness found in association with human skin outstrips that found with cultural dependent methods. Here only a narrow range of organisms are recovered with a close phylogenetic association [17]. This means that to protect drug development, greater emphasis should be placed on environmental controls (such as effective air filtration and air change rates to address contamination deposited into the air-stream) and through effective personnel gowning (clean suits, masks and gloves), coupled with good practices for personnel training. A further area of consideration is with the selection of effective disinfectants.

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Volume 1 Issue 3 June 2015