The Molecular Revolution in Cutaneous Biology: Investigating the Skin Microbiome

Heidi H. Kong[1,2] and Julia A. Segre[2,3]

Building upon the knowledge garnered from investigations utilizing traditional culturing methods, advances in sequencing technologies have catalyzed a revolution in studying human-associated microbes: bacteria, fungi and viruses. Skin microbiome research in healthy individuals and patients with dermatologic disorders has provided insights into the complexity and biogeography of human skin microbes. The continual developments in sequencing and analyses will provide increasingly sophisticated tools to interrogate human-associated microbes, ultimately to improve our understanding of health and disease.

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INTRODUCTION: HISTORY OF MICROBIOME

The fusion of technologic developments and scientific inquiry underlie historical investigations into the intimate relationships between humans, microbes (bacteria, fungi, viruses, and microorganisms such as mites) and health. Pioneers such as Antonie van Leeuwenhoek (1632–1722) handcrafted microscopes to observe "an unbelievably great company of living animalcules" in dental plaque (UCMP, 2015). Louis Pasteur (1822–1895) developed innovative laboratory glassware and experimental methods to culture bacteria, advancing both food preservation methods and vaccine development. Robert Koch (1843–1910) established stringent guidelines to evaluate causation in infectious disease, proving that bacterial agents caused anthrax and tuberculosis. Over the centuries, general knowledge of microbial-human relationships has broadened alongside greater awareness of scientific and technological limitations. For example, Koch's famous postulates require that causative microbes be propagated in pure culture, which predates the concept of viral diseases. There is increasing recognition that some microbes are difficult or impossible to grow in pure culture and may require other organisms to grow as co-culture or to function in a host (Byrd and Segre, 2016). For decades, the disparity between total cell counts and cultivable cell counts has been called the "great plate count anomaly," highlighting the difficulty in culturing most organisms under standard laboratory conditions.

Rather than relying solely on traditional culturing and phenotypic characteristics, Woese and others began sequencing the signature 16S ribosomal RNA (rRNA) gene to identify bacteria (Woese and Fox, 1977). The subsequent advances in genomic technologies, combined with the progressive reduction in the cost of sequencing, have led to a revolution in the use of sequencing to study microbial populations. Direct genomic sequencing has the advantage of avoiding potential difficulties in cultivating microbial isolates and can provide a more comprehensive assessment of the microbiome (Kong, 2011). More detailed reviews specifically focusing on technical aspects of 16S rRNA gene sequencing have been published (Jo et al., 2016; Kuczynski et al., 2012), including one focused on skin bacteria (Meisel et al., 2016).

The term *microbiome* refers to microbes, their genomes, and their environment (Marchesi and Ravel, 2015). The National Institutes of Health Human Microbiome Project and European MetaHIT were launched 10 years ago to spur research into the microbiome in humans and to provide resources for the broader scientific community (Human Microbiome Project Consortium, 2012; Qin et al., 2010). As a result, there has been a substantial increase in investigations into the microbiome.

THE MICROBIOME OF HEALTHY SKIN

The skin is an ecosystem consisting of microbial communities living in a range of physiologically and topographically distinct niches including sebaceous/nonsebaceous, hair-bearing/glabrous, moist/dry, and creased/noncreased regions (Grice and Segre, 2011; Scharschmidt and Fischbach, 2013). Hair follicles, sebaceous glands, eccrine glands, and apocrine glands provide microenvironments associated with their own microbiota. Characterizing the microbiota that inhabit specific sites may provide insight into the balance between cutaneous health and disease throughout an individual's life. Skin microbiome investigations may also provide some insights into why certain dermatological disorders (for example, atopic dermatitis or psoriasis) manifest at stereotypical skin sites during specific decades of life.

Skin microbes have long been of interest, especially with regard to cutaneous diseases and infections, including atopic dermatitis, acne vulgaris, and dandruff (Kligman et al., 1976; Leyden et al., 1987; Marples, 1969; Marples et al., 1971; Noble, 1993). The Human Microbiome Project selected skin as one of the body sites to study in a large cohort of healthy individuals. Earlier research using 16S rRNA gene sequencing showed that not only were skin bacterial communities distinct from oral mucosa, vaginal

[1]*Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA;* [2]*Associate Editor; and* [3]*National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, USA*

Correspondence: Heidi H. Kong and Julia A. Segre, National Human Genome Research Institute, National Institutes of Health, 49 Convent Drive, Building 49, Room 4A26, MSC 4442, Bethesda, Maryland 20892, USA. E-mail: konghe@mail.nih.gov or jsegre@nhgri.nih.gov

Abbreviations: ITS, internal transcribed spacer; rRNA, ribosomal RNA

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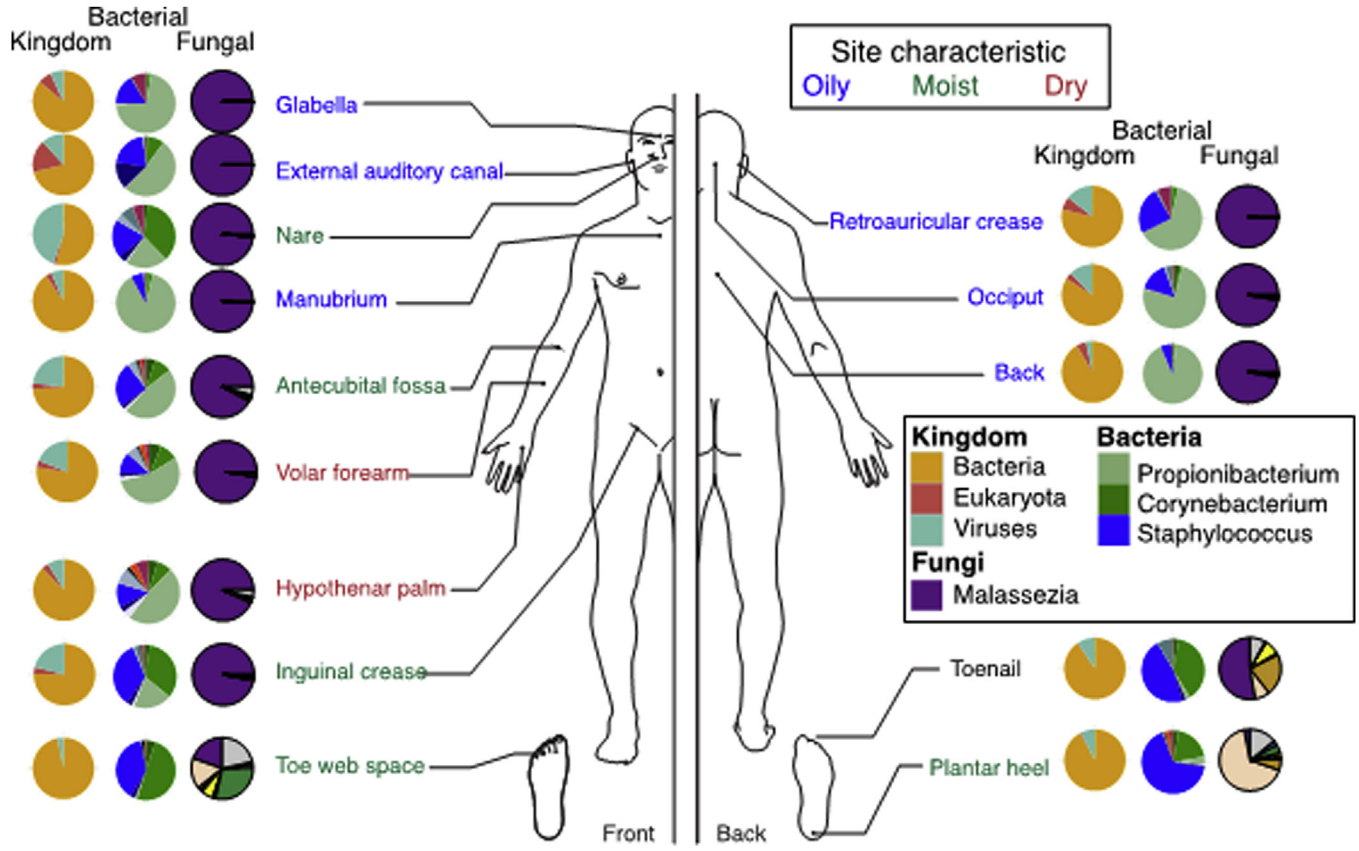

Figure 1. Topographical distribution of microbial kingdoms, bacteria, and fungi on a representative healthy subject. Skin shotgun metagenomics defines relative abundance of viral, bacterial, and fungal components of the microbial community. These sites represent three microenvironments: sebaceous (blue), dry (red), and moist (green). Toenail (black) is a site that does not fall under these major microenvironments and is treated separately. Pie charts represent consensus relative abundance of the different categories of kingdoms, bacteria, and fungi. Bacterial sequences are grouped into the three major genera that dominate the human microbiome (*Corynebacteria, Propionibacteria,* and *Staphylococcus*). Additional colors represent minor components of the skin microbiome. Drawing adapted from data presented in Oh et al. (2014).

mucosa, nares, and stool, but also specific to the niche of the skin surface being studied (Costello et al., 2009; Gao et al., 2007, 2008; Grice et al., 2008, 2009; Human Microbiome Project Consortium, 2012). Certain skin characteristics such as highly sebaceous sites on the head and upper trunk were more likely to be *Propionibacterium* predominant compared with moist skin creases or broad regions of skin (Grice et al., 2009; Grice and Segre, 2011). The varied topography of human skin offers a unique opportunity to study how the body's microenvironments influence the functional and taxonomic composition of microbial communities.

The skin microbiome is dynamic during a human lifespan. Immediately after birth, skin bacterial communities differ based on mode of delivery: cutaneous 16S rRNA gene signatures of vaginally delivered neonates resemble vaginal bacteria, and neonates delivered by cesarean resemble cutaneous bacteria, possibly from direct exposure to individuals or the operating room environment (Dominguez-Bello et al., 2010; Shin et al., 2015). In infants, during the first year of life, the skin bacterial communities show high interindividual variation, along with tremendous diversity in both community composition and timing of bacterial acquisition (Capone et al., 2011). During the transition through puberty, the skin microbiome again shifts dramatically from predominance of Firmicutes (Streptococcaceae), Bacteroidetes, and Proteobacteria to more lipophilic Corynebacteriaceae and Propionibacteriaceae (Oh et al., 2012). Further alterations during later stages of life have not yet been explored.

SKIN MICROBIOME IN DERMATOLOGIC DISORDERS

In addition to studies in healthy individuals, 16S rRNA gene sequencing has been used to study the skin microbiome in different patient populations. Children with atopic dermatitis showed a statistically significant increase in the relative abundance of staphylococci, specifically *Staphylococcus aureus* and *Staphylococcus epidermidis* (Kong et al., 2012). The high staphylococcal relative abundance was most notable in sites of disease predilection and decreased with disease resolution and treatment. Patients with primary immunodeficiency syndromes, including autosomal dominant Hyper-IgE syndrome (Job's syndrome), who manifest with eczema and other systemic disorders, harbored bacteria and fungi not typically found in control subjects (Oh et al., 2013). Different strains of *Propionibacterium acnes* were associated with lesional versus nonlesional skin of acnes vulgaris patients. Moreover, the transcriptional profiles of acne patients exhibited specific down-regulation of the vitamin B12 biosynthetic pathway, providing an interesting possible connection to the

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