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Spatial and temporal variability of the human microbiota

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Abstract

The knowledge that our bodies are home to microbes is not new; van Leeuwenhoek first saw the microbes of the mouth and gut over three centuries ago. However, next generation sequencing technologies are enabling us to characterize our microbial consortia on an unprecedented scale, and are providing new insights into the range of variability of our microbiota and their contributions to our health. The microbiota far outnumber the human component of our selves, with 10 times more cells and at least 100 times more genes. Moreover, while individuals share over 99.9% of their human genome sequence, there are vast differences in the microbiome (the collection of genes of our associated microbes). This raises the question of the extent to which our microbial community determines our human physiological responses and susceptibility to disease. In order to develop technologies that allow us to manipulate the microbiome to improve health we must first understand the factors that influence spatial and temporal variation, stability in response to perturbation, and conditions that induce community-wide changes.

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Spatial and temporal distribution of the human microbiota

Many distinct microbial communities are distributed across the body and the differences among these communities are stable over time [1]. The majority of our microbes are found in the gut, and the microbiota of the gut and mouth are the most distinct communities [1]. However, there is extensive heterogeneity among the communities associated with skin on different parts of the body [1,2]. Skin sites such as the index finger and the soles of the foot harbour communities much different from each other, and often have greater diversity than the gut microbiome [1]. At each body site there are significant differences in the composition of the microbiome across people, as differences between individuals are greater than variation within individuals over time [1]. Moreover, the differences between these communities at different sites or between people are not subtle: they can be detected with as few as ten sequences per sample [3]. Thus, studies concerned with differentiating communities should focus on including more samples rather than sequencing to a greater depth of coverage [3]. Additionally, microbial ecology studies performed before 2005 (when high-throughput sequencing became available) should be thoughtfully considered rather than disregarded.

Each of us harbours a unique microbial consortium that is generally stable over time and robust to perturbation. Differences in the microbiota among individuals are striking: twins share fewer than 50% of the species-level operational taxonomic units (OTUs) in their gut microbiota [4], and just 13% of the species-level OTUs are shared among the palms of different individuals [5]. Despite these large differences in community membership, gene content of the gut microbiome is broadly similar across people and constitutes a core microbiome at the functional level [6]. The observation that an individual's skin microbiota is unique and stable over time prompted the hypothesis that the microbial community could

be used to forensically identify people, and in fact a computer mouse can be traced back to the person who regularly uses it with up to 95% accuracy [5]. The microbiota at other body sites such as the mouth and vagina show more overlap in taxonomic composition across the population. For example, the majority of species-level OTUs in the oral microbiota are shared across individuals and Lactobacillus species are the dominant taxa in the vaginal communities of most women (reviewed in [7]).

Development of the microbiota

While the microbiota are generally stable, the community composition can be altered by factors ranging from long-term diet to disease to therapeutic intervention. The largest changes in our microbial communities occur during the first years of life, and the development of the microbiome is influenced by many factors, including microbial ecology, genetics and early environment. Humans and other vertebrates are born with very few microbes and acquire our characteristic microbiota from the environment each generation. Acquisition of microbial symbionts begins immediately after birth and progresses from a simple community to a microbiome resembling that of an adult by 2.5 years of age [8]. The early environment encountered by infants plays a key role in populating the microbiome, beginning with the mode of delivery [9]. Babies born vaginally have a microbial community that is similar to their mother's vagina, while the communities of babies born by Caesarean section resemble human skin communities [9]. Early diet also plays a role in shaping the gut microbiome, which in turn may impact the susceptibility of babies to infections (reviewed in [10]). Factors such as breast feeding and vaginal birth result in increased similarity of the maternal and infant microbiome [9]; however, the communities of children are unique and adult-like by 2.5 years of age [8].

Changes in the microbiota in health and disease

Altered microbial communities (dysbiosis) have been implicated in a range of disease states, including obesity, diabetes, bacterial vaginosis and skin disorders, among others [11]. The crucial role of the microbiota in such diseases is demonstrated by the ability to transfer phenotypes associated with microbial communities (e.g. obesity) when the microbiota is transferred from donor to recipient. For example, transplanting the gut microbiota has been shown to cause disease in genetically normal recipients [12] or cure disorders in diseased recipients [13]. The composition of the microbiota can also be manipulated either to cause disease or to improve health, e.g. by altering diet [7,14]. Altering microbial communities, such as through transplantation of whole communities, the introduction of beneficial microbes (probiotics) or the directed removal of specific harmful microbes (narrow-spectrum antibiotics), is thus a promising avenue for therapeutic treatments. However, determining how to reliably alter the microbiome to treat disorders will require a detailed understanding of the variation in the microbiome of healthy individuals across body sites and over time, how microbiome variation with disease states deviates from this baseline variation, and the factors that sustain both harmful and helpful bacteria on and in our bodies.

Concluding statements

The human microbiota shows a remarkable amount of diversity at different sites within an individual, at the same site within an individual over time, and between different individuals. These conclusions are robust and supported even by relatively low-resolution methods. The number of studies and samples per study are growing exponentially and will provide the power to detect patterns useful in identifying and treating disease, assuming methods that enable detection and visualization of spatial and temporal patterns continue to be developed [7,15]. The emerging evidence that these complex microbial communities affect our health and can be altered to change physiological state or even cure disease is compelling and provides an ideal path forward for therapeutic interventions: we are all 99.99% the same in terms of our 'human' genome but 70–90% different in terms of our microbial communities. Further, our microbiomes are a lot easier to change than our genomes; indeed each of us has profoundly changed our microbiome during our lifetimes.

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