

BIOTECH Basics

The Human Microbiome

Clostridium



What you need to know:

- **The human microbiome is the collection of microorganisms (primarily bacteria) that live in and on the human body.**
- **Microbial cells outnumber human cells by 10 to 1.**
- **The Human Microbiome Project (HMP) is a large-scale collaborative study to identify the populations of microbes.**
- **The HMP has revealed enormous diversity, providing researchers with a map of the healthy human microbiome.**

Imagine a thriving metropolis, inhabited by millions. Like many large communities, it is grouped into distinct neighborhoods – the Upper East Side, Old Town, the manufacturing district, Little Italy and the high rises along the waterfront. Using existing transportation systems, the citizens in this metropolis travel from one region to another, carrying out daily functions. Over time, neighborhoods transition as a new group of tenants replaces the previous residents. Periodically, periods of civil unrest sweep through the region, leading to the destruction of entire populations. Afterward, a period of calm restores equilibrium and the inhabitants flourish.



Streptococcus

This story should sound familiar: It takes place every day on and within each of us. It's the story of our microbiome: the collection of microscopic organisms – primarily bacteria, but also viruses and fungi – that are found on skin, throughout the digestive system and inside various body cavities like the mouth and nose. We serve as the infrastructure for these thriving communities, providing nutrients and a favorable climate for growth. Scientists estimate there are 100 trillion microbes on and inside every individual. As a point of reference, this is 250 times the number of stars present in the Milky Way! Although

each microbe is one-tenth to one-hundredth the size of a human cell, in total, microbes in and on the human body outnumber human cells. Collectively, the microbiome accounts for two to five pounds of an average adult's bodyweight.

Before you reach for the antibacterial soap or ask your physician for a prescription, consider this: the vast majority of these microbial inhabitants are helpful. In the digestive system, bacteria break down plant material into digestible pieces. Other species make vitamins that we cannot produce on our own. The bacteria on our skin secrete a moisturizing film that keeps the skin supple, preventing cracks that could serve as entry points for harmful pathogens.

The Human Microbiome Project

Until recently, scientists knew very little about the inhabitants of the human microbiome and how they interact with each other and human cells. Enter the Human Microbiome Project (HMP), a five-year study cataloging the microbiome of nearly 250 healthy Americans. In June 2012, more than 200 scientists from 80 institutions simultaneously published a collection of papers describing the initial findings of this microbial census. The results provide insight on the landscape of the healthy microbiome and offer tantalizing clues on the relationship between microbes and disease.

Before becoming part of the study, subjects were examined for evidence of exist-

ing infection. More than half of those initially recruited were rejected because they were not completely healthy and 80 percent of the final subjects had to first be treated by a dentist for gum disease or cavities. Individuals were sampled at multiple sites in the mouth, nose, crook of the elbow and lower digestive tract (figure 1). Women were additionally sampled throughout the reproductive tract. Many subjects were resampled over a two-year period to identify changes over time. In all, more than 5,000 samples were obtained from 242 individuals.

Historically, bacteria and other microbes have been studied by culturing them in dishes. As most bacteria do not thrive under these conditions, only a small fraction of the total bacterial population had been cataloged. Thanks to the development of relatively inexpensive, high-throughput DNA sequencing, the HMP was able to identify microbes by direct analysis of their genetic sequence. This gave researchers a snapshot of the bacterial populations and their relative abundance at any given site on the human body. More than 3.5 terabases (3.5×10^{12}) of DNA sequence were obtained – a jaw-dropping amount.

The findings

The researchers discovered more strains of bacteria than anyone had imagined – over 10,000 different species. Scientists estimate this accounts for between 80 and 99 percent of the actual number of human microbial species. Totaled, these microbes possess nearly

For more information:

HMP Data Analysis and Coordinating Center - As with other large-scale, publically funded projects, the data gathered from the Human Microbiome Project are freely accessible. This site includes links to the published research papers highlighting the findings and their implications.

www.hmpdacc.org

Frontiers: Human microbes - a radio podcast from BBC Radio 4 that highlights the Human Microbiome Project.

www.bbc.co.uk/programmes/b011jv8r

*Tending the Body's Microbial Garden – an article from The New York Times about the human microbiome written by Carl Zimmer. It mentions an interesting approach to treating *C. difficile* in the gut.*

www.nytimes.com/2012/06/19/science/studies-of-human-microbiome-yield-new-insights.html



Lactobacillus

eight million bacterial genes; 360 times more than the number of genes present in the human genome.

Each person's specific collection of microbes is unique, containing about 1,000 different strains. There is a great deal of variation from person to person and less than half of an individual's microbiome may be shared with his or her neighbor. This "personalized" population is likely influenced by factors such as diet, environmental exposures and genetic contributions. The microbiome is also influenced by early life experiences such as being born by cesarean section - missing that inoculation from bacteria present in the birth canal - or being fed breast milk, nourishment containing over 600 bacterial species.

Each sampled body site contained varying microbial communities, but the sites were each characterized by key bacterial groups. For example, bacteria from the genus *Bacteroides* dominate the gut while various *Streptococcus* species are common in the mouth.

Researchers found that microbiomes can change over time. If an individual became sick and took an antibiotic, specific bacterial species were often wiped out. The antibiotic not only impacted the bacteria that caused the illness, but also related species that were part of the normal microbial community. The microbiome eventually re-established its equilibrium, although the affected bacteria may have been replaced with a different species - the equivalent of a neighborhood



Bacteroides

in transition. *Clostridium difficile* is one such bacteria that can invade the intestine when the normal gut bacteria have been destroyed as a side effect of antibiotics. These bacteria can lead to severe diarrhea and inflammation of the colon and are difficult to eradicate once established.

A better understanding of the microbiome could lead to microbe-boosting treatments that encourage the growth of native bacteria, preventing the expansion of harmful strains.

Such an approach could offer a powerful alternative or follow-up to antibiotics. Another possibility is using probiotics - directly adding the beneficial bacteria, seeding colonization and expansion. Notably, the science of probiotics is in its infancy and limited data is available to support claims of efficacy. Findings from the HMP will be useful as this field matures.

A separate study identified altered microbial communities during pregnancy. The microbiome of the female reproductive tract undergoes significant change, reducing the number of different microbes. Early in the first trimester, a strain of bacteria known as *Lactobacillus johnsonii* becomes dominant. This species is normally found in the digestive tract, where it produces enzymes that help digest milk. Scientists speculate that during delivery a baby will ingest some of these bacteria which then migrate to the intestine to help the infant digest milk.

Surprisingly, researchers found that nearly every individual carried so-called opportunistic pathogens - microorganisms that peacefully coexist with the rest of the microbiome but under unusual circumstances can cause illness. These included low levels of destructive strains of *Escherichia coli* and the ulcer-causing *Helicobacter pylori*. Scientists look to future research to understand why and under what conditions these bacteria become harmful.

Making peace with our microbiome

The vast majority of the bacteria that comprise the human microbiome have helpful functions in our bodies. Hopefully, the findings from the HMP can help change public perception of bacteria from invaders that must be destroyed to organisms that by and large are useful and even valuable for human health. In an interview with *The New York Times*, Julie Segre, a researcher at the National Human Genome Research Institute, stated, "I would like to lose the language of warfare. It does a disservice to all the bacteria that have co-evolved with us and are maintaining the health of our bodies." Returning to the earlier image of a teeming metropolis, this is the equivalent of saying that because we know that a few individuals misbehave, all inhabitants must be troublemakers.

A plethora of new research questions have sprung from the HMP's initial results. These include understanding how microbes initially colonize our bodies and how the human im-

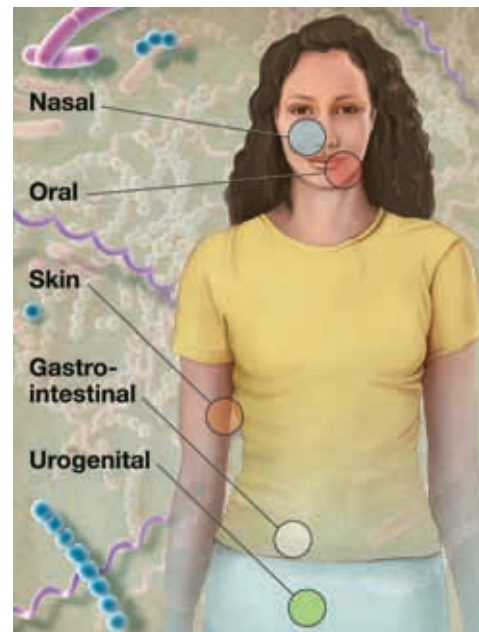
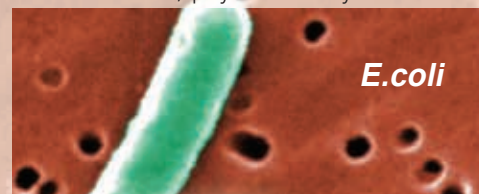


Figure 1 - a subset of the sampling locations for the HMP (image credit: NIH Medical Arts and Printing)

mune system - programmed to identify and destroy foreign organisms - allows and controls microbiome populations. Having a map of the healthy microbiome is already allowing researchers to seek out microbial changes associated with disorders like Crohn disease, ulcerative colitis, acne, psoriasis and immunodeficiency.

In the future, physicians may consider in-



E.coli

formation from your microbiome in making diagnoses and treatment decisions offering another data point along with your family history, genetic information and medical record, toward individualized medicine.

- Neil Lamb, Ph.D.

director of educational outreach

Connections to HudsonAlpha

Jian Han, M.D., Ph.D., a HudsonAlpha faculty investigator, is working on several projects related to the microbiome. Two R10K projects are being designed to explore the microbiome: one in collaboration with the Karolinska Institute of Sweden to compare the microbiome and immune repertoire before and 30 days after beginning a vegetarian diet. A second R10K project proposes to examine the impact of traditional Chinese medicine.