



in complex ways that help determine our health. The intestinal microbiome is currently the most researched, but there are also microbiomes in the mouth, on the skin, and even small amounts in the lungs which were once presumed to be completely sterile. New and cheaper techniques for analyzing microbial genetics with “shotgun” metagenomic sequencing have led to advances in understanding the microbiome, while older methods of culturing organisms on sterile media missed more than half of the microbiome’s inhabitants. It has become clear that while bacteria make up the majority of its residents, our internal ecosystem also contains viruses (the “virome”) and fungi (the “fungome” or “mycobiome”). Though research into all aspects of the microbiome is in its infancy, this area of investigation holds great promise in helping to diagnose and treat the afflictions that cause human suffering.

The “Mycobiome”

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Medical technology and therapeutics advance at breakneck speeds these days, but the latest advance in understanding disease and its treatment is coming from something wholly nontechnical – human stool. It turns out that this most maligned of all the body’s effluents may hold the keys to explain everything from deadly infections to allergies to psychiatric disease. And, in some situations, human stool itself has become a medication.

A major insight came with the “microbiome,” the understanding that every crevice of the human body contains a complex ecosystem of microorganisms that compete, cooperate, and interact with each other and with their hosting human

The fungal microbiome in particular appears to play an important role in calibrating the human immune system, even though fungi (yeasts and molds) make up a relatively small proportion of the microbiome as compared to bacteria. In mice guts,

bacteria outnumber fungi by 1000-to-1 (Dollive et al., 2013), with human guts likely hosting a similar ratio. Dr. Michael Mansour, an infectious disease specialist researching the mycobiome at Massachusetts General Hospital (MGH), believes that the immune system’s ability to sense certain fungi in the gut helps regulate its activity. Though this idea needs to be further fleshed out by more research, it suggests a new way of understanding a variety of bowel disorders.

Much of the initial research into the mycobiome involves simply describing it and its inhabitants in both healthy and ill people. For instance, the human mouth and nose in healthy people are dominated by species of *Cladosporium*, *Aspergillus* and *Penicillium* (Ghannoum et al., 2010), fungi common in indoor and outdoor environments. In patients with HIV infection, however, the resulting degradation of the immune system allows the mouth mycobiome to be taken over by yeasts of the genus *Candida*. This explains why HIV patients often suffer from “thrush,” an overgrowth of a white, pasty fungal patina on the tongue



and palate caused by *Candida* and treated with anti-fungal medications. Similarly, the vagina's mycobiome is normally dominated by the yeast *Candida* (Drell et al., 2013), and more numerous bacteria keep the amounts of this yeast at relatively low levels. When antibiotics kill off the dominant bacterial community, however, the vaginal mycobiome can flourish into a Candidal "yeast infection."

In the human gut mycobiome, the most populous of the human body's microbiomes, researchers have found members of all major fungal phyla. *Candida* yeasts appear to dominate in the gut, making up roughly 23-76% of fungal residents (Ott et al., 2008).

Varying amounts of other yeasts include members of the genus *Saccharomyces*, which has been used to bake bread and ferment wine for millenia (Ott et al., 2008). Molds commonly found in the gut include species of *Penicillium*, *Galactomyces*, *Trichosporon*, and *Rhodotorula* (Ott et al., 2008). As variable as a face, everyone's mycobiome is slightly different, but the exact determinants of its inhabitants in an individual are not yet known. Much of it may be genetic, along with the influence of antibiotic and antifungal medications taken. A study of the gut mycobiomes of mice found that, of over 100 species of fungi found in mouse stool, representing over 50 fungal genera, only 1.5% were

also found in the the food eaten by those mice (Iliev et al., 2012). This suggests that the gut mycobiome does not simply depend on what environmental fungi are consumed in food.

The differences between individual mycobiomes can predict risk for serious diseases. Though some intestinal fungi, including species of *Candida* and Mucorales, can cause serious, systemic infections, the healthy immune system is able to confine them to the gut. In the critically ill or those with compromised immune systems, these fungi are able to cross from the gut into the bloodstream, a process called "translocation." The organisms can then spread to and infect distant organs such as the eye,

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valves of the heart, or the liver and spleen. Translocation and subsequent systemic disease may involve only certain bits of gut fungi, such as DNA, RNA or peptidoglycans, crossing into the bloodstream and initiating immune responses resulting in distant disease (Cui et al., 2013). Understanding how more virulent strains of fungi colonize the human microbiome and cause disease could one day help prevent and treat a variety of medical conditions.

The most important revelations to-date about the mycobiome are the changes that occur in disease states. Several diseases that were never thought to have any connection to fungi, including hepatitis B, cystic fibrosis, eczema and inflammatory bowel disease (IBD), have been found to have strong associations with particular changes in the mycobiome (Cui et al., 2013).

Some of the most promising discoveries concern patients with Crohn's disease, a form of IBD that can cause debilitating intestinal disease, especially in children. Studies show that children with Crohn's disease have changes in the mycobiome, "dysbiosis," such as overall high levels of fungi in their guts with increased fungal diversity in comparison to healthy children. Certain fungi are found in greater abundance in the intestines of Crohn's patients as compared to healthy controls, including *Candida*, *Saccharomyces cerevisiae*, *Clavispora lusitaniae* and *Cyberlindera jadinii* (Ott et al., 2008; Lewis et al., 2015). Despite recent media fanfare over another study of Crohn's patients in France and Belgium, there does not appear to be one particular fungal species associated with this disease. The findings are intriguing, but their significance is not yet known. Some of these mycobiome changes could be the **result** of the disease rather than its cause, or perhaps the differences are simply the result of taking antibiotics or immunosuppressants, common therapies for Crohn's disease.

Based on studies of gut fungi, however, researchers have already developed better ways to diagnose Crohn's, a diagnosis that currently requires invasive scopes and biopsies. Studies have found that people with Crohn's disease often have higher levels of antibodies in their blood against fungi found normally in the gut, suggesting that inflammation of the

intestines in Crohn's disease allows the immune system to be more exposed to fungal gut inhabitants. This is especially true with the yeast *Saccharomyces cerevisiae*, a normal resident of the gut but one more abundant in Crohn's patients. Measuring the level of bloodstream antibodies against this yeast is already helping to improve the diagnosis of Crohn's. Furthermore, looking simply at the fungi found in the stool might one day diagnose Crohn's disease, without scopes or bloodtests being necessary. One study of stool fungi in Crohn's, for instance, showed *Clavispora lusitaniae* to be the most predictive of the disease (Lewis et al., 2015).

Some of the most interesting aspects of the microbiome are studies in ecology – they involve the interactions between microorganisms inside the human body. Bacteria, viruses and fungi interact with each other in the human gut, mouth, lungs and between the toes, often in similar ways as in the soil, and these interactions seem to play a role in certain diseases. In the lungs of people with cystic fibrosis, where researchers have found decreased levels of fungal diversity compared to healthy people, *Candida* yeasts appear to compete against the bacterium *Pseudomonas* (Cui et al., 2013). The lungs become a battlefield for warfare between these microorganisms, however the same two species seem to collaborate in causing infected skin wounds. Inside the mouth, the bacterium *Streptococcus mitis* has long been implicated as a cause of dental cavities, however research suggests that more important may be the complex interaction between this bacterium and *Candida* yeasts (Metwalli et al., 2013). This inter-Kingdom collaboration produces biofilms on the teeth that appear to cause cavities. Similarly, in life-threatening infections called "sepsis," *Candida albicans* may interact cooperatively with the virulent bacterium *Staphylococcus aureus* (Bittinger et al., 2014). The full extent of these bacterial-fungal interactions is still a mystery, and many questions remain. For instance, do fungi produce antibiotics to kill bacteria in the human microbiome as they do in soil? The answer is not yet known, but it seems clear that infections long recognized by the medical community may turn out to be more complicated than we thought.

All of this research must eventually lead to improved treatments, the business end of new knowledge. Current therapeutic experiments entail transferring the microbiome (including bacteria, fungi, and viruses) from one person into another. In other words, eating another person's stool. At MGH, Dr. Elizabeth Hohmann is conducting "fecal transplant therapy" trials to treat stubborn intestinal infections resistant to the strongest antibiotics. In this process, stool from healthy donors who have undergone extensive screening is put into a blender, leftover chunks are strained out, and the remaining slurry is freeze-dried and packed into gelatin capsules for patients to swallow – an easy, and thankfully tasteless, delivery mechanism that brings the stool further down the gastrointestinal tract. This treatment transfers the entire microbiome, and studies show that virtually all of the bacteria ingested survive the trip through stomach acid to arrive alive in the colon. But little is known about how well the fungal elements survive. According to Mansour, "fungi are 10-log more hardy than bacteria," so they probably make it just fine.

Hohmann and Mansour are embarking on a new study to use stool transplant prophylactically in patients who have undergone bone marrow transplants. These patients undergo intensive levels of immunosuppression and are at high risk of complications, including "graft-versus-host disease" in which the white blood cells transplanted from a bone marrow donor into a patient actually attack the patient's organs. Mansour believes that specifically the fungal elements present in the fecal transplants will help recalibrate the immune system to prevent it from attacking the patient. He plans to analyze whether or not the prophylactic stool transplants prevent serious complications of bone marrow transplant, as well as the specific role the mycobiome plays.

Fecal transplant therapy is similar to the concept of "probiotics," where one species of bacterium such as *Lactobacillus* or one species of fungus such as *Saccharomyces boulardii* are ingested. Probiotics are a common therapy for diarrhea related to taking antibiotics – they are thought to

repopulate the gut microbiome and restore its normal function. They have also been proposed as treatment and prevention for a wide variety of conditions and health maintenance; however recent research has largely thrown cold water on their efficacy for many diseases. Fecal transplant therapy may prove more effective. Hohmann describes taking one species of probiotic, whether bacterial or fungal, as “pissing in the wind. With fecal transplant you are treating yourself with an ecosystem,” which she expects will be shown to be more effective. Further research may isolate specific aspects of the microbiome, or mycobiome, that are effective and then therapy can be a bit more refined than transplanting whole stool.

For now, many challenges and unanswered questions remain in understanding the microbiome and its fungal portion, including its role in both disease causation and treatment. Mycobiome research is in its infancy, but its preliminary results cannot be “poo-poo”ed. It seems clear that the next

frontier in understanding the human organism may lie in understanding the trillions of microbes living in and on us. These microbes may hold secrets about our health, our predispositions to disease and our destinies.

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