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Researchers investigating the many ways we get by with a little help from trillions of our bacterial friends

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Everyone's got a personal collection of microbiota. You could think of yours as your unique internal pet—at up to 3 percent of your body mass, it's as hefty as a teacup Yorkie or a large guinea pig—requiring care and feeding. In turn, your microbiota provide essential services: extracting energy from food, absorbing and generating vitamins and amino acids and forming barriers against infective invaders. If researchers are correct, your microbiota might also fight diabetes, obesity and cancer; stimulate your immune system; break down toxins; and boost your overall health.

So exactly what are microbiota? They are the more than 10,000 species of bacteria, fungi and viruses that inhabit your gut, nose, mouth, throat, skin and urogenital tract. Professor Simin Nikbin Meydani, director of the Jean Mayer USDA Human Nutrition Research Center on Aging (HNRCA) at Tufts, likens the collective organisms to a major internal organ that is more metabolically active than even the liver.

She says nutritionists' excitement about the emerging picture of our microbiota is based partly on the discovery that the organisms are not the innocent bystanders scientists once imagined, and partly on the equally startling realization that gut bacteria could have an impact on the entire body—potentially determining, for instance, whether an individual is obese or lean, or predestined to health or disease.

The U.S. government's $173 million Human Microbiome Project (the microbiome being the collective genes of the microbiota, which outnumber your own human genes 150 to 1) is designed to propel knowledge to a new level. Just last year, 200 scientists reported the results of five years of collecting samples from more than a dozen body sites on more than 200 study participants. They found hundreds of never-before-described fungal species as well as other indications that they had just scratched the surface of the scope of the microbiome's structure.

To add to the challenge, everyone's microbiome appears to be unique. It is readily modified by diet, its multiple microorganisms seem to have overlapping roles, and "nobody understands what happens when all this gets modulated," says Associate Professor Martin Obin, a researcher in the Obesity and Metabolism Laboratory at the HNRCA.

Scientists around the world, including many at the HNRCA, are accelerating their research on exactly what these microscopic allies do for us, and how to get them to do it better. At the HNRCA, current research ranges from studying the immunity-boosting and cancer-fighting effects of the plant components that bacteria digest for us to exploring a little-understood form of vitamin K generated by microflora in the colon.

Gut instincts

Several hundred species of bacteria, along with some fungi and protozoa, inhabit our digestive tract, the largest reservoir of microorganisms in the human body. If what HNRCA scientists and others suspect about intestinal microbes pans out, the knowledge could revolutionize the way we think about gut bacteria in relation to weight loss, immunity, disease and the creation of essential nutrients.

The "good" bacteria in our intestines have a symbiotic relationship with

our bodies. They survive on food that passes through, gleaning energy from the parts that we cannot digest ourselves. They occupy real estate along the intestinal wall where pathogens might otherwise set up shop; they produce substances that drive off or kill invading pathogens and behave as low-level antigens, inducing intestinal lymphatic tissues to churn out natural antibodies that prevent "bad" bacteria from invading.

The intestines send out substances that may favor certain bacteria. The microbiota, in turn, alter the intestinal lining, influencing its tendency to store or burn fat. Understanding that relationship holds out a tantalizing possibility: Tweaking the microbiota might lead to new ways to address the obesity epidemic.

Andrew S. Greenberg, director of the HNRCA Obesity and Metabolism Laboratory and the Atkins Professor in Nutrition and Metabolism at the School of Medicine, studies the complex interplay among microbiota, diet and hormones that governs food absorption and metabolism.

He hopes to illuminate this "symphony" of interactions that can tip the balance toward burning fat, for instance, or storing it. "We are actually on that hunt right now, and we have data to support that these pathways may alter the storage of fat," he says.

Previously, researchers hadn't thought about the role of the intestines in regulating these metabolic processes. "The intestines were the forgotten organ in terms of obesity," he says. "Who would think that the intestines regulate food intake?" But studies have shown that microbiota direct the intestines toward certain pathways that enable fat, glucose or cholesterol to be absorbed. Gastric bypass surgery seems to promote weight loss not only by reducing food intake but also by encouraging the microbiota to process fat in a certain way.

Scientists may be able to alter that pathway in a way that affects gut

bacteria, says Greenberg, whose work in this arena in mice is being extended to humans. To regulate fat absorption, it would be necessary to tweak how gut bacteria interact with the intestine itself—a feat that Greenberg sees not only as possible, but likely in the near future.

Immunity boosters

Beyond weight control, the interplay between what we eat and our microbes seems to affect our immune system. Professor Mohsen Meydani, director of the Vascular Biology Laboratory at the HNRCA, along with Simin Meydani, who is also director of the Nutritional Immunology Laboratory, are seeking to quantify how consuming whole versus refined grains changes the population of "good" bacteria that keep the digestive tract running smoothly, protect against pathogens and, in turn, boost the immune system.

Very few studies have investigated whole grains' effect on gut immunity, but eating fiber-rich grains seems to be beneficial, producing reduced levels of the inflammation that is tied to heart disease, cancer and mortality. No one has shown exactly how whole grains do that, but it could be by interacting with the immune cells that reside in the gastrointestinal tract.

The cells can generate signals that could be transferred to cells and tissues way beyond the gut, boosting the body's capacity to deal with toxins, allergens and harmful microorganisms, Simin Meydani notes. Or they could produce short-chain fatty acids associated with anti-inflammatory effects and enhanced immune response. They might also increase the acidity of the gut, creating an unfavorable environment for unwanted microorganisms.

In an ongoing study of 80 subjects led by Simin and Mohsen Meydani, half will consume a whole-grain, high-fiber diet, and half will consume

refined grain. After six weeks, DNA sequencing, done in collaboration with researchers at Tufts Medical School, will allow scientists to analyze the change in ratio of certain bacteria and their effects on the immune system.

Churning out vitamins

Your microbiota also work as vitamin-production plants. Bacteria in the gut synthesize vitamins, and those that they don't use are excreted to benefit their host. In humans, gut bacteria secrete vitamin B12 and a less familiar micronutrient called vitamin K.

Professor Sarah L. Booth, associate director of the HNRCA, says that other than its accepted role in blood clotting, little is understood about the physiological functions of vitamin K. Even less is understood about forms of bacteria-produced vitamin K called menaquinones.

Booth and her colleagues suspect the huge variation in gut bacteria might help explain the wide variation in vitamin K levels found in the general population. "We've been so focused on one form of vitamin K, we have neglected the form produced in the gut," she says.

As the director of the only U.S. laboratory dedicated to studying vitamin K nutrition, Booth is hopeful that advances in DNA sequencing will help launch new research. Vitamin K is one of the few vitamins for which the Recommended Daily Allowance is unknown—we know only that "adequate intake" equals 90 to 100 micrograms per day from such dietary sources as spinach, kale and other dark, leafy greens.

How much of an individual's vitamin K is generated within the gut and how much comes from diet? "We haven't had the tools to study this," Booth says. "Work on gut microbiomes in relation to nutrients has always mentioned vitamin K, and yet we know so little about the role of

gut production and whether it has an impact on health."

Booth and her research colleagues are looking at whether increasing whole grains and dietary fiber modifies bacterial production and, in turn, vitamin K production in the gut.

Cancer clues

Not all bacteria, of course, provide benefits. Certain microbes amplify inflammation in the lining of the stomach or intestines and have been implicated in gastrointestinal cancer. Other gut bacteria may be associated with the development of colorectal tumors. But little is known about how diet and bacteria—both good and bad—interact to influence cancer risk. Ongoing studies by the HNRCA's Cancer Cluster are looking at just that.

A study led by Jimmy Crott, a researcher in the HNRCA's Vitamins and Carcinogenesis Laboratory, is comparing the gut microbiota of human subjects who have intestinal tumors to the microbiota of those who do not. The study also looks at how dietary patterns and the intake of specific nutrients correlates to the species of microbes they host.

In rodent studies, Xiang-Dong Wang, director of the Nutrition and Cancer Biology Laboratory, and Ligi Paul Pottenplackel of the Vitamin Metabolism Laboratory are looking at the effects of a high-fat diet and genetically induced obesity on the microbiota and the rate of liver and intestinal cancer.

Assistant Professor Oliver Chen, a scientist at the Antioxidant Laboratory at the HNRCA, is part of a team looking at polyphenols—phytochemicals commonly found in vegetables, legumes, chocolate, cranberries and green tea. All other things being equal, people who eat a lot of foods containing polyphenols have shown a reduced risk

of chronic disease. Given polyphenols' low absorption rate in the upper gastrointestinal tract, their benefits may play out amid the microflora in the colon.

Chen is looking at what is left over from the polyphenols once the gut microflora break them down and examining the extent to which these products affect immunity, especially in colon cells. The polyphenols may even change the bacteria themselves. "We hope to see if polyphenols can play a prebiotic role to modify the microbiota to a more favorable profile," he says.

Collectively, Crott says, "these studies will further our understanding of the complex interaction between diet, the gut microbiome and cancer."

Laurence Parnell, a computational biologist in the Nutrition and Genomics Laboratory at the HNRCA, uses cutting-edge techniques to look at the nutritional benefits of a healthy microbiome. "We're less interested in the specific bacterial species and more concerned with the metabolic potential of the population as a whole," Parnell says.

For instance, his lab analyzes the breakdown products of food in the gut, blood and urine to see what was eaten and whether it was processed in ways that make nutrients available to cells in the body. "For us, this gets at the function of the microbiome and the biological response that can be so important to the onset and progression of obesity, aging and such disorders as cardiovascular disease, type 2 diabetes and stroke," he says.

Researchers at the HNRCA are excited about the cross-fertilization of disciplines. Nutritionists are now collaborating with Parnell and other computational biologists as well as with geneticists, microbiologists, gastroenterologists, mathematicians and computer scientists to determine what defines a healthy human microbiome. The resulting understanding of the microbiome's connections to human health may lead to a new

wave of disease prevention and treatment in which very small, historically unheralded entities have big effects.

Get cultured

Probiotic—defined by the Food and Agriculture Organization of the United Nations as a live microorganism that confers a health benefit—has become a buzzword signaling a boost for your personal microbiome, much like designer fertilizer for your prize rosebushes.

Similarly, prebiotics—indigestible food ingredients such as fiber—are digested by "good guy" bacteria in the lower intestine, says Martin Obin, an expert on obesity and metabolism at the HNRCA. "The byproducts then go into the bloodstream and do good things," helping to digest food, prevent infections and bolster the immune system.

Growing appreciation for gut microbiota has spawned U.S. and European industries centered on "friendly" bacteria. Besides tubs of yogurt, probiotics are popping up in soy beverages, salsa, dill relish, ketchup and even a microcapsule coating on bread. Probiotics in capsules or gummy bears promise billions of live cultures per dose to ensure digestive health and "general well-being." Probiotics' unproven claims range from preventing colds and curing yeast infections to altering brain activity and reducing cholesterol.

Between 2003 and 2008, the number of probiotic foods and beverages produced worldwide more than doubled, according to Datamonitor, a food industry watchdog. In 2011, consumers spent $28 billion on probiotic foods and supplements, according to the research firm EuroMonitor International.

Yet the science lags behind sales. Few of the additives or supplements have been tested as rigorously as conventional drugs. (In 2010, both a

Nestlé subsidiary and Dannon agreed to drop probiotic claims for separate products, and last year, Europe completely banned the terms "prebiotic" and "probiotic" in food industry marketing.)

So far, with a few exceptions, such as preventing or treating certain kinds of diarrhea in children, clear-cut evidence of probiotic effectiveness is lacking. But promising research continues. Studies in mice, for example, indicate certain strains of probiotics could offer protection from metabolic syndrome, a catch term for the obesity, insulin resistance, high triglycerides, high cholesterol and other symptoms that an alarming number of middle-aged people develop.

Obin found that in mice fed a high-fat diet, probiotic strains of the bacteria Lactobacillus and Bifidobacterium prevented weight gain and improved insulin sensitivity. Obin is hopeful they could do the same in humans.

Provided by Tufts University

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