

IMMUNITY STARTS IN THE GUT

Gut microbes do far more than just help with digestion. They play a crucial role in the immune system, helping to guard against infections, diseases and cancer **By Sandeep Ravindran**



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YOUR IMMUNE SYSTEM KEEPS YOUR BODY safe from a variety of diseases. And when it comes to immunity, it turns out you can trust your gut.

About 70% to 80% of the body's immune cells, which monitor and respond to potential threats, live in the gut. "It makes sense, because it's a prime area of interactions with foreign material and has a high potential to encounter infections," says Michael Howitt, an assistant professor of pathology at Stanford University. Microbes and toxins can hitchhike their way into the body through food.

In addition to guarding against harmful intruders, the gut's immune cells interact closely with the 100 trillion microbes—the bacteria, viruses, fungi and microscopic organisms known as protozoa—

that form the gut microbiome. It has become increasingly clear that these gut microbes are integral to protecting human health, influencing a person's susceptibility to infectious and autoimmune diseases and even certain types of cancer.

Healthy microbes play an important role in maintaining the physical and chemical barriers associated with the intestinal lining, which serve as a first line of defense against infections. In addition, gut microbes can also activate various immune cells, such as the B and T cells responsible for targeting bacteria, viruses and cancer cells.

How the gut and immune system interact

The immune system and gut microbiome are constantly talking to each other. For its part, the immune system exerts its influence by helping decide the composition of the gut microbiome. "The immune system differentiates between the harmless and extremely important commensal microbes that live in our gut and those that are pathogenic and pose a deadly threat to humans," says Eran Elinav, professorial chair in immunology at the Weizmann Institute of Science in Israel. He has identified one particular collection of proteins within the immune system

that senses small molecules secreted by microbes to distinguish friend from foe. "Once it makes the decision, it either creates the optimal environment for the good microbes to thrive in the gut or induces a very potent immune response against pathogens," says Elinav.

The immune system can also use antibodies to dictate which bacteria are allowed to live in the gut and what they're allowed to do. For example, antibodies can bind to a bacterium and prompt it to express fewer genes, making it less motile and less invasive. "It's basically a way of saying, 'I'll let you stay here if you don't express these genes that are harmful to me,'" says June Round, associate professor of microbiology and immunology at the University of Utah. "That's an example of the immune system pruning or sculpting the microbiota," the collection of microbes living in the gut.

Beneficial gut microbes also shape immunity by helping the body develop appropriate inflammatory and other immune responses against pathogens. The microbiota also influences a regulatory arm of the immune system, which shuts off immune and inflammatory responses and helps the body tolerate its own tissues. "Those responses are really important when you're thinking about autoimmune diseases like multiple sclerosis or inflammatory bowel disease (IBD), and even allergies and asthma," says Round.

Gut microbes help promote the development and functioning of the immune system in both humans and mice. "Mice that don't have a microbiome and are completely sterile, called germ-free mice, miss the development of whole arms of

the immune system,” says Elinav. As a result, germ-free mice have fewer immune cells to fight off harmful microbes or regulate the inflammatory response.

But even small shifts in the microbiota influence health and immunity, and the interplay between them has far-reaching effects. “People have extended what happens in the gut immunity to sites in the body farther afield, connecting it to arthritis or certain neurodegenerative diseases,” says Howitt.

Diversity and disease

Everyone’s gut microbiome varies based on many factors, including genes, gender, age, location, diet and lifestyle. A healthy microbiota tends to contain a diverse mix of microbes.

Using antibiotics or eating highly processed foods can cause microbial diversity to plummet. The loss of beneficial microbes frees up space and nutrients for pathogens and other microbes that increase gut inflammation and are associated with inflammatory diseases. “One of the most consistent things you see in individuals with inflammatory bowel disease is they have several *E. coli*-like species that are increased in abundance,” says Round. Studies have shown that transferring these bacteria from a human with IBD into a mouse can increase inflammation in the mouse gut.

Gut microbes also affect tumor formation. Certain gut bacteria induce immune cells that can kill tumor tissue. An imbalanced gut microbiota may have more bacterial species that stimulate tumor formation and lack those that are protective, leading to increased susceptibility to cancer.

What’s in the gut may even affect the effectiveness of anticancer therapies. Immunotherapies, which are currently some of the most promising anticancer treatments, act by encouraging the body’s immune response to attack cancer cells. Not all patients respond equally well to these therapies, and the gut microbiome might be to blame. “In most cases, immunotherapy doesn’t work for individuals with colorectal cancer, and many people have speculated it’s because the microbiota is inducing a certain response that doesn’t allow that immunotherapy to work,” says Round. Researchers have now identified gut

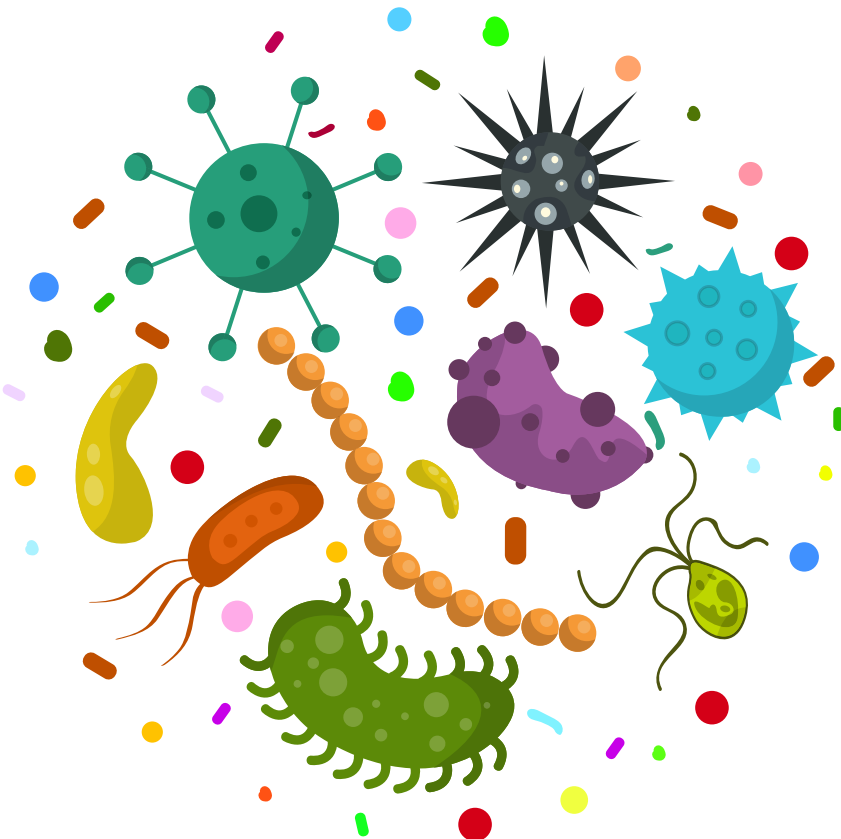
bacteria that could potentially enhance one’s response to immunotherapy. “That could be a really cool combination therapy, where you give someone a microbe and then give them immunotherapy and help fight their cancer,” says Round. Such combinations have shown promise in mice, and researchers are investigating whether they could have similar effects in humans.

Researchers have also uncovered links between the gut and the brain. The gut microbiota can impact the development and severity of the neurodegenerative disorder amyotrophic lateral sclerosis (ALS), or Lou Gehrig’s disease. “The gut microbiome impacts this very faraway disease by secreting small molecules known as metabolites, which can impact cellular function and disease development and progression in the brain,” says Elinav. Because the bloodstream transports these metabolites to different sites

of the body, “you can potentially explain how microbes that live in one place in our body could impact health and disease at a different site,” he says.

Researchers are also studying the interaction between the gut microbiome and SARS-CoV-2, the virus responsible for the COVID-19 pandemic. Some studies have found lower bacterial diversity and fewer beneficial microbes in the gut of patients with COVID-19, although it’s an open question whether such changes might affect the transmission or severity of the disease. Changes to the gut microbiota could also potentially explain some of COVID-19’s long-term effects on the body, including fatigue, shortness of breath and joint pain. “There are so many studies showing how important the microbiota is for the eradication and fighting of viruses that I have no doubt that the microbiota is going to matter for COVID-19 as well,” says Round.

Beneficial microbes influence the body’s ability to develop appropriate inflammatory immune responses against disease-causing microbes



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Improving immunity through the gut The gut offers an attractive pathway to influence disease response and health. “Anything that you put into your mouth and you ingest into your body is going to have an opportunity to interact with the microbiota,” says Howitt.

One approach that’s had success in clinical trials is fecal microbiota transplantation (FMT), which involves transplanting a preparation of fecal bacteria from a donor into a recipient’s colon. Often conducted via colonoscopy or pills, FMT has been effective at treating diarrhea caused by *Clostridium difficile*. “FMT is kind of the gold standard when people have recurrent *Clostridium difficile* that does not respond to antibiotics,” says Howitt.

You can also do plenty to modify your own gut makeup. Eating dietary fiber—found in fruits and vegetables, whole grains and nuts—is associated with beneficial health effects in part because it’s good for your gut bacteria. “A high-fiber diet is better at feeding the good bacteria, and it helps enhance microbial diversity,” says Round. Beneficial bacteria feast on fiber to produce short-chain fatty acids, which can enhance certain immune defenses. They can induce regulatory T cells, which have been shown to help prevent autoimmune diseases,

allergies and IBD in mice. Fiber intake also appears to have favorable effects on metabolism, like improved insulin resistance. Conversely, there’s some evidence that a low-fiber Western diet can decrease microbial diversity and increase susceptibility to pathogens and inflammation.

It’s not just what you eat, but when you eat that matters. Simply changing when you eat during a 24-hour cycle may alter the microbiome’s composition and function and affect the immune system’s behavior. Elinav has shown that disrupting these interactions in mice increased susceptibility to Crohn’s disease, an inflammatory disorder and one type of IBD.

One way to reintroduce good bacteria into the gut—after a dose of antibiotics, for example—is to consume them as probiotics. Probiotic bacteria, such as *Lactobacillus* and *Bifidobacterium*, can out-compete pathogenic bacteria and thus prevent them from being able to infect the gut. Studies have found that probiotic supplementation could help prevent diarrhea, respiratory infections and immune-related diseases like allergy and eczema.

However, for all their promise, probiotics have their limits. “The vast amount of literature associated with probiotics in most cases is very confusing, with some studies pointing toward improvement ... but other well-designed

studies showing exactly the opposite,” says Elinav. He’s found at least one reason for this discrepancy: the ability to be colonized by external microbes and probiotics is highly individual and influenced by one’s existing microbiome. “We could predict whether a person would welcome or not welcome probiotics based on that person’s initial microbiome configuration,” he says.

It turns out these individual differences may hold true not just for probiotics but for any food. “We found that people react differently even when they consume the same exact food,” says Elinav. He has been able to use artificial intelligence to predict a person’s unique response to food based on their gut microbiota and factors such as their dietary habits, blood parameters and physical activity.

Elinav used this approach to predict how people respond to sugars and fats, and is working on a follow-up study analyzing how diet and the microbiome affect inflammation and Crohn’s disease. “This gives rise to the possibility of using data-driven and science-driven approaches to come up with individualized dietary interventions for different people,” he says.

Precisely tailoring diet and probiotics to an individual’s gut microbiome could help them achieve greater health benefits—and make the most of the link between immunity and the gut. ■