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Bio2Q Human Biology Microbiome Quantum Research Center

Keio University Human Biology-Microbiome-Quantum Research Center (Bio2Q)

How do signals of distress from the gut reach the brain, and how does the brain attempt to respond?

Bio2Q Researchers

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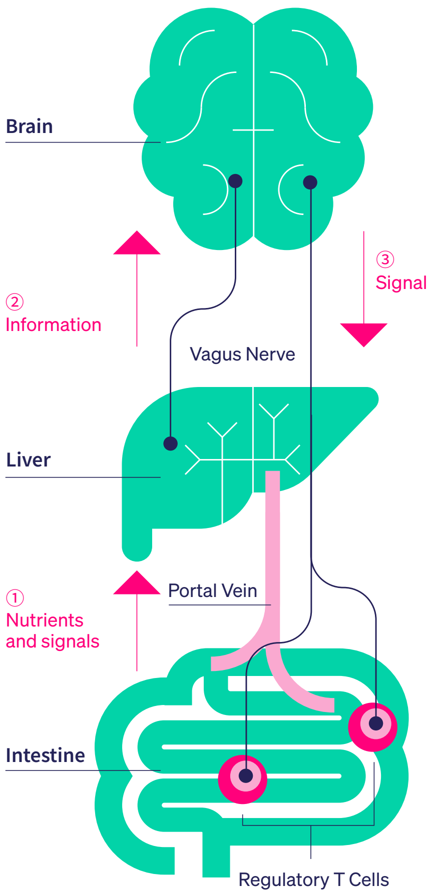
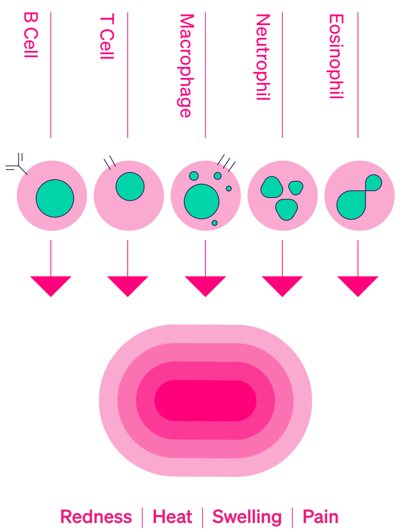
DEC. 2025

ISSUE 09



Information about the gut environment is transmitted to the liver via the portal vein, where it is processed and sent to the brain through the vagus nerve. The brain issues signals to regulatory T cells, helping regulate immune responses.



Inflammation is a defensive response in which immune cells gather to protect the body from physical stimuli or infection.

Could you tell us about your research?

As a gastroenterologist, I have focused my research on the gut.There are diseases known as inflammatory bowel diseases—such as ulcerative colitis and Crohn's disease—that can cause the sudden onset of diarrhea, abdominal pain, bloody stools, and fever. Their causes remain unknown, and they are officially designated as intractable diseases in Japan. Currently, they are considered incurable. I originally had an interest in the immune system and chose to specialize in inflammatory bowel diseases as a way to apply immunology in clinical medicine. Even so, there is still no cure.

However, as I treated more patients, I began to notice that although these illnesses are considered intestinal diseases, they sometimes lead to liver issues, skin conditions, or arthritis. It began to seem that these diseases affect not just the intestines, but also other organs and tissues—leading me to consider them systemic illnesses. I also noticed that ulcerative colitis can suddenly worsen, and after listening closely to patients, I found it often flares up during periods of intense stress—such as a divorce or the loss of a pet—which led me to suspect a connection with the brain. Gut disorders are closely linked to the brain: stress can worsen gut symptoms, while binge eating or excessive drinking may contribute to neurological conditions. As a result, my current research centers on the gut–brain connection.

Let's start with the basics: what is inflammation?

Inflammation is the process in which immune cells responsible for the body's defense gather at the site of a problem. For example, when you are stung by a bee, the body responds to the venom by sending immune cells to the site, resulting in heat, redness, swelling, and pain—a signal that something strange has entered the body. So inflammation is not inherently harmful; it is a mechanism the body uses to heal itself. However, when the immune response becomes excessive, inflammation may persist—as in ulcerative colitis or Crohn's disease—and cause lasting damage.

Have you discovered anything about the relationship between the gut and the brain?

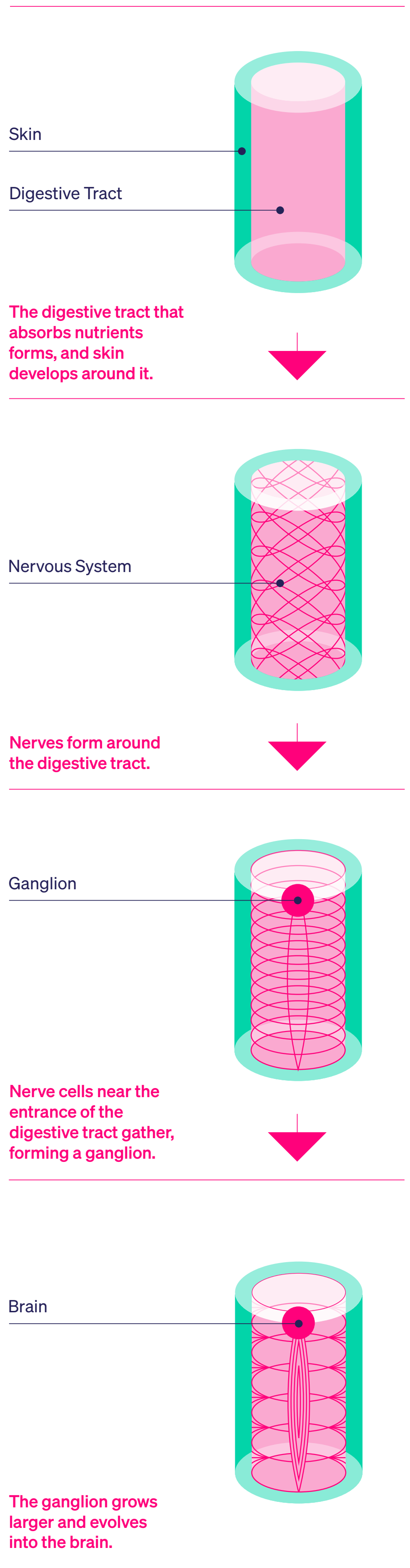
We discovered a pathway involving the liver in the communication between the gut and the brain, which was published in Nature in 2020.

This research was preceded by a discovery made about five years earlier, when a Japanese researcher developed a technique for severing the vagus nerve connected to the liver in mice. Curious to observe the effects, I learned the method and carried out the procedure myself. As part of the process, we also examined the gut—our area of expertise—and, to our surprise, found that the number of T cells responsible for regulating gut immunity had decreased. There is no direct pathway for information to travel from the liver to the gut. This led us to suspect that a vagus nerve reflex might be involved, in which signals travel from the liver to the brain and are then sent back to the gut. That realization led us to discover that the liver functions as a controller of regulatory T cells. Regulatory T cells are immunosuppressive cells that patrol the gut like police officers, keeping the immune response from overreacting. When these crucial cells are reduced, the gut can no longer suppress excessive immune activity, making it more susceptible to inflammation and serious illness.

For example, drastic changes in diet, such as binge eating or heavy drinking, can disrupt the balance of gut microbiota, triggering distress signals from the gut. This information is delivered through the portal vein, which carries nutrients from the gut to the liver. There, the liver processes and integrates the data, effectively acting as an information hub for the gut. The liver then transmits a signal to the brain via the vagus nerve, indicating that the gut is in distress. In response, the brainstem sends a signal back, aimed at restoring balance in the gut. Uncovering this previously unknown route of communication was one of our most significant research breakthroughs.

[1] Nature is a world-renowned scientific journal based in the United Kingdom, publishing cutting-edge research in science and technology.

[2] The vagus nerve is a key part of the parasympathetic nervous system within the autonomic nervous system. It extends to various organs throughout the body and regulates functions such as vocal cord movement, heart rate, digestion, and glandular secretion.



Do you think these discoveries could help in treating inflammatory bowel disease?

That's exactly what I'm working on now. Interestingly, in contrast to what I described earlier, we also found that electrical stimulation of the liver increases the number of regulatory T cells. We're currently exploring how to harness this effect to suppress immune activity and treat ulcerative colitis. The concept is somewhat similar to Eastern medicine practices like acupressure or acupuncture— stimulating specific nerves to trigger reflexes that promote healing. I see great promise in this approach as a potential therapeutic strategy.

The gut is often called the "second brain." It really does seem to be in constant communication with the brain, doesn't it?

The word gut has long carried emotional weight—not just in English, where we speak of "gut feelings" and "having guts," but in Japanese as well. Phrases like hara ga suwatte iru (literally, "one's belly is settled") reflect the idea that the gut is the seat of inner strength and resolve. In that sense, the gut really does embody something like spirit.

From a biological perspective, that actually makes perfect sense. Primitive animals first developed a digestive tract to sustain life, and to protect it, they evolved skin. Next came the nerves, which allowed the organism to regulate gut movement and absorb nutrients. As life became more complex, simple nerves were no longer sufficient. A neural cluster began to form near the entrance of the digestive tract. Over time, that cluster grew larger and eventually became what we now call the brain. So from an evolutionary standpoint, the gut came first—and the brain came later. It's only natural that the two remain deeply connected.

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When did the connection between the gut, brain, and other organs begin to attract serious scientific attention?

The concept of multiple organs influencing one another is known as "organ crosstalk." In particular, research on the gut–brain axis has accelerated over the past two decades. In the past, a village might have had just one doctor who treated every kind of illness. But as medical science advanced, the sheer volume of information grew exponentially, and the field became increasingly specialized. And while specialization is essential, it has also raised concerns about losing sight of the forest for the trees. The idea that "the mind controls the body," as the old saying goes, suggests that people have long sensed the importance of the gut–brain connection. What was lacking, however, were the tools to investigate it.

Breakthroughs in neuroscience and other cutting-edge technologies have driven the development of organ crosstalk research. Techniques such as optogenetics, which uses light to activate specific neurons; chemical genetics, which uses chemical compounds to manipulate gene function; and viral tracing methods that label neural pathways by infecting neurons with viruses have all contributed to major advances. Thanks to these innovations, research into inter-organ communication—especially the gut–brain axis—is now flourishing.

That said, there is still so much we don't know. I often encourage young researchers to take on bold, unconventional topics. "Do something crazy," I tell them. Conventional research will get done by someone else—if not today, then within five years. What I hope to see are young scientists who take on uniquely ambitious challenges, ones that could move medicine forward by a hundred years.

Do you have a message for our younger readers?

If you've already found something that truly fascinates you, you're one of the fortunate ones, and I hope you'll pursue it with everything you've got. Curiosity is the key.

When I was in elementary school, I spent most of my time playing. Around third grade, my parents finally said that if I wasn't going to study, then I should at least read manga, and gave me a comic book biography of Thomas Edison. I remember being struck by the fact that Edison didn't study much either and was constantly getting scolded by his teachers. According to the story, one day Edison was looking at train tracks and asked his mother, "Why do the rails look narrower in the distance, even though they're the same width?" He had discovered perspective all on his own. That story moved me deeply, and I still remember it vividly to this day. If you want to be a researcher, I hope you'll nurture that kind of curiosity—that ability to look at something ordinary and see it differently, just like Edison did with perspective. Follow your interests wherever they lead you.

If you find something that fascinates you, pursue it with everything you've got. Strive for unique, imaginative thinking, just like Edison. Curiosity is the key.

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What is Bio2Q?

Bio2Q is a world-class research center at Keio University. It aims to use quantum computing and AI to analyze the interaction between Human Biology and Microbiome, revealing uncharted territories of the human body and developing new treatments for intractable diseases.

It is the first private university to be selected for the World Premier International Research Center Initiative (WPI) program promoted by the Ministry of Education, Culture, Sports, Science and Technology (MEXT).

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