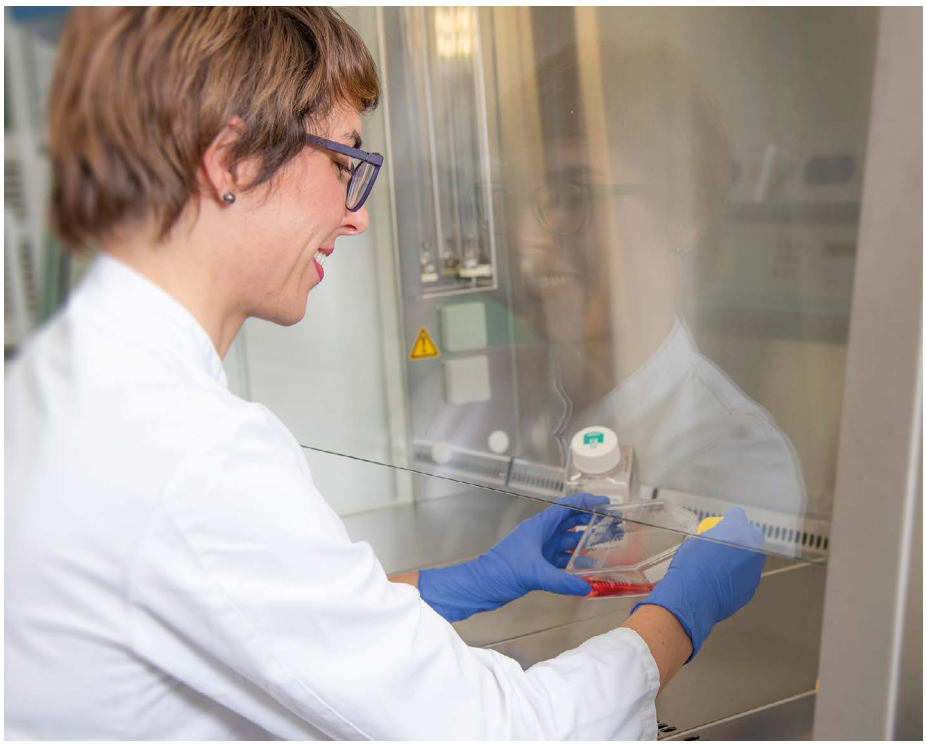
A gut feeling

Intestinal microbes shape the course of diseases such as Crohn's disease, type 1 diabetes and multiple sclerosis — and could even help to keep them in check. **By Elizabeth Svoboda**



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Anne-Katrin Pröbstel is a neurologist at the University Hospital of Basel in Switzerland.

As neurologist Anne-Katrin Pröbstel treated people with multiple sclerosis (MS), she began to notice something unusual. MS is understood to make the body's immune cells attack the central nervous system. Pröbstel and her colleagues at the University Hospital of Basel in Switzerland therefore treated people with a drug called rituximab, which lowers immune B cell counts. The treatment relieved inflammation and reduced the risk of relapse. Another drug, atacicept, gets rid of even more B cells. Yet when specialists prescribed atacicept, it paradoxically had the opposite effect to rituximab[1]. "It triggered relapses," Pröbstel says. "Nobody had a clue why."

Her best theory was that gut-bacterial activity was part of the answer. Rituximab seemed to work because it knocked down the particular B cells that make the inflammation-causing immunoglobulin G antibodies. But atacicept affected a different population of B cells found predominantly in the lining of the gut. These B cells, activated by bacteria, produce interleukin 10 (IL-10), which dials down inflammation. Perhaps, Pröbstel hypothesized, these gut-microbe-activated B cells were keeping MS symptoms in check, and therefore needed to be preserved.

Detective work such as this is starting to reveal just how profoundly the community of microbes in our guts affect immunity. People "are not one organism — we are a superorganism", says Emrah Altindis, a biologist and diabetes specialist at Boston College in Newton, Massachusetts. "We've evolved with microbes for hundreds of thousands of years. They have been regulating our immune systems." Some gut microbes spur immune overactivity, studies suggest, whereas others might protect against autoimmune flare-ups.

Scientists have long explored the part that gut microbes play in autoimmune conditions that affect the digestive system, such as Crohn's disease and type 1 diabetes. But research is also revealing that gut microbes can affect autoimmune processes in far-flung regions, such as the brain. Continuing gut bacterial studies could one day give rise to personalized treatments for autoimmune conditions or even therapies that stop the conditions from emerging.

A fine-tuned mix

Although most autoimmune conditions have a strong genetic component (see page S57), environmental factors also nudge the immune system to overreact, and gut microbes could be key to this. One line of research suggests that exposure to chemicals such as pesticides, cigarette smoke and mercury could change the gut microbial community in ways that leave people more vulnerable to autoimmune responses[2].

When gene sequencing for microbial populations became affordable in the 2000s, scientists began to note how the gut microbes of people with autoimmune disease diverged from those of healthy people. Those with type 1 diabetes, for instance, tend to have more gut bacteria of the *Parabacteroides*[3] genus than unaffected people, whereas people with Crohn's disease harbour high levels of adherent-invasive *Escherichia coli* (AIEC) bacteria, so named for its ability to stick onto and invade intestinal cells.

There are a few ways in which gut microbes might shape immune response directly, says Eran Elinav, an immunologist and microbial specialist at the Weizmann Institute of Science in Rehovot, Israel. First, some microbes interfere with the gut's ability to keep ingested substances in the digestive system. If compounds pass through the gut lining, they can promote an overactive immune response — a well-established mechanism in Crohn's disease[4].

Certain microbes also churn out compounds that closely resemble harmless ones produced in the body. Over time, this can train the body to mount a strong autoimmune response to these harmless molecules, causing inflammation and tissue damage in people with ulcerative colitis, type 1 diabetes and lupus.

Important pathways

In autoimmune disorders that directly affect the digestive organs, such as Crohn's disease

and type 1 diabetes, researchers have made advances in fitting gut bacteria into the bigger immunity picture.

Associations between AIEC bacteria and Crohn's disease have been known for years, with researchers theorizing that these stubborn microbes fuel disease episodes by irritating the gut mucosa. This year, immunologist Randy Longman and his team at Weill Cornell Medicine in New York City reported that AIEC bacteria make propionate, a compound that triggers inflammation by regulating immune cells called phagocytes in the gut lining[5]. These phagocytes, in turn, spur the body to produce IL-1β – a compound that stimulates swelling and a powerful immune response.

Longman's team also worked out a potential strategy for reversing this damaging process. They genetically tweaked the AIEC bacteria so that they stopped producing an enzyme needed to make propionate. When the team administered these engineered bacteria to mice with a Crohn's-like condition, the mice showed signs of reduced intestinal inflammation.

Longman points out that AEIC bacteria are present in many people, not just those with Crohn's disease. But he suspects that AIEC bacteria have more damaging effects in people with Crohn's. "The data suggests that it's a feed-forward cycle," Longman says – certain bacteria drive gut inflammation, and that inflamed state allows the harmful bacteria to flourish. "Understanding how to break the cycle," he says, "seems to be something that's critical."

Other microbes might help type 1 diabetes to develop by producing molecules that mimic life-sustaining insulin. Altindis and his colleagues have reported that viruses in the gut produce peptide molecules that are similar to insulin, which could lead the immune system to attack the insulin producing cells of the pancreas[6] (see page S64).

Far-flung connections

The proliferation of certain gut bacteria could also be driving autoimmune processes far beyond the digestive system. Pröbstel knew that certain gut microbes helped the immune system to maintain equilibrium, and she suspected that in some of the people she studied with MS, gut-bacterial activity might be activating immune B cells that controlled MS-related inflammation. "We wanted to understand how, potentially, gut microbiota shape the B cell responses, because they have a very intense interaction," she says.

To investigate, Pröbstel recruited a group of people with MS who had active disease and another group in remission. In both groups, she tracked the number and location of gut-lining B cells that produced the anti-inflammatory substance IL-10 (ref. 7). These cells respond to the presence of gut bacterial species such as *Akkermansia muciniphila* and *Eggerthella lenta*, which tend to be abundant in people with MS.

Pröbstel's cell tracking led her to a shocking conclusion: in people who were experiencing MS flare-ups, these bacteria-activated gut-lining cells were travelling through the bloodstream to the brain, migrating to specific sites where MS-related tissue damage was most severe[7]. "That is not something that was anticipated," she says.

> **"Is the microbiome different because these people are sick, or is it different because it causes disease?"**

Once they cross from the bloodstream into cerebrospinal fluid and brain tissue, these B cells seem to speed up healing in part by secreting IL-10, which helps to counter the brain swelling characteristic of active MS. Pröbstel plans to investigate whether bacterial probiotic treatments can enhance the activity of these B cells in people with this debilitating disease and lessen their chances of relapse.

Road to treatment

Studies such as Pröbstel's are exciting because they add concrete detail to researchers' understanding of how gut microbes drive biological processes involved in autoimmune disease. Microbial immunology is rich in correlational studies, but these do not establish whether microbes bring about a particular autoimmune state, or simply venture in after disease has taken hold. "Is the microbiome different because these people are sick, or is it different because it causes disease?" Altindis asks. "We need mechanistic studies to better understand these links."

As researchers investigate how certain microbes provoke specific immune responses, they inch closer to when this information could be used to change the treatment of autoimmune disease. "If you have sorted out which microbes are bad for the immune system and are triggering, you can think about mechanisms to deplete them," Pröbstel explains.

A first step could be using microbes to help physicians select the best possible treatment for a person. In 2020, researchers at the University of Helsinki studied two groups of people with inflammatory bowel disease, who were given the first-line drug infliximab. Those who did not respond to the treatment had more types of pro-inflammatory microbe, such as *Enterobacter* bacteria and *Candida* yeast[8]. A gut microbiome analysis might therefore help physicians to decide whether infliximab is the best treatment to try.

Ultimately, autoimmune specialists hope to create therapies tailored to the microbiome of individual people. For example, if someone with Crohn's disease had their gut microbes sequenced and the results showed an excess of harmful *E. coli*, they could one day take a bespoke probiotic to balance their gut flora and reduce intestinal inflammation.

It might also be possible to tailor a probiotic treatment to a person's genetic code. Most people with type 1 diabetes, Altindis points out, have one of a handful of human leukocyte antigen (HLA) haplotypes – groups of genes that regulate the immune system. Years from now, a child found to bear one of these high-risk HLA types could conceivably be given a bacterial regimen to stop the immune flare-ups that lead to diabetes onset.

Such therapies are many years and numerous bacterial studies away. Although probiotics are sometimes given to treat Crohn's today, they are not yet targeted to the specific microbial imbalances that give rise to symptoms. Faecal transplants, for instance, provide an indiscriminate mix of gut bacteria from healthy people to those with autoimmune disorders. "In 2021, we're still thinking about microbiome treatments that are very non-personalized," Elinav says.

But the work already being done to uncover the ways in which the gut microbiome affects autoimmunity gives researchers cause to think that they are on the right track. They hope to deliver more tailored and targeted gut microbe treatments in the coming decade. "How do we see a patient in the clinic, assess their microbial susceptibility, and then figure out a tailored regimen for treatment? That's the ideal," Longman says. "These studies put us on the road to be able to do that type of work."

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