Intestinal Bacteria Promote and Prevent Inflammatory Bowel Disease

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Scientists search for drug candidates in some very unlikely places. Not only do they churn out synthetic compounds in industrial-scale laboratories, but they also scour coral reefs and scrape tree bark in the hope of stumbling upon an unsuspecting molecule that just might turn into next year's big block buster. But one region that scientists have not been searching is their guts. Literally.

Now, a team of researchers at Harvard Medical School, Brigham and Women's Hospital, and the California Institute of Technology have demonstrated that a molecule produced by bacteria in the gut's intestinal microflora can eliminate symptoms of inflammatory bowel disease (IBD), a condition that includes Crohn's disease and ulcerative colitis, in animal models.

"Given the sheer number of bacteria in the gut, the potential for discovering new molecules that can treat a whole range of these diseases is promising," says Dennis Kasper, co-lead author on the study, professor of medicine and microbiology and molecular genetics at Harvard Medical School, and director of the Channing Laboratory at Brigham and Women's Hospital.

The study will appear as the cover story in the May 29 issue of *Nature*.

Scientists have known for many decades that the mammalian gut is an ecosystem teeming with approximately 1,000 different species of bacteria, species as distinct from the host as a single-cell amoeba in pond

scum. Rather than causing disease, these bacteria are responsible for protecting against infection and aiding digestion. An increasing number of scientists also suspect that recent increases in asthma and even certain food allergies are caused by disruptions in the delicate balance of this intestinal ecosystem.

In 2005, Kasper and Sarkis Mazmanian, then a postdoc in Kasper's lab and now an assistant professor of biology at the California Institute of Technology, discovered that a species of intestinal bacteria called Bacteroides fragilis could restore immune system balance in mice that were bred to lack intestinal bacteria. A particular product of B. fragilis, a sugar molecule called polysaccharide A (PSA), recovered the equilibrium of a certain subclass of immune system cells (called Th1 and Th2) whose levels became skewed when bacteria in the gut were absent. The researchers referred to PSA as a "symbiosis factor," one that established a beneficial link between bacteria and mammals. This was the first study in which such a link was demonstrated.

Interestingly, when the study was completed, Kasper and Mazmanian found in these mice an abundance of immune system cells that were known to protect against colitis and Crohn's disease. In the current report, the groups decided to expand these findings and explore potential links between PSA and inflammatory bowel disease.

When immunocompromised mice with a specific pathogen-free microbiota were given an intestinal bacterium called Helicobacter hepaticus, they soon developed "rip roaring" IBD, according to Kasper. However, when Helicobacter was combined with B. fragilis, the mice were fine. Further experiments revealed that PSA—the special sugar molecule—was the key factor in preventing IBD. In fact, when mice were given Helicobacter combined with PSA purified from B. fragilis bacteria, they showed no symptoms of IBD.

“But then the key question was, if PSA was essential for preventing these animals from coming down with either colitis or Crohn’s, how did it do it"” says Kasper. “What was the mechanism"”

The answer came by studying a subset of interleukins, that is, molecules secreted by immune cells.

Previous studies had shown that two particular interleukins, called IL-17 and IL-23, promote intestinal inflammation and are present at high levels in IBD patients. Here, while the researchers found IL-17 and IL-23 in the guts of animals who had received Heliobacter alone, these interleukins were absent from animals who had also received both PSA-producing B. fragilis and purified PSA.

“We realized that something in PSA must be preventing the inflammation that causes colitis and Crohn’s, which would explain the reduction in IL-17 and IL-23,” says Kasper.

This hunch brought the researchers to consider a third interleukin, IL-10. The opposite of IL-17 and IL-23, IL-10 is anti-inflammatory and had previously been shown to protect against experimental colitis.

The researchers once again administered Helicobacter and PSA-active B. fragilis (the combination that had previously led to healthy mice), only this time they included an antibody that blocked IL-10. As a result, the mice all came down with IBD.

“This demonstrated for us the mechanism by which PSA protects against IBD,” says Kasper.

Indeed, the researchers deduced that PSA prompts immune system cells to secrete IL-10, which in turn suppresses the inflammation caused by IBD. In other words, PSA is an anti-inflammatory.

This research should encourage people (including many scientists) to consider the vast potential for beneficial contributions to human health by “good” bacteria. And what’s more, “This is the first time that a beneficial molecule produced by intestinal bacteria has been shown to work therapeutically in an animal model,” says Mazmanian.

The researchers caution that these findings do not promise any near-term treatments for IBD. “PSA might do the same thing in humans, and it might not,” says Kasper.

However, the mechanism that they’ve discovered should persuade scientists and drug manufacturers to consider new sources for expanding the drug pipeline.

“There is currently no effort to develop molecules that are naturally made by bacteria to use therapeutically,” continues Mazmanian. “This study opens up that possibility.”

Source: Harvard Medical School