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Intestinal Bug May Prevent Inflammatory Bowel Disease

David Cameron

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S cientists 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 a molecule that just might turn into next year's blockbuster. But one region that scientists may not be checking is their guts. Literally.

Now a team of researchers at HMS, Brigham and Women's Hospital, and the California Institute of Technology has demonstrated in animal models 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.

"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," said co–lead author Dennis Kasper, a professor of microbiology and molecular genetics at HMS, the William Ellery Channing professor of medicine at Brigham and Women's Hospital, and director of the Channing Laboratory. The study appears in the May 29 *Nature*.

Scientists have known for many decades that the mammalian gut is an ecosystem teeming with approximately 1,000 different species of bacteria. Rather than causing disease, these bugs are responsible for protecting against infection and aiding digestion.

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, the sugar molecule polysaccharide A (PSA), reestablished the equilibrium of Th1 and Th2 lymphocytes, 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 the intestinal bacterium 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 was the key factor in preventing IBD.

But what was the mechanism? The answer came by studying a subset of interleukins.

Previous studies had shown that two particular interleukins, IL-17 and IL-23, promote intestinal inflammation and are present at high levels in bowel disease patients. Though the researchers found these molecules in the guts of animals who had received Helicobacter alone, the interleukins were absent from animals that had also received 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," said Kasper.

This hunch led 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, only this time they included an antibody that blocked IL-10. As a result, the mice all came down with inflammatory bowel disease.

"This demonstrated for us the mechanism by which PSA protects against IBD," said Kasper. The researchers deduced that PSA prompts immune system cells to secrete IL-10, which suppresses the inflammation caused by the disease.

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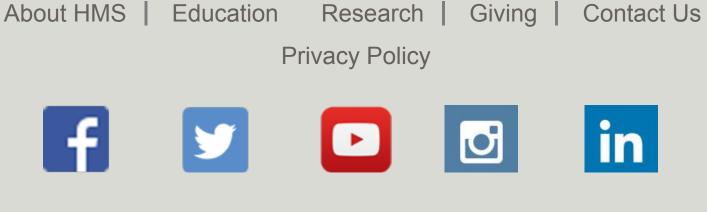
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