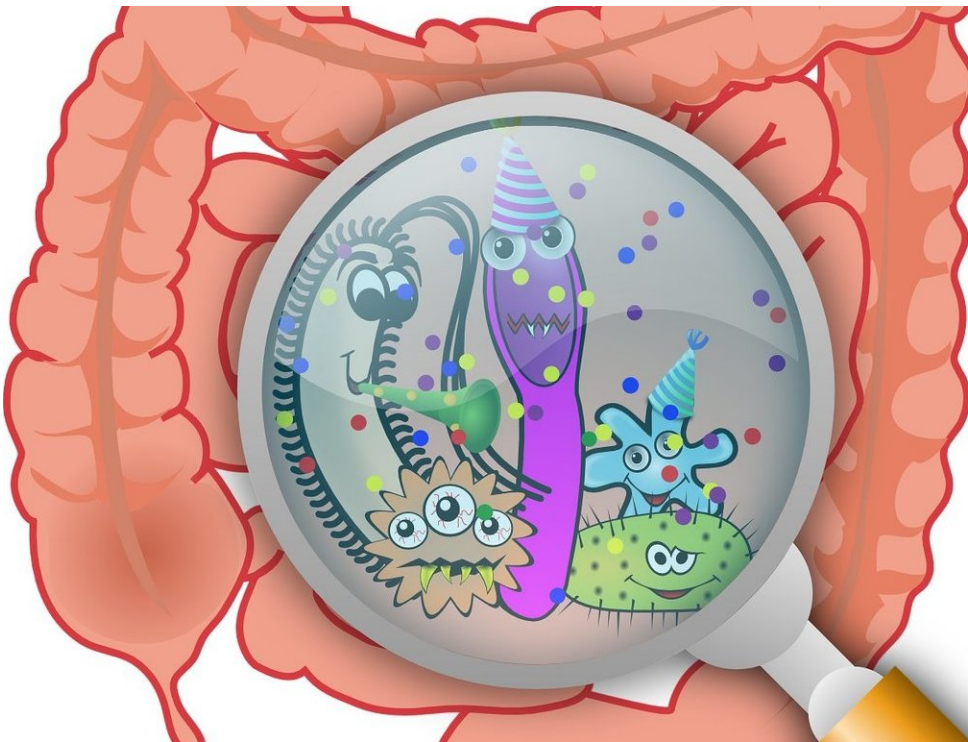


Scientists link ulcerative colitis to missing gut microbes

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About 1 million people in the United States have ulcerative colitis, a serious disease of the colon that has no cure and whose cause is obscure. Now, a study by Stanford University School of Medicine investigators has tied the condition to a missing microbe.

The microbe makes metabolites that help keep the gut healthy.

"This study helps us to better understand the disease," said Aida Habtezion, MD, associate professor of gastroenterology and hepatology. "We hope it also leads to our being able to treat it with a naturally produced metabolite that's already present in high amounts in a healthy gut."

When the researchers compared two groups of patients—one group with [ulcerative colitis](#), the other group with a rare noninflammatory condition—who had undergone an identical corrective surgical procedure, they discovered that a particular family of bacteria was depleted in patients with ulcerative colitis. These patients also were deficient in a set of anti-inflammatory substances that the bacteria make, the scientists report.

A paper describing the research findings will be published online Feb. 25 in *Cell Host & Microbe*. Habtezion is the senior author. Lead authorship is shared by Sidhartha Sinha, MD, assistant professor of gastroenterology and hepatology, and postdoctoral scholar Yeneneh Haileselassie, Ph.D.

The discoveries raise the prospect that supplementing ulcerative colitis patients with those missing metabolites—or perhaps someday restoring the gut-dwelling bacteria that produce them—could effectively treat intestinal inflammation in these patients and perhaps those with a related condition called Crohn's disease, Habtezion said.

A clinical trial to determine whether those metabolites, called secondary bile acids, are effective in treating the disease is now underway at Stanford. Sinha is the trial's principal investigator, and Habtezion is the co-principal investigator.

Surgery often required

Ulcerative colitis is an inflammatory condition in which the immune system attacks tissue in the rectum or colon. Patients can suffer from heavy bleeding, diarrhea, weight loss and, if the colon becomes sufficiently perforated, life-threatening sepsis.

There is no known cure. While immunosuppressant drugs can keep ulcerative colitis at bay, they put patients at increased risk for cancer and infection. Moreover, not all patients respond, and even when an immunosuppressant drug works initially, its effectiveness can fade with time. About one in five ulcerative colitis patients progress to the point where they require total colectomy, the surgical removal of the colon and rectum, followed by the repositioning of the lower end of the small intestine to form a J-shaped [pouch](#) that serves as a rectum.

These "pouch patients" can lead quite normal lives. However, as many as half will develop pouchitis, a return of the inflammation and symptoms they experienced in their initial condition.

The new study began with a clinical observation. "Patients with a rare genetic condition called familial adenomatous polyposis, or FAP, are at extremely high risk for colon cancer," Habtezion said. "To prevent this, they undergo the exact same surgical procedure patients with refractory ulcerative colitis do." Yet FAP pouch patients rarely if ever experience the inflammatory attacks on their remaining lower digestive tract that ulcerative-colitis patients with a pouch do, she said.

The Stanford scientists decided to find out why. Their first clue lay in a large difference in levels of a group of substances called secondary bile acids in the intestines of seven FAP patients compared with 17 patients with ulcerative colitis who had undergone the pouch surgery. The investigators measured these metabolite levels by examining the

participants' stool samples.

Primary bile acids are produced in the liver, stored in the gallbladder and released into the digestive tract to help emulsify fats. The vast majority of secreted primary bile acids are taken up in the intestine, where resident bacteria perform a series of enzymatic operations to convert them to secondary bile acids.

Prior research has suggested, without much elaboration or follow-up, that secondary bile acids are depleted in ulcerative colitis patients and in those with a related condition, Crohn's disease, in which tissue-destroying inflammation can occur in both the colon and the small intestine.

The researchers confirmed that levels of the two most prominent secondary bile acids, deoxycholic acid and lithocholic acid, were much lower in stool specimens taken from the ulcerative colitis pouch patients than from FAP pouch patients. Clearly, the surgical procedure hadn't caused the depletion.

Diminished microbial diversity

These findings were mirrored by the scientists' observation that microbial diversity in the specimens from ulcerative colitis pouch patients was diminished. Moreover, the investigators showed that a single bacterial family—Ruminococcaceae—was markedly underrepresented in ulcerative colitis pouch patients compared with FAP pouch patients. A genomic analysis of all the gut bacteria in the participants showed that the genes for making enzymes that convert primary bile acids to secondary bile acids were underrepresented, too. Ruminococcaceae, but few other gut bacteria, carry those genes.

"All healthy people have Ruminococcaceae in their intestines,"

Habtezion said. "But in the UC pouch patients, members of this family were significantly depleted."

Incubating primary bile acids with stool samples from FAP pouch patients, but not from ulcerative colitis pouch patients, resulted in those substances' effective conversion to secondary bile acids.

In three different mouse models of colitis, supplementation with lithocholic acid and deoxycholic acid reduced infiltration by inflammatory immune cells and levels of several inflammatory signaling proteins and chemicals in the mice's intestines, the researchers showed. The supplements also mitigated the classic symptoms of colitis in the mice, such as weight loss or signs of colon pathology.

All three mouse models are considered representative of not just ulcerative colitis but inflammatory bowel disease in general, a category that also includes Crohn's disease. So the findings may apply to Crohn's disease patients, as well, Habtezion said.

In an ongoing Phase 2 trial at Stanford, Sinha, Habtezion and their colleagues are investigating the anti-inflammatory effects, in 18- to 70-year-old ulcerative colitis pouch patients, of oral supplementation with ursodeoxycholic acid, a naturally occurring secondary bile [acid](#) approved by the Food and Drug Administration for treatment of primary biliary sclerosis and for management of gall stones.

More information: Information about the trial, which is still recruiting people, is available at <https://clinicaltrials.gov/ct2/show/NCT03724175>.

Provided by Stanford University Medical Center

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