Study points to potential new treatment for inflammatory bowel diseases

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People with inflammatory bowel diseases develop inflammation of the intestine that can cause thickening of the gut wall and life-threatening blockage of the intestinal tube. Twenty to 50 percent of people with Crohn's disease and ulcerative colitis are affected over their lifetime by this poorly understood condition, called "fibrosis."

"Currently there are no approved treatments for this condition, beyond

surgery, to remove the blocked section of intestine," says Dr. Simon Hirota, Ph.D., Canada Research Chair in Host-Microbe Interactions and Chronic Disease, and member of the Snyder Institute for Chronic Diseases at the University of Calgary's Cumming School of Medicine.

A new study led by Hirota and published in the journal *Cellular and Molecular Gastroenterology and Hepatology*, opens the door to developing a potential treatment for fibrosis. The study involved researchers at the University of Calgary and the Albert Einstein College of Medicine in New York.

The research teams investigated bacteria residing in the human gut—"the inner tube of life"—that release chemical substances called microbial metabolites (products of metabolism) that block inflammation and gut wall thickening. In people with inflammatory bowel diseases, these metabolites are present at reduced levels, as are the natural sensors that the body uses to detect them.

Hirota explains that while repair in the gut is necessary after injury, the "over-exuberant," constant repair seen with inflammatory bowel diseases leads to disease-causing changes in the gut wall.

"We're now starting to think about not only the lining of the gut playing a role in sensing and responding to metabolites, but also the fibroblast cells just below the lining," Hirota says.

The researchers looked at a specific chemical receptor—or sensor—in the gut called PXR that's involved in helping the gut heal. They focused on the interplay between this receptor and a metabolite called IPA.

Using cells from mice the researchers removed the PXR receptor, enabling them to determine which cells were involved in the interplay between the chemicals released by gut bacteria and the host. They used

cells from the human gut to verify their findings in the animal model.

The findings suggest that drugs designed to target these sensors may provide a new treatment to prevent inflammation-associated gut blockage. Co-author Dr. Sridhar Mani, MD, and his research group have produced synthetic compounds based on the structure of the IPA metabolite that have been shown to inhibit inflammation—much like the natural IPA does.

"This new research has produced a field-driving publication that clearly implicates PXR as an important target for fibrosis," says Mani, professor at the Albert Einstein College of Medicine. "We hope to now use microbial metabolite mimicry as a strategy to target PXR to prevent this dreaded complication of IBD."

A next step would be to conduct clinical trials to see if the synthetic compounds have a beneficial effect on fibrosis and the remodeling process in the human gut. Hirota says that ideally, the "synthetic metabolite" would be in a form that could be ingested and would pass through the stomach and be released in specific areas of the gut that are affected.

More information: Kyle L. Flannigan et al, The Pregnane X Receptor and Indole-3-Propionic Acid Shape the Intestinal Mesenchyme to Restrain Inflammation and Fibrosis, *Cellular and Molecular Gastroenterology and Hepatology* (2022). DOI: 10.1016/j.jcmgh.2022.10.014. www.cmghjournal.org/article/S2 … (22)00225-9/fulltext

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