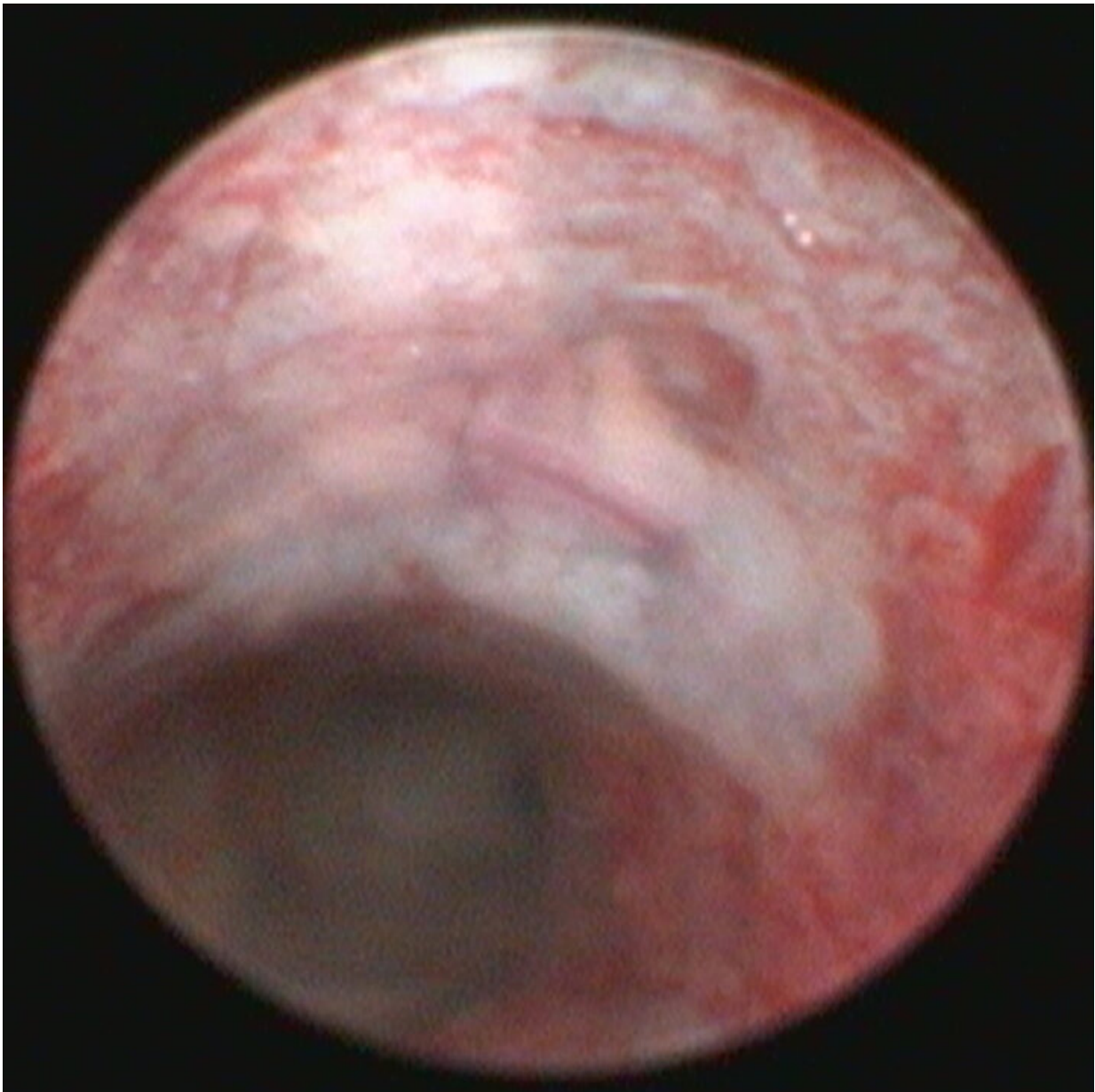


Researchers discover new drug target for inflammatory bowel disease

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Colonoscopic image of mice lacking the Pak2 gene showing severe colon inflammation. Credit: UT Southwestern Medical center

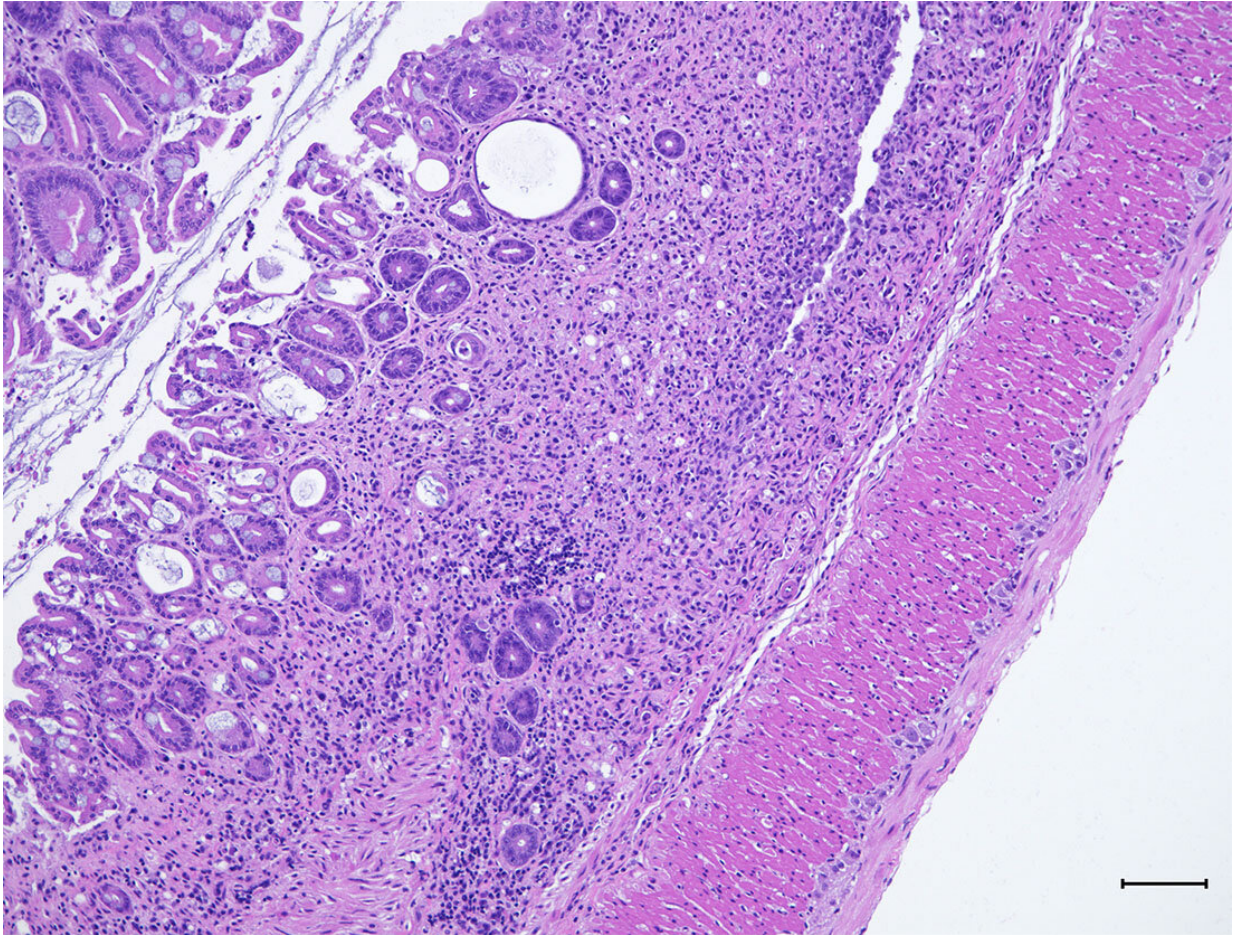
A set of interacting molecules in immune cells of the gut is responsible for preventing the inflammation seen in inflammatory bowel diseases (IBD), UT Southwestern researchers report in a new study. The findings, published in *Cell Reports*, suggest a new drug target for treating IBD and related conditions.

"We discovered a fundamental mechanism that inhibits inflammation in the gut," said Venuprasad Poojary, Ph.D., Associate Professor of Internal Medicine and Immunology at UT Southwestern and a member of the Harold C. Simmons Comprehensive Cancer Center.

"Understanding these kinds of basic details about the immune system is essential for developing new strategies to treat inflammatory diseases."

Inflammatory bowel diseases, which include Crohn's disease and [ulcerative colitis](#), are characterized by chronic and severe inflammation of the gastrointestinal tract. Treatments for the diseases exist, but often suppress the [immune system](#) throughout the body, leading to side effects and an increased risk of infection. Drugs that more specifically target the gut are a longstanding goal.

Researchers already knew that heightened levels of the immune molecule IL-17 are associated with the worst symptoms of IBD. But while drugs targeting IL-17 have been developed for psoriasis, they have been ineffective at treating IBD; they also pose the problem of impacting immune cells throughout the body.



Histology showing colon tissue damage of mice lacking the Pak2 gene. Credit: UT Southwestern Medical center

In the new study, Dr. Poojary and his colleagues probed what other molecules interact in the inflammatory cells that produce IL-17 in the the gut. Their experiments turned up a protein called Pak2. When the researchers blocked Pak2 in mice, the animals lost weight, had more colon inflammation, and showed other symptoms of IBD, including diarrhea and blood in their stools. In the presence of Pak2, however, the IBD-like inflammation eased.

Further experiments revealed that Pak2 binds to ROR γ t, a protein that activates the IL-17 gene. But while ROR γ t acts like an accelerator for inflammation by boosting levels of IL-17, Pak2 acts like the brakes. Dr. Poojary's team showed that Pak2 acts to degrade ROR γ t and prevent it from activating the IL-17 gene.

"We clearly showed that turning up this pathway can inhibit colon inflammation, and we think this pathway could be targeted to attenuate this inflammation as well," said Dr. Poojary.

His lab is now planning follow-up studies to develop drugs that could encourage the Pak2 brakes on [inflammation](#). The research could have implications beyond IBD, he added.

"Although we studied this in the context of bowel diseases, we think this pathway is probably also applicable to other [inflammatory diseases](#) including multiple sclerosis and rheumatoid arthritis," he said.

More information: Mahesh Kathania et al, Pak2-mediated phosphorylation promotes ROR γ t ubiquitination and inhibits colonic inflammation, *Cell Reports* (2022). [DOI: 10.1016/j.celrep.2022.111345](https://doi.org/10.1016/j.celrep.2022.111345)

Provided by UT Southwestern Medical Center

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