

Solving the gut inflammation puzzle

September 18 2018

Inflammatory bowel disease (IBD), an umbrella term for a number of gut disorders—including ulcerative colitis and Crohn's disease—remains a clinical challenge. Current treatments don't work for all patients, and many stop working over time. But despite their different responses to treatment, all IBD patients share a commonality: intestinal inflammation. Better understanding what drives gut inflammation is therefore important for finding medicines that work effectively and consistently for patients.

Now, researchers from Sanford Burnham Prebys Medical Discovery Institute (SBP), in collaboration with scientists at Technion—Israel Institute of Technology, have identified a protein that drives intestinal inflammation. This finding highlights new opportunities for creating targeted therapeutics. The study published today in *Cell Reports*.

"Scientists have long known that proteins associated with inflammation can also be linked with IBD. In fact, a U.S. Food and Drug Administration (FDA)-approved clinical diagnosis for IBD relies on some of these proteins. Yet, the cause for the intestinal inflammation remained unknown," says Yu Fujita, M.D., Ph.D., first author of the paper and a postdoctoral fellow in the laboratory of Ze'ev Ronai, Ph.D., a professor at SBP's NCI-designated Cancer Center. "Our study has found this mystery player to be a protein that is part of the cell's protein homeostasis system, RNF5."

First, the researchers created mice that lacked the RNF5 gene. These mice displayed limited symptoms of intestinal inflammation, but when

exposed to an inflammation-inducing agent, the mice developed severe IBD, indicating RNF5 plays a critical role in this disease. Biochemical analysis for proteins that may be regulated by RNF5 identified S100A8, a protein that was previously linked to a number of inflammatory disorders and commonly used for detection of IBD.

"Once we identified S100A8 as a protein regulated by RNF5 in the cells that line the gut, we realized we may have identified an important player in IBD," adds Ronai.

Indeed, higher levels of S100A8 were found in the cells that line the gut, and also in the blood of mice that lacked RNF5, making it a suspect in the etiology of [intestinal inflammation](#). When S100A8 was inactivated in the blood using neutralizing antibodies, the severe IBD symptoms were halted. This pointed to its role in driving the disease and as a potential target for IBD therapeutics.

"Our findings indicate that RNF5 is the lock that keeps a key inflammatory protein under control. Once this lock is broken, 'Pandora's box' is opened, and S100A8 is released to cause inflammation," says Ronai.

To confirm these findings in a human disease setting, the scientists tested intestinal tissue samples from 19 [patients](#) with ulcerative colitis and compared these to samples from healthy people. Disease severity was linked to lower levels of RNF5 and higher levels of S100A8—mirroring symptoms in the mice that lacked RNF5.

"People with IBD are in urgent need of new treatments," adds Ronai. "These results support pursuit of therapeutic reagents that neutralize S100A8, or a RNF5 modulator. RNF5 also appears to be a potential predictor of disease severity, and could be used as a diagnostic marker."

William Jeffery Sandborn, M.D., director of the Inflammatory Bowel Disease Center at UC San Diego Health, who was unaffiliated with the study, comments, "Nearly every day I work with IBD patients who are struggling to keep their disease under control. Better treatments that work for more patients are urgently needed. Although early, this study points to several promising targets that could lead to more personalized medicines or new diagnostics for IBD, a subject for future independent investigations."

Avoiding unnecessary treatment

TNF inhibitors, which stop [inflammation](#), are a common IBD treatment. However, this treatment doesn't work for all patients. Predicting who will benefit from TNF inhibitors is important, as the medicines have serious side effects and should only be taken if necessary.

To see if there was a link between RNF5 and response to TNF therapy, the scientists assessed the level of RNF5 and S100A8 in patients that either responded or did not respond to TNF treatment. They found the samples from the non-responders had low levels of RNF5.

"This finding indicates RNF5 could help predict which IBD patients will respond to anti-TNF therapy," says Ronai. "Measuring RNF5 might be a useful biomarker that helps IBD patients and doctors avoid unnecessary treatments."

More information: *Cell Reports* (2018). [DOI: 10.1016/j.celrep.2018.08.057](https://doi.org/10.1016/j.celrep.2018.08.057)

Provided by Sanford Burnham Prebys Medical Discovery Institute

Citation: Solving the gut inflammation puzzle (2018, September 18) retrieved 26 April 2024 from <https://medicalxpress.com/news/2018-09-gut-inflammation-puzzle.html>

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