

Study details machinery of immune protection against inflammatory diseases like colitis

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Scientists report a protein made by a gene already associated with a handful of human inflammatory immune diseases plays a pivotal role in protecting the intestinal tract from colitis.

St. Jude Children's Research Hospital investigators led the research, which points to possible new strategies for combating colitis. Colitis is a chronic inflammatory disease associated with colon damage, resulting in [abdominal pain](#), bleeding and other symptoms.

The work also expands the link between the Nlrp3 protein and Crohn's disease, said Thirumala-Devi Kanneganti, Ph.D., assistant member of the St. Jude Department of Immunology and the paper's senior author. Md. Hasan Zaki, Ph.D., a St. Jude postdoctoral fellow, is first author of the study, which appears in the March 18 online edition of the journal *Immunity*.

Researchers demonstrated that in a [mouse model](#) of colitis, Nlrp3 plays a pivotal role in keeping the [intestinal tract](#) intact, thus preventing further damage that occurs if intestinal bacteria leak into the body. Nlrp3 works by anchoring a large, multi-protein complex known as the Nlrp3 inflammasome where the messenger protein [interleukin 18](#) (IL-18) is made. IL-18 belongs to a family of molecules known as [cytokines](#), which shape the body's immune response. In this study, researchers showed IL-18 produced by the Nlrp3 inflammasome helped mice maintain

healthy colon by triggering production of more epithelial cells to compensate for those damaged or destroyed by colitis.

"This paper provides the basis for more effective, potentially disease-modifying approaches to treatment," Kanneganti said. She added that in this study, scientists showed the specific pathway activated in the epithelial cells lining the colon for IL-18 production.

Previous studies linked changes in the NLRP3 gene to several auto-inflammatory problems in which a person's immune system mistakenly attacks healthy tissue. The gene is part of the body's innate immune response. That is the branch of the [immune system](#) programmed to act immediately against infectious diseases and other threats.

"I believe if we target molecules that are part of the innate immune response we can find cures for many diseases, including cancer," Kanneganti said. She and her colleagues focused on Nlrp3 in colitis after reports that patients with Crohn's disease, another disorder characterized by chronic intestinal inflammation, had low levels of the protein.

In a series of experiments, scientists demonstrated that the Nlrp3 inflammasome not only helps protect against chemically induced colitis in mice, but also showed how and where in the body the protection occurred. The researchers demonstrated that in response to colitis, the Nlrp3 inflammasome is activated in the epithelial cells lining the colon, where IL-18 can be produced.

Investigators also established that IL-18 is crucial for protecting the colon from colitis. In fact, researchers reported that injecting IL-18 into mice that lacked the molecule eased [colitis](#) symptoms.

Provided by St. Jude Children's Research Hospital

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