Research finding could lead to targeted therapies for inflammatory bowel diseases

19 November 2015

UT Southwestern Medical Center researchers have shown that a pathogen-sensing molecule plays a vital role in keeping gastrointestinal (GI) systems healthy.

The molecule - called Absent in Melanoma 2, or AIM2 - detects the DNA of harmful microorganisms (pathogens) and regulates inflammation in the gut. AIM2 is present in all immune and epithelial cells, which make up a large part of the intestine's cell population and help to maintain a healthy gut.

Findings from the new study, published online today in *Cell Reports*, could someday be valuable in treating conditions such as inflammatory bowel diseases (IBDs) and colorectal cancer, said senior author Dr. Hasan Zaki, Assistant Professor of Pathology at UT Southwestern.

"We've shown in an animal model that AIM2 detects the cytosolic presence of microbial DNA in the gut," Dr. Zaki said. "This detection activates cell-signaling pathways that produce antimicrobial peptides, suppress the growth of harmful bacteria, and maintain the integrity of the intestine's epithelial barrier.

"Our findings also suggest that defects in AIM2 may alter DNA sensing and thus contribute to intestinal inflammatory disorders such as IBD, ulcerative colitis, Crohn's disease, and colorectal cancer," he said. "By extension, manipulation of the AIM2 signaling pathway may be a promising treatment option for these conditions."

The healthy human intestine is populated with trillions of microorganisms (collectively referred to as the microbiota) - some that are beneficial to our health and some that induce disease. The immune system's ability to detect and kill the pathogens while preserving the beneficial microorganisms is vital to intestinal health.

The immune system maintains homeostasis - the proper balance - of bacteria in our gut, said Dr. Zaki, and the AIM2 pathway is a central part of this maintenance.

"When AIM2 detects the DNA of pathogens in immune and epithelial cells, the protein activates a molecular machine called the inflammasome," he explained. "The inflammasome in turn activates the enzyme caspase-1, which then produces two proteins (IL-1? and IL-18) that play important roles in the GI tract, including activation of immune cells, induction of antimicrobial peptides, and regulation of epithelial cell proliferation."

"Defects in AIM2-mediated inflammasome activation lead to growth of IBD-causing bacteria like E. coli, as well as dysregulated inflammation and compromised healing of intestinal injury," Dr. Zaki said.

Although more research is necessary, these findings have promising implications for the treatment of bacteria- and inflammation-related gastrointestinal illnesses, including IBDs and colitis-associated colorectal cancer.

"AIM2 may be a future therapeutic target to regulate altered microbiota and dysregulated inflammation in the GI system," said Dr. Zaki.

Provided by UT Southwestern Medical Center