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Form of Crohn's disease traced to disabled gut cells

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Scientists report online this week in *Nature* that they have linked the health of specialized gut immune cells to a gene associated with Crohn's disease, an often debilitating and increasingly prevalent inflammatory bowel disorder.

The link to immune cells intrigued researchers at Washington University School of Medicine in St. Louis because they and others believe Crohn's disease is caused by misdirected immune responses in the intestine that damage gut tissue. In addition, cells in the mouse model scientists used for the study had altered genetic activity that could lead to increased production of certain hormones. Those same hormones are elevated in some Crohn's patients.

"We now have a significant new piece of the puzzle that is Crohn's disease, but not the solution just yet," says senior author Herbert W. "Skip" Virgin, M.D., Ph.D., the Edward Mallinckrodt Professor and head of the Department of Pathology and Immunology. "As many as 30 different areas in human DNA have potential links to Crohn's disease, and to develop new treatments it's going to be essential to find out how each of them, as well as environmental factors, contribute to the disorder."

Crohn's disease is one of the most common inherited bowel disorders. In 2002, epidemiologists estimated that it affected 400,000 to 600,000 patients in North America. Symptoms include diarrhea, abdominal pain, vomiting and weight loss. The condition can lead to partial or full

intestinal blockages, which can require surgical treatment.

Research previously revealed that some Crohn's disease patients have a mutation in a gene known as Atg16L1. The mutation increases risk but doesn't automatically lead to Crohn's disease. To learn more, Ken Cadwell, Ph.D., a postdoctoral student in Virgin's lab, created and studied two lines of mice with a genetic alteration that reduced their ability to make the Atg16L1 protein.

Cadwell and his colleagues found decreased Atg16L1 protein had pronounced effects on Paneth cells, which are immune cells in the lining of a portion of the small intestine. These cells make proteins and antimicrobial peptides that they package as granules and secrete into the intestine to defend the body against infection.

"When they have less Atg16L1, the Paneth cells survive, but their ability to secrete granules is significantly impaired," Cadwell says.

Virgin consulted with co-authors Ellen Li, M.D., Ph.D., and Thaddeus Stappenbeck, M.D., Ph.D., Washington University researchers who study and treat Crohn's disease patients at Barnes-Jewish Hospital. When surgery becomes necessary to repair a patient's bowel, Li collects samples removed from the intestine for research. Selecting tissue from patients with mutated Atg16L1, researchers compared human Paneth cells to cells from their mouse model and found what Virgin calls "striking similarities."

To learn how Atg16L1 helps the Paneth cell, scientists conducted a follow-up experiment where a related gene, Atg5, was knocked out in mice. Like Atg16L1, Atg5 contributes to an important process called autophagy that lets cells consume and reuse their own resources and may have other functions as well. Paneth cells in this line of mice had impairments similar to the first line, suggesting that Atg16L1's

contributions to the Paneth cell may be linked to autophagy.

"We don't yet know why having abnormal Paneth cells would predispose a person to Crohn's disease or to what degree other genes linked to Crohn's may affect the Paneth cell, but those are just a few of the very interesting questions to follow up on from these results," Virgin says.

Source: Washington University

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