Gene associated with ulcerative colitis uncovered by researchers

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For as long as seven-year-old Jonathan Wexler can remember, he has taken sweet orange medicine every day to manage his ulcerative colitis symptoms. When he was only eight months old, Jonathan became the youngest patient to be diagnosed with ulcerative colitis, a form of inflammatory bowel disease (IBD), at The Hospital for Sick Children (SickKids).

In a new study led by SickKids and the University of Toronto, researchers identified a gene that may play an important role in the development of ulcerative colitis. The results strongly implicate the RAC1 gene as a potential target for new therapies.

Over the past decade, the number of children living with inflammatory bowel disease (IBD) in Ontario has increased by 30 per cent, mostly due to the increased diagnosis of kids under 10 years old. IBD is thought to be caused by a combination of genetics and an immune response to bacteria in the gut, but the exact cause remains unknown.

This study, published in the August 1 edition of Gastroenterology, is the largest Canadian study of its kind. It included over 3,000 participants from Toronto, the United States and Scotland. The average age of participants was 16. The study was first conducted in a local discovery cohort and found that increased RAC1 gene expression was associated with susceptibility to ulcerative colitis. Scientists took this discovery to the next step and tested this association in animal models. They found that reducing RAC1 gene expression led to protection from developing

the disease.

Ulcerative colitis is a chronic disease characterized by inflammation in the colon. It affects more than 250,000 Canadians. People living with ulcerative colitis experience a variety of symptoms including bloody stool, sudden urgency, stomach pain, cramps and nausea. It can also affect a child's growth. Ulcerative colitis is managed by medications, surgery, as well as diet and lifestyle changes, but without treatment it can be debilitating and life-threatening.

"This discovery is particularly exciting because we didn't just find a gene; we discovered its role in causing ulcerative colitis," said Dr. Aleixo Muise, lead author of the study and an assistant professor of pediatrics and laboratory medicine and pathobiology at U of T.

Patients with IBD who had increased expression of the RAC1 gene experienced increased inflammation in the colon. Research on animal models showed that when the gene was blocked or reduced, the experimental colitis was much less severe. The scientists found that blocking RAC1 expression led to reduced inflammation and protection from developing the disease.

"Understanding the genetics of IBD will help lead to novel diagnostic tools and treatments," explains Muise, who is also a scientist and staff gastroenterologist at SickKids. "The next step is to further comprehend the role of this gene and develop treatments that reduce the amount of RAC1 expression, or block it altogether."

Muise adds that because RAC1 is expressed in most cell types and cell processes, it likely plays a role in other autoimmune diseases, like rheumatoid arthritis, psoriasis and diabetes.

"It is remarkable that RAC1 plays a conserved role in regulating immune

responses from plants to man. This paper suggests that the immune pathways regulated by RAC1 are important for development of a human disease," explained Dr. John Brumell, principal investigator of the study and senior scientist in Cell Biology at SickKids.

“As far as we know Jonathan will be taking medications for ulcerative colitis for the rest of his life,” says Bernie Wexler, Jonathan’s father. “My hope is that ongoing research will lead to improved treatments and ultimately improved quality of life for Jonathan and others who are living with ulcerative colitis.”

Provided by University of Toronto