Blood biomarker predicts complicated Crohn's disease years before diagnosis: Study

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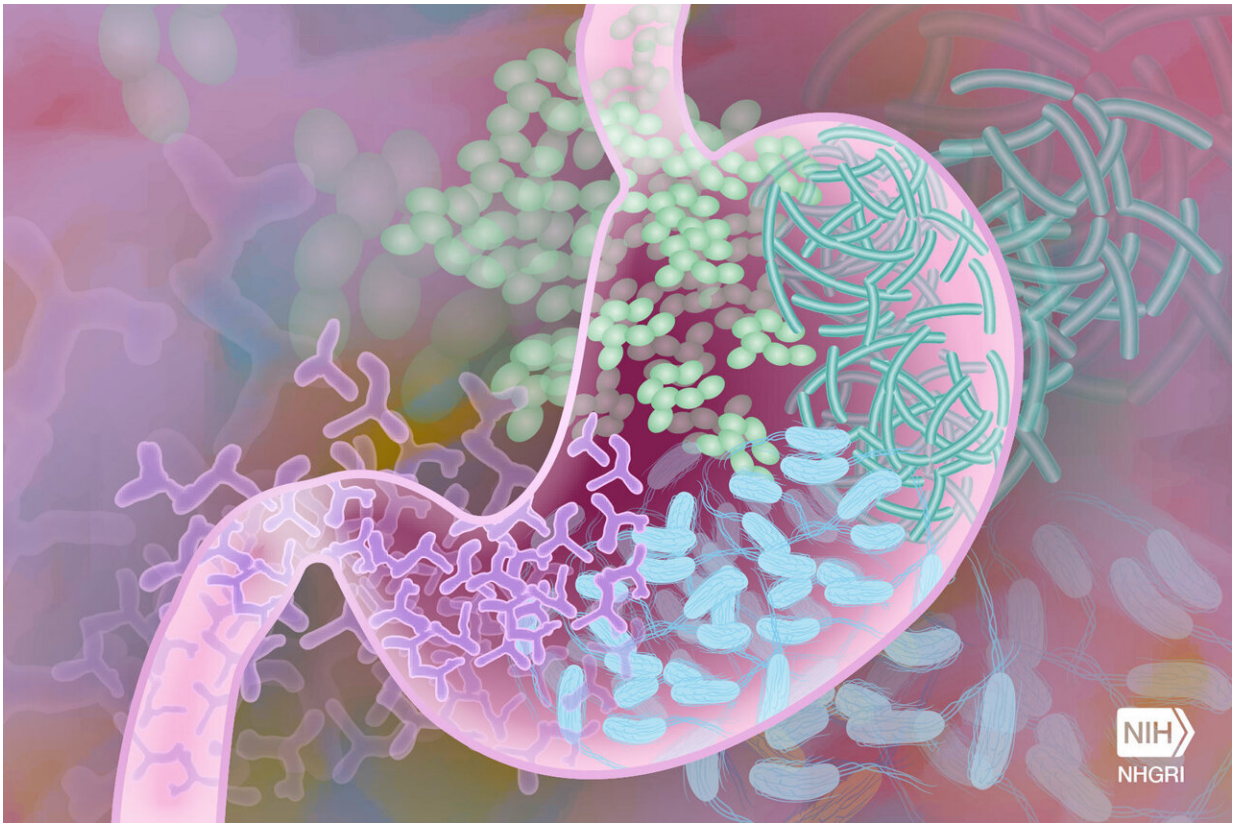

Illustration of bacteria in the human gut. Credit: Darryl Leja, National Human Genome Research Institute, National Institutes of Health

An international team led by a University of Toronto researcher has found that an antibody detectable in blood predicts severe Crohn's

disease and is detectable up to seven years prior to disease diagnosis.

Crohn's disease is a chronic inflammatory condition of the intestine, for which simple and effective biomarkers prior to diagnosis are lacking. A blood test could provide a quick, cost-effective and non-invasive way to assess risk for complicated Crohn's, which may enable preventive strategies before subclinical inflammation leads to chronic symptoms.

"Our team identified a serological biomarker for Crohn's disease that also participates in its pathogenesis and occurs years before the disease shows its full clinical spectrum," said Arthur Mortha, an assistant professor of immunology in U of T's Temerty Faculty of Medicine, who coordinated the study with Professors Jean-Frederic Colombel and Sacha Gnjatic at the Icahn School of Medicine at Mount Sinai in New York and an international team of researchers from France and Portugal.

"The current arsenal of therapeutics that causes relieving remission in Crohn's patients is good but suffers limitations. A biomarker or predictive indicators to guide interventions are a clinical need," said Mortha, who holds the Tier 2 Canadian Research Chair in Mucosal Immunology. "In addition, our characterization of this biomarker suggests it is a suitable therapeutic target for intervention and maybe even prevention."

The journal *Gastroenterology* published the findings today.

The biomarker for complicated Crohn's disease is an antibody produced by antibody-secreting cells in the gut. These antibodies prevent communication among intestinal immune cells by binding and blocking the function of a protein called a cytokine. This cytokine— Granulocyte Macrophage-Colony Stimulating Factor—sustains immune balance in the intestine by promoting protective and anti-microbial immunity.

Mortha and his colleagues showed that in a large subset of Crohn's patients, these antibodies neutralized the protective effects of the cytokine and disrupted intestinal homeostasis. Those changes were detectable in the blood of patients years before diagnosis and led to a weakening of the immune system that over time resulted in damage to the lower part of the small intestine—a condition known as complicated ileal Crohn's disease.

The researchers used blood samples from the U.S. Department of Defense Serum Repository to identify and characterize the biomarker. They studied samples collected annually over a decade from 220 military personnel who developed Crohn's and compared them to patients with ulcerative colitis and hundreds of healthy controls.

The biomarker strongly predicted risk for complicated ileal Crohn's, although not all patients with the antibody showed the exact same form and severity of the disease, which Mortha said highlights the multi-factorial nature of the condition. The biomarker was present in about a quarter of patients who developed Crohn's.

Importantly, the team also found they could preserve the protective effects of the cytokine by manipulating its biochemical features. Engineered versions of the cytokine with improved biochemical features can be made practically invisible to the antibodies, Mortha said.

"Our system allows us to see how the antibodies in each patient specifically neutralize the cytokine. We are now engineering cytokines that can escape neutralization by these antibodies within individual patients," Mortha said. This approach could enable highly personalized therapies that reverse the paralyzing effects of the antibodies and restore immune balance in the intestine, Mortha said.

Crohn's disease affects about 0.3 percent of the world's population, and

its incidence is increasing. In Canada, which has one of the highest rates of Crohn's, more than 135,000 people live with the condition, which can cause abdominal pain, diarrhea, weight loss and anemia, among other symptoms.

"Maintaining a strong gut immune system is essential to control the commensal microbes living in our intestine," said Mortha, who completed doctoral studies in Germany and postdoctoral training in New York before setting up his lab at U of T in 2016.

"It's mind-blowing that our mucosal immune system is capable of sustaining a defense against the enormous numbers of microbes in the gut, and that we're not in complete agony," Mortha said. "The past decade has taught us a lot about the modes of communication used by our gut immune cells to establish a healthy balance at this interface. It is now time to bring what we have learned to use."

More information: Arthur Mortha et al, Neutralizing anti-GM-CSF autoantibodies recognize posttranslational glycosylations on GM-CSF years prior to diagnosis and predict complicated Crohn's Disease., *Gastroenterology* (2022). DOI: 10.1053/j.gastro.2022.05.029

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