Marker may help target treatments for Crohn's patients

Thursday, October 4, 2018 - 10:54am

"We are not at the point at which we are able to perform personalized medicine on this, but at the very least we think it can lead to better clinical trial designs," said Dr. Praveen Sethupathy '03, associate professor in the Department of Biomedical Sciences. Photo by Rachel Philipson.

Crohn's disease (CD), a chronic inflammatory condition of the intestinal tract, has emerged as a global disease, with rates steadily increasing over the last 50 years. Experts have long suspected that CD likely represents a collection of related but slightly different disorders, but until now it has not been possible to predict accurately which subtype of CD a patient is likely to develop.

In a study published Oct. 4 in the journal JCI Insight, Cornell and University of North Carolina researchers report they have pinpointed a single molecule – microRNA-31 (miR-31) – the levels of which predict whether a patient has subtype 1 or subtype 2 of the disease.

This is important because patients with subtype 1, unlike subtype 2, often do not respond well to medications and develop strictures – extreme narrowing of the gut tube, requiring surgery once it develops. Markers like miR-31 could

be useful in the future for clinicians to predict whether a patient should pursue pre-emptive surgery before the condition worsens.

"We are not at the point at which we are able to perform personalized medicine on this, but at the very least we think it can lead to better clinical trial designs," said Praveen Sethupathy, associate professor in the Department of Biomedical Sciences at Cornell's College of Veterinary Medicine and a senior co-author of the study, along with Terrence Furey, associate professor of genetics, and Dr. Shehzad Sheikh, associate professor of medicine, both at UNC.

Clinical trials have generally grouped all patients together when testing a new therapy for CD, and that leads to inconsistent results across the group, Sethupathy said. Using miR-31, researchers potentially could separate individuals with CD into subtypes in order to more accurately determine if a particular drug works for one subtype and not the other.

In the study, the researchers also used a state-of-the-art artificial gut, called an intestinal organoid, that allowed them to culture human biopsy samples while retaining the basic physiology that exists inside a human. "This innovative system can serve as a personalized testing platform to screen therapeutic agents before administering them to patients," Sheikh said.

The researchers also used cutting-edge genomic techniques to track the abundance of different molecules in the colon tissue of more than 150 pediatric and adult patients. MicroRNAs control the extent to which a target gene is turned on. They function as negative dials – the greater the abundance of a microRNA, the more a target gene will be suppressed. Data from genomic sequencing technology allowed the researchers to make their miR-31 discovery.

"Our study hints that it's not only that miR-31 could be a predictive indicator of clinical outcome, but also that it could be functionally relevant in driving the disease," Sethupathy said.

Future work will explore exactly what miR-31 does and what role it might play in the integrity of the gut epithelium. "Our long-term goal, extending the work of this study, is to better understand at the molecular level why CD is so different in its presentation across patients, and to use this knowledge to develop more effective therapies," Furey said.

Benjamin Keith, a UNC graduate student in the labs of Furey and Sheikh, and in Sethupathy's lab, where he has visitor status at Cornell, is the paper's first author.

This study was funded by the Crohn's & Colitis Foundation, the National Institute of Environmental Health Sciences, the National Institute of Diabetes and Digestive and Kidney Diseases, the American Diabetes Association, the National Institute of General Medical Sciences, the National Cancer Institute, the Helmsley Charitable Trust, the UNC Nutrition Obesity Research Center, the UNC Center for Gastrointestinal Biology and Disease and the UNC University Cancer Research Fund.

By Krishna Ramanujan

This story originally appeared in the Cornell Chronicle.