Dysfunctional gene may be culprit in some Crohn's disease cases

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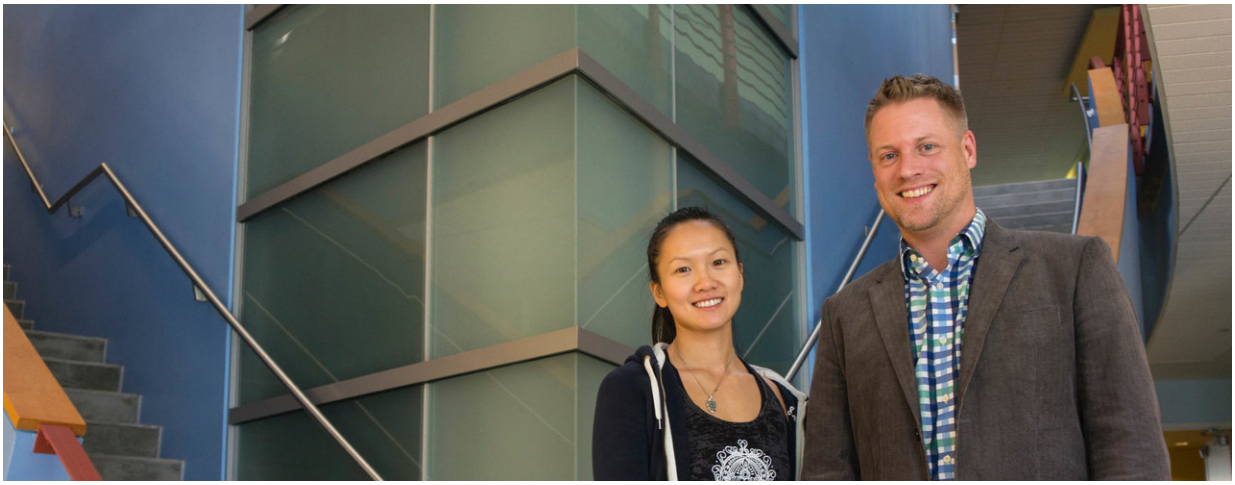

The study was led by TSRI Graduate Student Mei Lan Chen and biologist Mark Sundrud Credit: Jeremy Pyle / The Scripps Research Institute

This holiday season, millions of people will gather at airports ready to board planes for destinations around the world. Depending on the environment at their destination, their suitcases may be filled with sunscreen and bathing suits, or heavy parkas and mittens.

Now, a new study from the lab of biologist Mark Sundrud, Ph.D., on the Florida campus of The Scripps Research Institute (TSRI), provides evidence that circulating immune cells may similarly adapt when they enter different tissues, which are like different environments in our

bodies. Moreover, the researchers found that inability to adapt may lead to disease.

The scientists hope understanding how immune cells adapt as they enter different tissues will spur the design of better, more specific, medicines.

"We need therapeutic strategies that specifically target chronic inflammation in the gut, skin or other tissues," Sundrud says, "instead of just generally suppressing the entire immune system."

The research was published Dec. 19, 2017, in the journal *Immunity*.

Sundrud's laboratory is working to understand the characteristics and functions of TH17 cells, a subset of immune cells that circulate throughout the body. These cells protect many types of tissues from infection, but they can also promote chronic inflammatory conditions like Crohn's disease, which specifically targets the intestinal tract.

Knowing TH17 cells need to function in a variety of tissue environments throughout the body, Sundrud's team wondered if and how these cells might use different tools to behave normally in one environment—or tissue—than they'd use in another. Perhaps activating one gene could be useful in the lungs, while activating another would be useful in the gut, the same way you might bring a bathing suit on a trip to Florida and a jacket if you're headed to Canada.

This study built on previous research from the Sundrud lab, which showed that when TH17 cells entered the intestine in human tissue samples, they increased the expression of a gene called MDR1.

But MDR1 is only known to transport chemotherapeutic drugs out of tumor cells, so why would it be expressed in immune cells in the gut?

The new study suggests that MDR1 is responsible for protecting TH17 cells in the gut from bile acids—detergent-like molecules produced by the liver that break down fats. Normally, the liver secretes bile acids after we eat to aid digestion. As food moves through the digestive tract, these acids are reabsorbed when they reach the ileum—the final portion of the small intestine—and the site of ileal Crohn's disease, the most common form of Crohn's.

"T cells only see high levels of bile acids in the ileum. They know this, and they adapt once they get there," says Sundrud.

This discovery led the researchers to identify a mechanism where ileal Crohn's disease appears to be induced by bile acids when T cell adaptation does not occur the way it should.

The team used a genetically modified mouse model to observe the expression and function of MDR1 in mice. They found that the gene's expression increased when the cells entered the ileum. But, in mice where the gene couldn't be activated in the gut, TH17 cells that were exposed to bile acids suffered severe oxidative stress. This stress caused the TH17 cells to become overactive, leading to Crohn's disease-like intestinal inflammation in mice.

Using bile acid sequestrants, an FDA-approved class of drugs used in transplant patients that absorb bile acids like a sponge, scientists were able to restore normal T cell function in the ileum and attenuate Crohn's disease in mice.

To establish the relevance of their findings, the team tested blood samples from healthy humans, as well as those with a variety of inflammatory bowel diseases, including Crohn's. They found a subset of patients with ileal Crohn's disease had severely impaired MDR1 expression.

Not only does this suggest that the cause of Crohn's disease in these patients may be oxidative stress due to dysfunctional MDR1, but that for the subset of patients with this dysfunction, bile acid sequestrants may be an effective treatment. Together with his collaborators, Sundrud hopes to fund a clinical study to test exactly that.

Provided by The Scripps Research Institute