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Scientists target possible cause of one form of bowel disease

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A possible cause of irritable bowel syndrome has been traced to a small piece of RNA that blocks a substance protecting the colon membrane, leading to hostile conditions that can produce diarrhea, bloating and chronic abdominal pain.

New research shows that this RNA segment sends signals that stop the activity of the gene that produces glutamine, an amino acid. Previous research has linked a shortage of glutamine in the gut with the seepage of toxins and bacteria through the intestinal wall, irritating nerves and creating disease symptoms.

Scientists say that trying to generate glutamine in the disordered bowel by silencing this RNA segment could open up a whole new way of thinking about treating the diarrhea-predominant type of irritable bowel syndrome (IBS). In the meantime, they are making plans to conduct a clinical trial to see if glutamine supplements could also reduce common IBS symptoms.

This form of the disorder is characterized by diarrhea and bloating as well as chronic abdominal pain that is difficult to treat. About a third of IBS patients have the diarrhea-predominant type, another third experience consistent constipation, and the rest experience alternating bouts of diarrhea and constipation.

In the Ohio State University study, researchers observed that in human tissue samples, the presence of this small piece of RNA was associated

with reduced activity by the gene that produces glutamine. Lower levels of glutamine were seen only in tissue samples from patients with the diarrhea-predominant type of IBS.

A group of these patients also had a condition called increased intestinal permeability, which allows toxins and bacteria into the colon that typically can't get in. The resulting irritation to nerves in the colon is believed to contribute to diarrhea and abdominal pain. The finding suggests that the glutamine deficiency is connected to the increased intestinal permeability, which dramatically increases the likelihood that diarrhea-predominant IBS symptoms will follow.

The researchers say that manipulating that tiny piece of RNA, known as microRNA-29a, has potential as a novel treatment for IBS. "We've known about characteristics of this disease, but we didn't know the reasons behind them. This study helps us connect everything together. Maybe if we can modulate the microRNA, we can heal the disease. That is our whole hypothesis," said QiQi Zhou, assistant professor of internal medicine at Ohio State and lead author of the study.

The research is published in a recent issue of the journal *Gut*.

While testing the effectiveness of glutamine supplementation in IBS patients could lead to a viable treatment for symptoms, the researchers say it is important to continue to pursue the underlying cause of IBS.

"We treat the disorder, but we still don't understand it completely," said study senior co-author G. Nicholas Verne, professor of internal medicine and director of the Division of Gastroenterology, Hepatology and Nutrition at Ohio State. "We often have to use multiple therapies to attack the symptoms, but the pain is by far the most difficult to treat. For some patients, the pain responds only to escalating doses of narcotics or tricyclic antidepressants.

"That's why if we had a specific target for an underlying structural defect, we could try to resolve that defect as a much more effective way to reduce the symptoms."

Zhou, Verne and colleagues are the first group of scientists to report on a link between microRNAs, glutamine deficiency and IBS. Most studies of microRNAs have identified their role in the development of cancer.

RNA in cells is responsible for using instructions carried in the DNA to make proteins, but microRNAs are small segments of RNA that, when they become overactive themselves, can block the protein-building process. Each microRNA can target numerous genes, but Zhou concentrated on microRNA-29a and its connection to the production of glutamine in this study because of glutamine's established connection to intestinal permeability.

The researchers collected intestinal tissue and blood samples from three groups: IBS patients with increased intestinal permeability, IBS patients with normal intestinal permeability and control participants with no bowel disease.

The samples showed that microRNA-29a levels were four times higher in the tissues of IBS patients with increased intestinal permeability than were levels seen in IBS patients with normal intestinal permeability conditions and in participants with no bowel disease.

The scientists further tested this relationship by manipulating the microRNA-29a in experiments. When the microRNA-29a levels were driven up, the function of the gene that produces glutamine was prevented and intestinal membrane permeability increased, as well. When the microRNA-29a was artificially silenced, gene function was active, glutamine was produced and the intestinal membrane permeability was closer to normal.

"We've only tested the one target gene, and we've shown that when the gene activity is low, or the gene is not expressed, that's when disease characteristics come into play," Zhou said. "But there still may be other target genes related to this process."

The study also sought to determine how much related genetic information was contained in blood microvesicles, which are tiny blood vessel membrane fragments. Because the heightened expression of microRNA-29a was also detected in microvesicles from IBS patients with increased permeability in this study, the scientists believe a specially handled blood sample could provide as much disease information as a tissue sample for diagnostic purposes.

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