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Human and mouse studies sharpen focus on cause of celiac disease

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Blocking a factor that can activate the human immune response against intestinal bacteria or certain foods could prevent the development of celiac disease in those most at risk, researchers report in the journal *Nature*.

The study, to be published early online Feb. 9, points to two chemical signals—interleukin 15 and retinoic acid, a derivative of vitamin A—as triggers for the inflammatory response to gluten, a protein found in many grains that causes celiac disease.

"We found that having elevated levels of IL-15 in the gut could initiate all the early stages of celiac disease in those who were genetically susceptible, and that blocking IL-15 could prevent the disease in our mouse model," said Bana Jabri, MD, PhD, associate professor of medicine and pathology, co-director of the Digestive Disease Research Core Center and a member of the Celiac Disease Center and Comprehensive Cancer Center at the University of Chicago.

"It also demonstrated that in the treatment of inflammatory intestinal diseases, vitamin A and its retinoic acid metabolites are likely to do more harm than good," she said.

"In a stressed intestinal environment," the authors note, "retinoic acid, which was thought to lessen inflammation in the intestine, acted as an adjuvant that promoted rather than prevented inflammatory cellular and humoral responses to fed antigen."

This pro-inflammatory effect in a stressed intestine may also help explain the connections between Accutane--a vitamin A metabolite given for the treatment of severe acne--and the onset of inflammatory bowel disease.

Celiac disease is a digestive disorder triggered by the protein gluten, found in wheat, barley and rye. The disease affects about one out of 100 people. Gluten can trigger an autoimmune reaction in the intestines of genetically susceptible people. This prevents the proper absorption of food and nutrients, and causes a variety of gastrointestinal and extra-intestinal symptoms.

The current treatment for celiac disease is a gluten-free diet. However, many patients, in particular adults, improve only partially on a gluten-free-diet. This diet is difficult to follow, costly and inconvenient. There is a growing interest in finding alternative therapies, such as a vaccine that could prevent disease development in genetically susceptible individuals.

Celiac disease is also associated with autoimmune disorders such as type-1 diabetes and autoimmune thyroiditis. Understanding celiac disease may speed the development of new therapies for these autoimmune disorders.

For this study, Jabri and colleagues combined insights and data from celiac disease patients, who had been cared for at the University of Chicago's Celiac Disease Center, with experiments using a mouse model of the disease, developed in her lab.

Moving back and forth between "human data, where we develop our ideas, and mouse experiments, where we test them," was extremely helpful, said Jabri. "In turn, the mouse model gave us insights into the human disease."

They knew that many patients with this disease had high levels of Interleukin 15 in their intestines. When the researchers increased the levels of this signaling molecule in mouse intestine, the mice developed all the early symptoms of celiac disease. Adding retinoic acid to the mix only made the symptoms worse.

When they blocked IL-15, however, the diseased mice reverted to normal, and were once again able to tolerate gluten.

Clinical trials of medications that block IL-15 are already underway for patients with rheumatoid arthritis, another inflammatory disorder. Early results, have been encouraging. Blocking IL-15 or IL-15 signaling may be a way to restore oral tolerance to gluten and allow effective responses to vaccines aiming at preventing development of celiac disease, Jabri said.

This study is the first to identify an abnormal pathway leading to loss of tolerance to dietary antigens. It suggests that a "dysregulated intestinal environment may be the underlying cause for food allergies," Jabri said. What type of dyregulation is responsible for food allergies, such as to peanuts, is not yet known.

Although the IL-15 plus retinoic acid combination leads to inflammation and tissue damage in those at risk for celiac disease, the authors suggest that for those who, for genetic reasons, are less susceptible, the same combination could help enhance vaccines against several bacterial infections that cause diarrheal diseases. Children in developing countries often lack vitamin A. But by vaccinating them with selected bacterial proteins plus vitamin A, instead of using live viruses, they may be able to reduce the risks and increase the protective response.

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