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Gut microbiome can play significant role in the body's response to gluten

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Investigators interested in celiac disease, a chronic gastrointestinal disorder caused by an immunologic response to the ingestion of gluten, have wondered why only 2% to 5% of genetically susceptible individuals develop the disease. Attention has focused on whether environmental determinants, including gut microorganisms, contribute to the development of celiac disease. Using a humanized mouse model of gluten sensitivity, a new study in *The American Journal of Pathology* found that the gut microbiome can play an important role in the body's response to gluten.

"Importantly, our data argue that the recognized increase in celiac disease prevalence in the general population over the last 50 years could be driven, at least in part, by perturbations in intestinal microbial ecology. Specific microbiota-based therapies may aid in the prevention or treatment of celiac disease in subjects with moderate genetic risk," explained lead investigator Elena F. Verdu, MD, PhD, Associate Professor, Division of Gastroenterology, Department of Medicine, Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, ON (Canada).

Using mice that express the human DQ8 gene, which makes them genetically susceptible to inflammatory responses to gluten, researchers compared immune responses and pathology in the guts of mice that differed in their gut microorganisms. The three groups were germ-free mice, clean-specific-pathogen-free (SPF) mice with microbiota free of opportunistic pathogens and Proteobacteria, and conventional SPF mice that were colonized with a mixture of microorganisms including opportunistic pathogens and Proteobacteria. For example, the microbial composition of conventional SPF mice included Staphylococcus, Streptococcus, and Helicobacter, but the clean SPF had none.

It is known that proliferation and activation of intraepithelial lymphocytes (IELs) is an early hallmark of celiac disease. Investigators observed that gluten treatment led to increased IEL counts in germ-free mice but not in clean SPF mice. The gluten-induced IEL response in germ-free mice was accompanied by increased cell death in enterocytes (the cells lining the gastrointestinal tract) as well as anatomical changes in the villi (the tissue protrusions lining the small intestine). The germ-free mice also developed antibodies to a component of gluten, known as gliadin, and displayed pro-inflammatory gliadin-specific T-cell responses. A non-gluten protein, zein, did not affect IEL counts, indicating that the response was gluten specific.

Conversely, in the mice colonized with limited opportunistic bacteria (clean SPF), the development of gluten-induced pathology was prevented compared to germ-free mice or conventional SPF mice with a more diverse microbiota. Interestingly, this protection was suppressed when clean SPF mice were supplemented with an enteroadherent E. coli isolated from a patient with celiac disease.

Gluten-induced pathology (ie, increased IELs in villi tips) was worse in conventional SPF mice than in clean SPF mice. To test if the presence of Proteobacteria such as Helicobacter and Escherichia in the conventional SPF animals affected the pathology, the investigators expanded Proteobacteria in conventional SPF mice using an antibiotic (vancomycin) during the perinatal period. Such expansion worsened gluten-induced pathology in conventional SPF mice, as measured by the number of IELs, possibly due to the presence of more Proteobacteria. "These studies demonstrate that perturbation of early microbial colonization in life and induction of dysbiosis (microbial imbalance inside the body), characterized by increased Proteobacteria, enhances the severity of gluten-induced responses in mice genetically predisposed to gluten sensitivity," noted Dr. Verdu.

In an accompanying Commentary, Robin G. Lorenz, MD, PhD, of the Department of Pathology at the University of Alabama at Birmingham, cautions that the specific role of Proteobacteria should not be over interpreted. Dr. Lorenz writes that these findings "implicate opportunistic pathogens belonging to the Proteobacteria phylum in celiac disease; however, this does not indicate that Proteobacteria cause celiac disease." Instead, there may be multiple potential mechanisms by which Proteobacteria enhance the exposure and immune response to gluten or gliadin, suggests Dr. Lorenz.

Celiac disease affects approximately 1% of the North American population, although it has been estimated that 83% of Americans with celiac disease are undiagnosed or misdiagnosed. According to the National Institute of Diabetes

and Digestive and Kidney Diseases, celiac disease is an immune disorder in which ingestion of gluten, a protein found in wheat, rye, and barley, triggers a series of responses that result in damage to the villi lining the small intestine, which are critical for absorption of nutrients. In addition to digestive symptoms (bloating, chronic diarrhea, constipation, nausea, and vomiting), celiac disease can lead to failure to thrive, slowed growth, and weight loss in children and anemia, bone or joint pain, depression, headaches, and fatigue in adults. Other potential environmental factors related to gluten sensitivity have been explored, such as the timing of exposure to foods containing gluten or breast milk versus formula feeding, but data are inconclusive to date.

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