

Turncoat T cells underlie assault on small intestine amid gluten-induced chaos of celiac disease

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Wheat, barley and rye contain a protein that can produce severe intestinal symptoms in people with celiac disease, and a team of scientists at Columbia University in New York has now identified distinct signatures of immune system cells that drive the disorder.

Celiac disease is marked by turncoat components of the immune system whose proliferation is triggered by dietary [gluten](#), a protein found in specific grains. Ingestion of gluten by those who are predisposed to the disease leads to a heightened inflammatory state, bloating, gas, constipation and even stunted growth among affected children. As serious as those symptoms are, they're just a few on a long and complex list.

Now scientists at the Columbia Center for Translational Immunology have conducted a series of experiments to unravel the immunological puzzle underlying [celiac disease](#), a condition for which there is no cure and the only treatment is the avoidance of gluten. The condition affects one in 100 people globally, according to the World Health Organization.

The disorder's inflammatory effects can have an impact on every organ in the body, and even though patients may be adhering to a [gluten-free diet](#), possibly close to 50% still have symptoms despite having eliminated the protein from daily intake. And while the role of ingested gluten is well known as the trigger of celiac disease, the precise immunological changes in the intestine involving two subsets of T cells had been only loosely defined until now.

Writing in *Science Immunology*, the team of New York City-based researchers has identified several mechanisms and cell groups that drive celiac disease, research that has helped them uncloak some of the persisting immunological mysteries about the condition. The researchers discovered, for example, that consuming gluten induces a rapid reprogramming of the alpha-beta and gamma-delta intraepithelial T cells in the small intestine, two key subsets of T cells.

To better understand the natural history of the disease, lead author of the new research, Dr. Adam Kornberg and colleagues, examined samples of the upper small intestine of 11 patients with active celiac disease who

had not yet begun gluten-free diets. The research also included an additional 19 patients with celiac disease who were previously gluten-free and subsequently re-challenged with gluten, and 17 healthy participants. The team's analyses revealed the unique disease-associated cellular signatures.

"Celiac disease is an autoimmune disease in which intestinal inflammation is induced by dietary gluten," explained Kornberg and a team of colleagues reporting in *Science Immunology*. "We performed multiplexed single-cell analysis of intestinal and gluten-induced peripheral blood T cells from patients in different celiac disease states and healthy controls.

"Untreated, active, and potential celiac disease were associated with an enrichment of activated intestinal T cell populations, including CD4⁺ follicular T helper cells, regulatory T cells, and natural CD8⁺ αβ [alpha-beta] and γδ [gamma-delta] T-intraepithelial cells," Kornberg added.

Indeed, a full repertoire of T cells is involved in the assault on the small intestine, which underlies the seriousness of celiac disease. But gluten directly induces the reprogramming of natural memory αβ and γδ intraepithelial T cells, inducing a detrimental inflammatory state in the gut. For patients in the study who received a gluten challenge—that is, consuming gluten as part of the research—the team found that it triggered a reprogramming of the key T cell subsets.

Prevailing scientific wisdom had long held that cellular mechanisms of the immune system alone caused changes in the intestine—specifically, interactions between helper and intraepithelial T cells lurking in the gut and peripheral blood. Yet, confirming this to be true remained elusive. The new study provides critical new evidence that corroborates this theory regarding the dynamics that drive celiac disease.

The disorder is also known by other names, such as celiac sprue and gluten-sensitive enteropathy. Regardless of what it's called, it damages the lining of the small intestine. To better understand the condition, it's perhaps best to appreciate what occurs in the gut when gluten is present. The immune systems of patients with celiac disease regard gluten as a foreign invader—an antigen—which triggers not only the T cell activity but the accompanying inflammatory response. Cells in the [small intestine](#) of people with celiac disease lose their normal configuration becoming flattened and unable to absorb vitamins and minerals.

Intestinal cells are not only remodeled, their crippled state paves the way to a cascade of medical problems. These conditions can range from anemia and telltale skin rashes on the elbows, knees, torso and scalp to chronic conditions that emerge as a direct consequence of a sustained inflammatory response and nutritional deficiencies. Upon diagnosis, people with celiac disease are commonly found to be deficient in fiber, iron, calcium, magnesium, zinc, folate, niacin, riboflavin, vitamin B12, and vitamin D.

The Celiac Disease Foundation in Woodland Hills, California notes that people who have first-degree relatives with celiac disease have a one in 10 chance of developing the disorder themselves. And while a timely diagnosis is key to controlling the condition, it sometimes takes six to 10 years for patients to receive an accurate diagnosis. Without a timely diagnosis, celiac disease can lead to type 1 diabetes, intestinal cancer, osteoporosis, thyroid disease, multiple sclerosis, infertility and miscarriage, among other medical problems, experts at the foundation say.

They also note that more children have celiac disease than Crohn's, ulcerative colitis and cystic fibrosis combined. But patients with celiac disease also have an increased incidence of microscopic colitis and inflammatory bowel disease. Worse, the later the age of celiac diagnosis,

the greater the chance of developing another autoimmune disorder, numerous studies have shown.

The team at the Columbia Center for Translational Immunology theorizes that the new light they've shed on the T cell repertoire's role in celiac disease may help illuminate similar mechanisms that underlie other autoimmune disorders. "Because [celiac disease] shares traits with other autoimmune diseases, these findings should prove informative beyond celiac disease," Kornberg and the other authors concluded.

More information: Adam Kornberg et al, Gluten induces rapid reprogramming of natural memory $\alpha\beta$ and $\gamma\delta$ intraepithelial T cells to induce cytotoxicity in celiac disease, *Science Immunology* (2023). DOI: [10.1126/sciimmunol.adf4312](https://doi.org/10.1126/sciimmunol.adf4312)

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