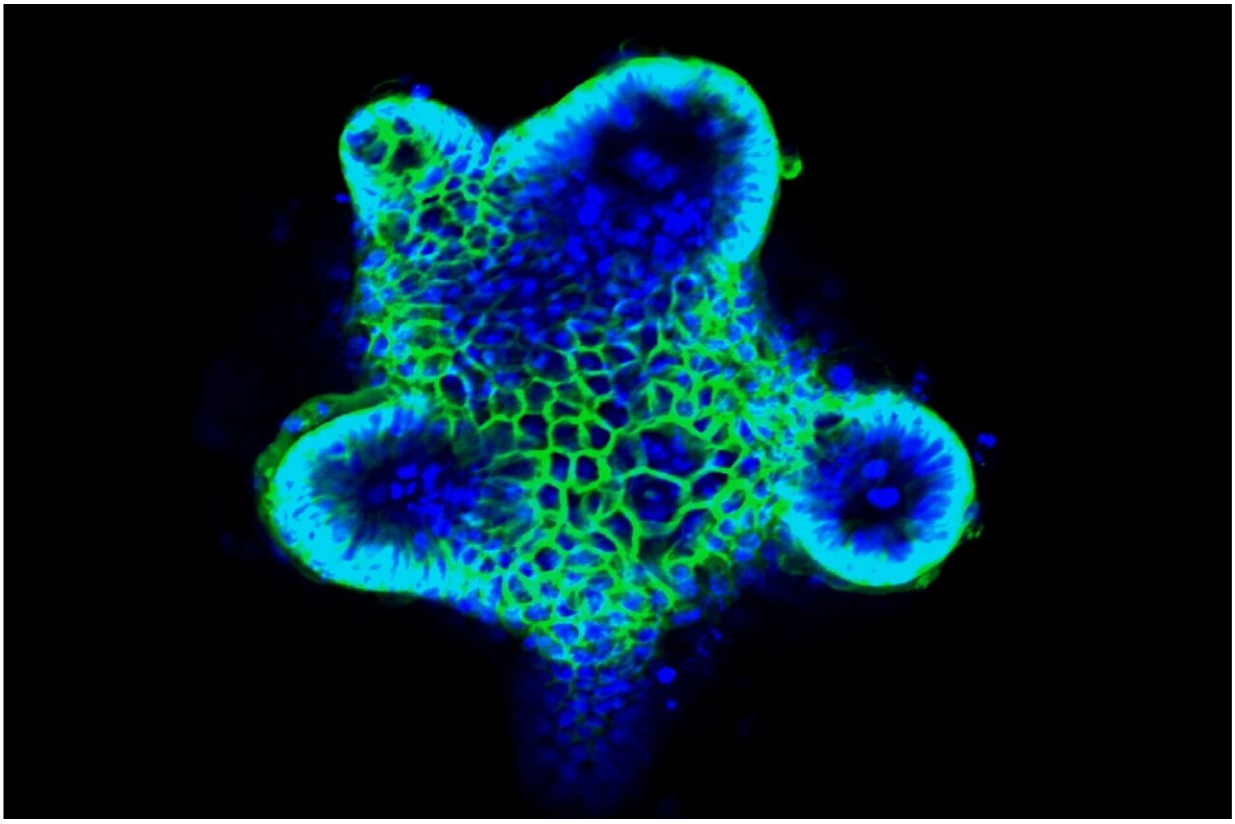
Researchers crack a key celiac mystery: Where the gluten reaction begins

August 9 2024



An organoid the researchers created as a model of the gut lining to study the reaction to gluten in celiac patients. Credit: McMaster University

People with celiac disease must navigate everyday life by avoiding gluten, a protein in wheat, rye and barley which can trigger painful

symptoms in the gut, impede the absorption of nutrients and raise the risk of other serious long-term issues.

The autoimmune disorder affects about 1% of the population. Its rate of occurrence has roughly doubled in the past 25 years, but there is no treatment available.

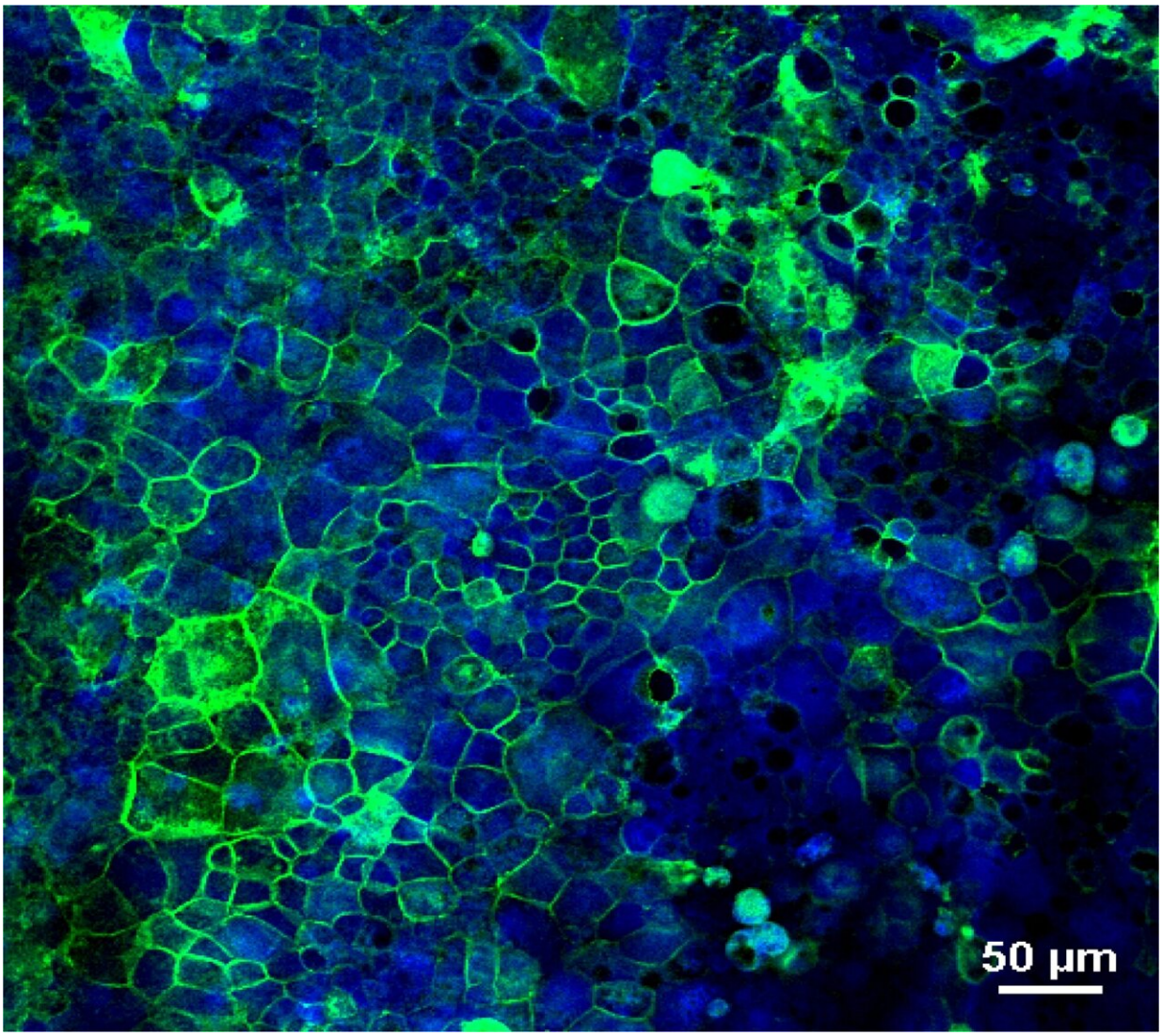
An interdisciplinary team of medical and engineering researchers centered at Canada's McMaster University and including colleagues from the US, Australia, and Argentina, has spent the last six years working to unlock a significant piece of the puzzle in the search for a cure: how and where the gluten response begins.

It had previously been thought that the inflammatory response to gluten occurred inside the gut wall and exclusively involved immune cells, but in a paper published in the journal *Gastroenterology*, the team has shown there is more to the story.

They found that the inner lining of the upper intestine, called the "epithelium" –composed of a variety of cells that are not classically part of the immune system—also plays an active role in directing the inflammatory response to gluten.

Using microscopic biomaterials in the laboratory, the team created a biologically functioning model of the intestinal epithelium which allowed the researchers to isolate the effects of specific molecules in the epithelial cells of people with celiac disease.

The model allowed the researchers to generate and observe the reactions under controlled conditions, an option that is simply not available in extremely complex gut environments of living beings.



A view of the interior of an organoid that researchers created to study the gut's reaction to gluten. Credit: McMaster University

They were able to observe how the molecules alert immune cells to the presence of gluten, and to conclude definitively that the epithelium plays a crucial role in activating the immune system in celiac disease.

Such a mechanism had been postulated before, but was never proven.

Answering this controversial question is expected to advance the development of new drugs.

"The only way we can treat celiac disease today is by fully eliminating gluten from the diet. This is difficult to do, and experts agree that a gluten-free diet is insufficient," says Elena Verdu, a corresponding author on the paper who is a professor of gastroenterology and director of McMaster's Farncombe Family Digestive Health Research Institute.

Precisely locating the spark of the immune response could stimulate research into drug delivery to inhibit this newly found role of the epithelium, using drugs already in clinical trials, Verdu says.

"This allowed us to narrow down the specific cause and effect and prove exactly whether and how the reaction takes place," says Tohid Didar, a corresponding author on the paper and an associate professor at McMaster's School of Biomedical Engineering who holds the Canada Research Chair in Nano-biomaterials.

Another significant finding from the study is that after detecting gluten, the epithelium sends stronger signals to immune cells if pathogens are also present.

This means that in the future it may be possible to detect the pathogen in a person at risk of developing the disease, and inhibit the interactions with gluten and the gut epithelium to prevent the disease, says the paper's lead author, Sara Rahmani, a Ph.D. candidate in the Verdu and Didar labs.

More information: Gluten dependent activation of CD4+ T cells by MHC class II-expressing epithelium, *Gastroenterology* (2024).

Provided by McMaster University