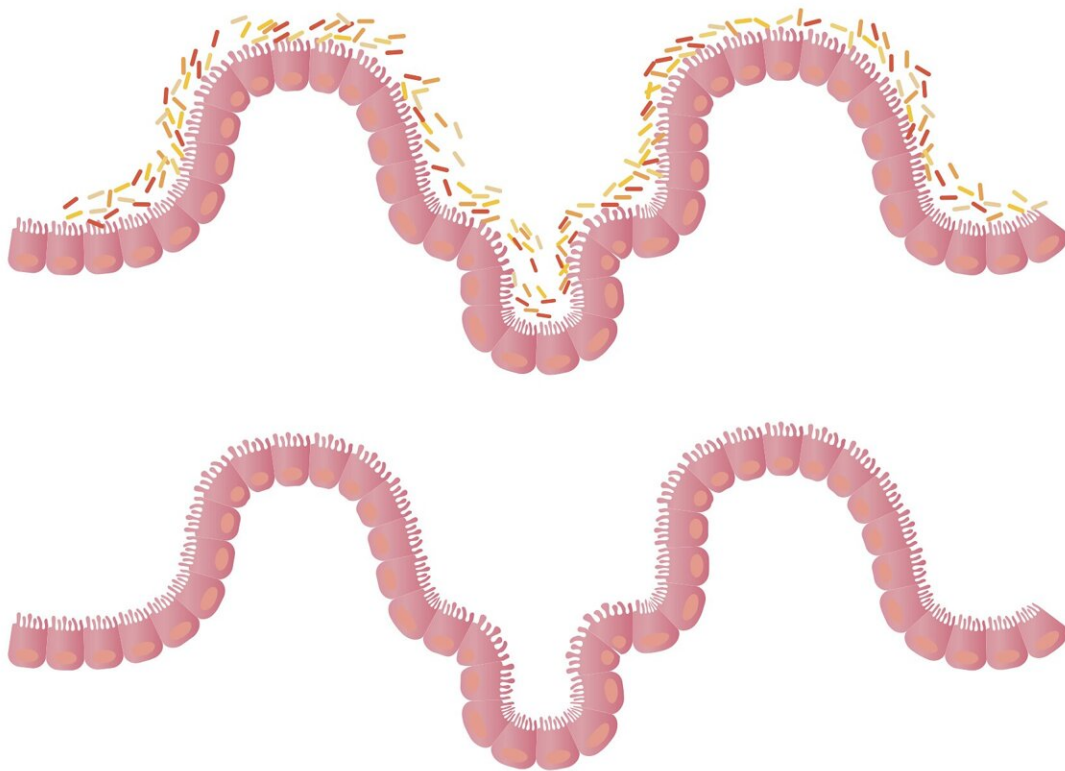


New understanding of the gut immune system may hold promise for Crohn's disease patients

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Tricks played by certain disease-driving gut bacteria might help explain differences in how patients experience Crohn's disease (CD)—a severe and painful chronic inflammatory bowel disease. A new study by researchers from DTU and 3 European universities shows that antibodies in the gut immune system, which line the stomach and intestinal walls and keep harmful bacteria at bay, may be crucial in understanding why some CD patients suffer more than others.

These antibodies—immunoglobulins—are integral to our immune system. They bind to pathogens such as bacteria, viruses, and fungi that enter the gut and cover parts of their cell surface. The term for this is "coating," which helps in several ways. For one, the coating effectively inhibits the bacteria from spreading and makes them lump together under certain circumstances. Also, it alerts the rest of the immune system and marks the pathogens for destruction.

The main issue regarding Crohn's disease, specifically, is that there isn't enough evidence to explain precisely why some people end up with severe inflammation in their gut. We also do not know the influence bacterial coating with different antibody types may have on this. Hence, there is currently no cure for Crohn's disease.

"We know that some bacteria can hide from the immune system, and in this study, we find that especially two—*Campylobacter* and *Mannheimia*—seem to be prevalent in severe cases. They appear to hold properties that allow them to escape from antibody coating while simultaneously being able to activate and cause an uncontrolled inflammation," says Susanne Brix Pedersen, a professor at DTU Bioengineering, Technical University of Denmark.

She is the corresponding author of the study "Specific gut pathobionts escape antibody coating and are enriched during flares in patients with severe Crohn's disease," recently [published](#) in the journal *Gut*.

The study shows that the immune system of patients with severe Crohn's disease holds a remarkably high coating of certain gut bacteria with a specific antibody type indicative of inflammation. At the same time, *Campylobacter* and *Mannheimia* can circumvent this coating.

An overlooked antibody is active in severe cases

Several types of antibodies fight off pathogens, and the primary antibody responsible for coating bacteria in the gut is Immunoglobulin A (IgA). Limited effort has been put into mapping out the roles of other antibodies, such as IgM and IgG, at mucosal surfaces.

However, the new paper shows that IgG plays a significant role in the gut immune system, especially concerning severe cases of Crohn's disease. This is somewhat surprising since IgG is found mainly in the blood and other body fluids and is generally considered a second line of defense against pathogens, whereas IgA is regarded as the primary antibody to prevent incoming pathogens from entering the body and bloodstream via the gut and other mucosal surfaces.

IgG exists as four subtypes: IgG 1, 2, 3, and 4. They serve different purposes in our immune system. While the paper shows that bacterial coating with IgG1 and IgG4 was indistinguishable between patients with Crohn's disease and healthy controls, the fraction of patients with severe Crohn's disease exhibited higher bacterial coating with IgG2.

The immune system of patients with severe CD is thus acting differently from healthy individuals *and* patients with less severe CD. This is important information since it may, with time, turn out that clinicians can use this altered state to have a so-called 'biomarker'—a measurable, biological indicator of more serious cases of CD.

"Although it is a bit weird to try and differentiate between people with

Crohn's disease because everyone is suffering, we do show that the level of IgG2 bacterial coating in Crohn's patients can be used to differentiate between those who have severe disease and those who may have a slightly milder disease course."

"It would be a bit far-fetched to call it a biomarker. Still, we do show a strong association between IgG2 bacterial coating and disease severity, and therefore have a good indicator that IgG2 plays a substantial role in the body's defense against bacterial infections associated with severe Crohn's disease," says Carsten Eriksen, first author of the paper and a postdoc at DTU Bioengineering and the Center of Excellence PREDICT.

He explains that these heightened levels of IgG2 coating of bacteria are rarely found in patients with milder symptoms or in people who don't have Crohn's disease.

Several possible outcomes

Further studies are needed to evaluate exactly how these results may be used to lessen the symptoms of severe cases of CD, but Susanne Brix Pedersen explains that the fact that we now know these bacteria can circumvent our immune system in this way provides an angle to explore further which other invasive bacteria might be able to do the same.

And also to explore how to produce constructs that mimic the effects of [antibodies](#), thereby hindering the targeted pathogens from causing inflammation. This approach may achieve a targeted coating of invasive bacteria responsible for worsening CD symptoms.

"Suppose we could provide the coating the [immune system](#) cannot handle alone. Then you might not have to take all sorts of other medications because you remove the thing causing the inflammation,"

she says.

"Today, we have no way of knowing who will end up with severe Crohn's and who will have a less serious disease course. Crudely put, we only know for sure just before they are on the operating table. However, if we could track the appearance of bacterial IgG2 coating in the gut, we may be able to use it as an actual biomarker and differentiate between patients," Eriksen says.

"In any case, I imagine clinicians looking at this research would be able to see that it is associated with several clinical outcomes, and they may find other ways to translate our results into the clinic to benefit patients."

More information: Carsten Eriksen et al, Specific gut pathobionts escape antibody coating and are enriched during flares in patients with severe Crohn's disease, *Gut* (2023). [DOI: 10.1136/gutjnl-2023-330677](https://doi.org/10.1136/gutjnl-2023-330677)

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