Study pinpoints specialized gut immune cells that can limit progression of inflammatory bowel disease

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Researchers at the Francis Crick Institute, King's College London and Guy's and St Thomas' NHS Foundation Trust have characterized a specialized type of immune cell, which plays a key role in protecting and repairing the cells in the healthy human gut.

These protective immune cells are depleted in inflammatory bowel disease (IBD), leaving patients vulnerable to disease progression and severe complications. The findings could lead to better clinical management and treatment options for people living with these conditions.

IBD is the collective term for Crohn's disease and ulcerative colitis, two currently incurable conditions which involve excessive inflammation in the gut, causing debilitating symptoms like pain and diarrhea. IBD is common, affecting 1 in 125 people in the UK, and its incidence is growing globally. Often starting in childhood and early adult life, it impacts some of the most socially and economically important periods of a person's life.

As part of their study, published today in *Science*, the researchers investigated tissue from over 150 patients at Guy's and St Thomas' NHS Foundation Trust, dissecting a major population of T cells called gamma delta (γδ) T cells in the colons of people with healthy guts and people with IBD.

In healthy guts, there was a unique specialized subset of gamma delta cells, termed V-gamma-4 (Vg4) cells, that intriguingly were significantly

altered and often conspicuously depleted in inflamed IBD samples.

Prior to this work, the team at the Crick and King's had identified molecules in the healthy gut epithelium (the cells lining the gut walls) which directly interact with Vg4 T cells. So, in this new study they tested whether losing this normal interaction between Vg4 T cells and the epithelium was underpinning disease.

To do this, the team looked at relatively rare individuals carrying a gene that severely limits this interaction, and found that whereas carrying this gene didn't increase the chance of developing IBD, for those who already developed Crohn's Disease, it significantly increased the risk of disease progression and the development of severe complications.

The researchers also observed that, in people whose inflammation had improved, those with restored Vg4 T cell function were less likely to relapse than those who did not. This suggests that assessing the status of Vg4 T cells could be a useful biomarker for disease progression.

Robin Dart, consultant gastroenterologist at Guy's and St Thomas' NHS Foundation Trust, said, "There's currently no cure for IBD, and for a significant proportion of the patients I treat, persistent relapses are distressing, severely impacting their day-to-day lives. Treatments tend to focus on reducing inflammation, but despite improvements in therapy, relapse rates remain high. So, we need to start targeting other areas, such as repairing the gut barrier, and γδ T cells, particularly Vg4 cells, may offer a way to do this."

People living with IBD are at an increased risk of developing colorectal cancer, especially when the disease is uncontrolled. In some cases, people develop cancerous or pre-cancerous gut lesions that need surgical removal.

Adrian Hayday, principal group leader of the Immunosurveillance Laboratory at the Crick, Kay Glendinning Professor of Immunobiology at King's College London, and leader of the study, said, "The links between uncontrolled IBD and particularly severe forms of colon cancer aren't well understood. So, it's fascinating that the key immune cell subset that we have identified as missing in IBD, may also be the same as the gut γδ T cells described by another group in Milan as having profound potential to attack colon cancer cells. We think that defects in these cells could conceivably link the two diseases."

"I see gut γδ T cells as a vacuum cleaner clearing up damage done by infections and toxins coming in through a door which has to be kept open in order for food to pass through. If the γδ T cells aren't working properly, damage accumulates, driving inflammation and potentially cancerous changes that can build to unchecked levels."

The next steps for the research are to investigate potential drug targets for the interactions between γδ T cell and the epithelial cells and to refine approaches for routinely monitoring gut γδ T cells as a much-needed marker for IBD progression versus recovery. The broader implications of this immune cell biology on different body surfaces should also be a focus.

This research took place with thanks to all consenting patients and to the NIHR BioResource for support in providing additional samples.

More information: Robin J. Dart et al, Conserved γδ T cell selection by BTNL proteins limits progression of human inflammatory bowel disease, *Science* (2023). DOI: 10.1126/science.adh0301. www.science.org/doi/10.1126/science.adh0301

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