Promising new lead in Crohn's disease

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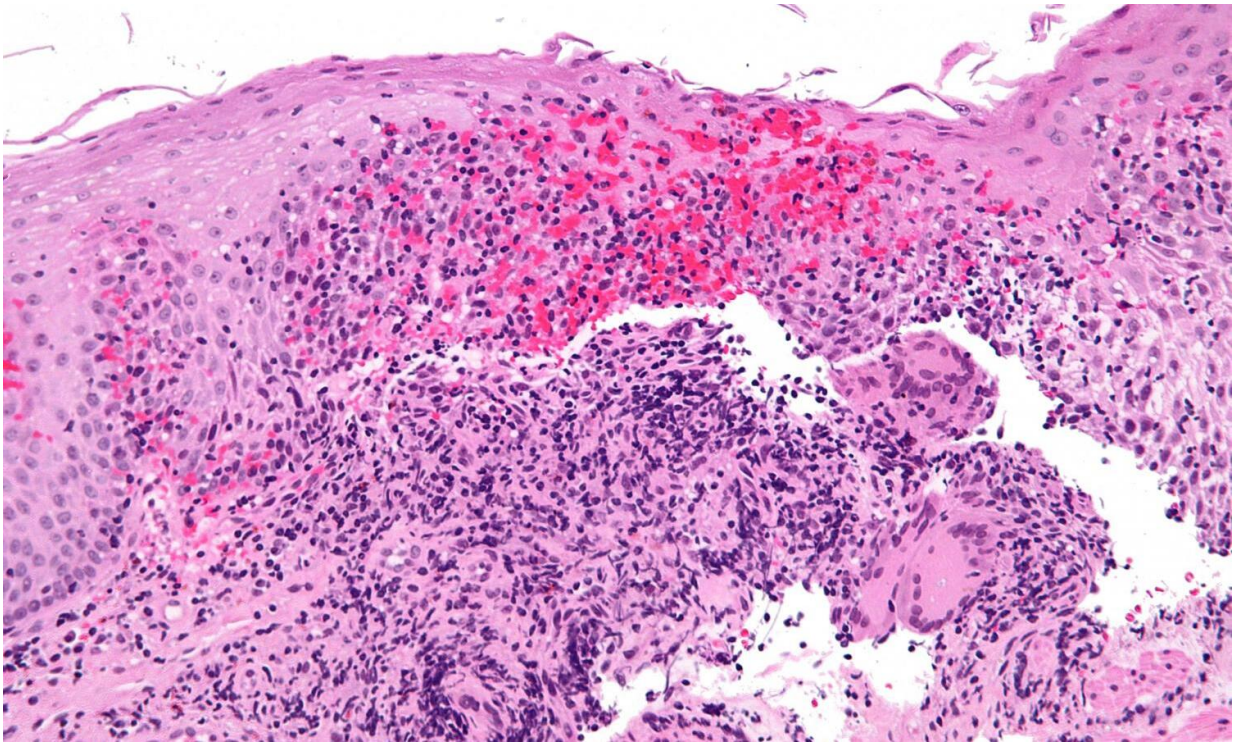

High magnification micrograph of Crohn's disease. Biopsy of esophagus. H&E stain. Credit: Nephron/Wikipedia

QIMR Berghofer researchers have identified a key driver of the aggressive gut disorder, Crohn's disease, a finding that could eventually lead to new treatments for the often-debilitating condition.

Crohn's disease—also known as inflammatory bowel disease—is

incurable and affects about 35,000 people in Australia.

QIMR Berghofer scientists found the protein PD-L2 was overactive in people with Crohn's disease.

The study was led by the head of the Molecular Immunology group, Dr. Michelle Wykes, and Dr. Graham Radford-Smith, who leads the Institute's Gut Health Laboratory and is a Deputy Director at the Royal Brisbane and Women's Hospital (RBWH) Department of Gastroenterology.

PD-L2 acts as a gatekeeper molecule in the body's immune cells, deciding if other molecules in the cells should react to a threat.

Dr. Wykes said her previous work examining the role PD-L2 played in diseases such as cancer and malaria led her to look at the part it played in Crohn's disease.

"Our past studies showed the PD-L2 protein was missing in the blood and tissue of cancer and malaria patients. This meant that other inflammation-suppressing molecules weren't being controlled, so they were suppressing the immune system too much," Dr. Wykes said.

"That's when we asked ourselves if the opposite was the case in Crohn's disease, which is characterized by excessive inflammation.

"And that's exactly what we found—that there was an excess of these PD-L2 "gatekeeper" proteins in the blood of Crohn's patients. This overabundance was obviously stopping other molecules from doing their jobs in suppressing inflammation.

"This was something that no one else had thought to look for, or had looked at in the same way."

The researchers examined blood and tissue samples from 29 patients who had been treated for Crohn's disease at the RBWH.

Lab testing showed that if antibodies that control PD-L2 were introduced to Crohn's disease cells from patients, then inflammation could be slowed down.

Dr. Radford-Smith said the study results could provide scientists with a new target for potential treatments.

"Crohn's disease is a chronic inflammatory disorder where the body appears to be generating its own inflammation against itself, and that's one of the reasons why the role of the "gatekeeper" molecule PD-L2 is so relevant," Dr. Radford-Smith said.

"This study is another important step in our understanding of Crohn's disease and opens up a new area to investigate.

"If we can understand why inflammation occurs in Crohn's patients, then we can work out strategies to treat, and possibly in the future, prevent the disease."

The study found there were also fewer immune-controlling dendritic cells in the lining of the guts of people with Crohn's disease.

"Our priority now is to try to secure funding to extend this research using a much larger group of patients to really test this new and important finding," Dr. Wykes said.

"Understanding inflammation in Crohn's will also add to our growing bank of knowledge that inflammation is a factor in many diseases.

"This is just the start. We believe that understanding this protein will

have big implications for a range of autoimmune conditions."

The study findings have been published in the journal *Clinical and Translational Immunology*.

More information: Rebecca Faleiro et al. Crohn's disease is facilitated by a disturbance of programmed death-1 ligand 2 on blood dendritic cells, *Clinical & Translational Immunology* (2019). DOI: 10.1002/cti2.1071