Scientists uncover the process behind protein mutations that impact gut health

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A new study led by researchers at St. Michael's Hospital and the Princess Margaret Cancer Centre in Canada and Zhejiang University School of Medicine in China has uncovered why a protein mutation that causes inflammatory bowel diseases is dysfunctional.

Published today in *Science*, the research focused on nucleotide-binding oligomerization domain-containing protein 1 and 2. Known as NOD 1 and NOD 2, these are protein receptors encoded by the NOD genes. They recognize bacterial products and prompt the immune system to act quickly to fight infection. Some variants of NOD 1 and NOD 2 cause a lack of immune response, while others overstimulate the immune system. Differences in the NOD 2 gene are associated with many diseases, including inflammatory bowel disease (IBD).

IBD causes sections of the gastrointestinal tract to become irritated and ulcerated, causing pain and discomfort to patients. Every year, more than 10,000 Canadians are diagnosed with these types of disorders.

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The team set out to understand the molecular process that determines how NOD 1 and NOD 2 recognize bacteria and how this impacts their ability to signal an appropriate immune response. The scientists collaborated over four years to uncover this function, and Dr. Fairn credits their success to a multidisciplinary and multinational effort that resulted in rigorous science.

They found that palmitoylation, the process by which fatty acids attach to proteins to alter the protein's location within cells, is essential to elicit

immune signaling of NOD 1 and NOD 2. In particular, they identified one enzyme that helps in the attachment of fatty acids to proteins—known as ZDHHC5—as the key to unlocking this process that alters NOD 1 and NOD 2 function.

"Our findings point to the potential importance of palmitoylation—too much or too little of this process can impact inflammation," Dr. Fairn said. "Now, the question is whether there is potential to fine tune this process to one day lead to treatment for a variety of inflammatory disorders."

The multinational research team hopes this work is a stepping stone to uncovering more about the molecular reasons behind why variants of these proteins impact gut health.

"There is more to the story—targeting NOD-based signaling is only one potential intervention of many that would be needed for a person with chronic inflammation and altered microbiome" said Dr. Fairn.

"Our striking observations bring us one step closer to a deeper understanding of the science behind diseases like Crohn's."

More information: "Palmitoylation of NOD1 and NOD2 is required for bacterial sensing" *Science* (2019). science.sciencemag.org/cgi/doi … 1126/science.aau6391

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