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Researchers describe strategies to decrease immune responses in IBD

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New research led by scientists at Beth Israel Deaconess Medical Center (BIDMC) helps explain the role of an immunosuppressive pathway associated with inflammatory bowel disease (IBD), a condition that develops in genetically susceptible individuals when the body's immune system overreacts to intestinal tissue, luminal bacteria or both.

The findings, published online in the journal *Nature Communications*, offer novel insights into the expression of the ecto-enzyme CD39 on immune cells and further illuminate the role of purinergic signaling in IBD.

"Adenosine triphosphate, or ATP, is the energy currency in all cells and is essential for all cellular metabolic processes," said senior author Simon C. Robson, MB, ChB, PhD, Chief of the Division of Gastroenterology at BIDMC and Charlotte F. and Irving W. Rabb Professor of Medicine at Harvard Medical School. "However, when ATP or related purines are released from cells or platelets—as might occur in the case of vascular or tissue injury—this process triggers inflammation and causes immune cells to become activated."

Regulatory immune cells control the immune system to ensure effector immune cells become fully functional only when needed to fight infections and defend against other attacks. When effector immune cells are inappropriately activated and not "regulated," these cells release high levels of cytokines, which in turn promote inflammation.

The interferon (IFN) gamma cytokine plays a key role in Crohn's disease and other autoimmune disorders in which the body's immune system attacks itself. "Chronic autoimmune diseases cause severe pain, morbidity, disability and—in the case of Crohn's disease—incapacitating intestinal and liver illness,as a consequence of unfettered inflammation," said Robson.

For the past decade, Robson's laboratory has been studying immune cell ectonucleotidases (CD39 and ENTPD family members as well as CD73) that regulate purinergic signaling through the catalytic conversion of proinflammatory extracellular ATP to immunosuppressive nucleosides, such as adenosine. In prior work, Robson, Francisco Quintana and other colleagues at BIDMC and Brigham and Women's Hospital demonstrated that these ectoenzymes are expressed at high levels by CD4+ FoxP3+ T regulatory cells, type 1 regulatory T cells and dendritic cells.

In this new paper, the authors investigated the expression of CD39 on Type 1 CD8+ (Tc1) immune cells. These Tc1 cells release large amounts of IFN gamma and, together with CD4 T cells, are thought to participate in immune responses in IBD.

Reactive oxygen species (chemically reactive molecules containing oxygen known as ROS) have also been shown to modulate CD4 T-cell function and proliferation. How ROS might regulate CD8 T-cell responses and purinergic responses had not previously been explored.

"Here, we have established that the generation of ROS linked to IFN gamma induction in CD8+ T cells is further accompanied by NADH oxidase-dependent CD39 expression, and the consequent upregulation [increased cellular response] of CD39, in turn, suppresses and inhibits interferon gamma production in neighboring CD39-CD8+ T cells," said Robson.

"In general, expression of CD39 is regulatory and anti-inflammatory with salutary effects in acute inflammation," he added. "This ecto-enzyme has the capacity to regulate the immune response, whether expressed on the endothelium lining the blood vessels or immune cells. CD39 is also a marker of cell activation and has been recently linked to immune exhaustion."

It is widely accepted that when an immune cell becomes regulatory, it can suppress activation. CD39 expression allows for the regulation of purinergic signaling to occur by scavenging extracellular nucleotides and generation of adenosine.

"We have now shown that modulation of purinergic signaling is applicable not only to CD4 T cells but also to CD8 T cells," said Robson. "Our studies to date suggest that strategies to regulate purinergic signaling and boost adenosine generation would ameliorate inflammation, as well as Tc1 immune responses in patients with interferon-gamma-dominant diseases, such as Crohn's disease."

Provided by Beth Israel Deaconess Medical Center