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Deficient protein GM-CSF production found to impair gut's immune tolerance

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The protein GM-CSF plays a critical role in maintaining immune tolerance in the gut, with defects in the protein increasing the susceptibility to inflammatory bowel diseases (IBD), according to a new mouse study by a team of researchers from the Icahn School of Medicine at Mount Sinai. IBD is a severe intestinal disease characterized by chronic intestinal inflammation that results from a dysregulated immune response to microbes and food antigens. Writing in the peer reviewed journal *Science* published online March 13, 2014, the research team writes that this advances our understanding of how commensal microbes can regulate intestinal immunity and should pave the wave for identifying new drug targets.

"These results are highly relevant to clinical inflammatory bowel diseases because GMSCF-impaired function is now emerging as one of the best predictors of IBD severity," said the study's senior author, Miriam Merad, MD, PhD, Professor in the Department of Oncological Sciences, the Tisch Cancer Institute and the Immunology Institute, at the Icahn School of Medicine at Mount Sinai.

GM-CSF is a cytokine that promotes the development and function of a group of gut resident macrophages and dendritic cells. Although GMCSF is mostly known for its role in inflammation, Dr. Merad's laboratory discovered that GM-CSF is produced in the normal gut by specialized cells called innate lymphocyte cells (ILCs) in response to microbiota signals. Strikingly, they found that microbiota-induced GM-CSF was required to imprint gut tissue resident macrophages and

dendritic cells with regulatory function that was critical to protect against inflammation of the gut. Deletion of the GM-CSF gene in the mouse led to reduction and impaired regulatory function of gut tissue macrophages and dendritic cells which compromised induction of tolerance to food antigens and increased mice susceptibility to IBD.

"These results represent a significant advance in our understanding of how commensal microbes can regulate host intestinal immune responses and suggest that the identification of downstream targets in macrophages and dendritic cells along the GM-CSF axis can help the rationale design of novel strategies for the treatment of IBD patients with defective GM-CSF function," explained Dr. Merad.

Drs. Merad and Mortha are now developing a multiscale approach to identify GM-CSF downstream targets using macrophages and dendritic cells isolated from GM-CSF deficient mice and exposed to recombinant GMCSF. The regulatory function of novel targets will be validated in collaboration with Judy H. Cho, MD, Ward-Coleman Professor of Medicine and Genetics and Genomic Sciences, and Assistant Chief of Research in the Gastrointestinal Division, and Jean Federic Colombel, MD, Professor of Medicine and Director of the Leona M. and Harry B. Helmsley Charitable Trust Inflammatory Bowel Disease Center, at they Icahn School of Medicine at Mount Sinai. They will study human macrophages and dendritic cells isolated from IBD patients with defective GM-CSF function, "The approach represents a step forward in personalizing how we treat patients with IBD," said Dr. Colombel.

Provided by The Mount Sinai Hospital