# Study reveals genetic and cellular mechanisms of Crohn's disease

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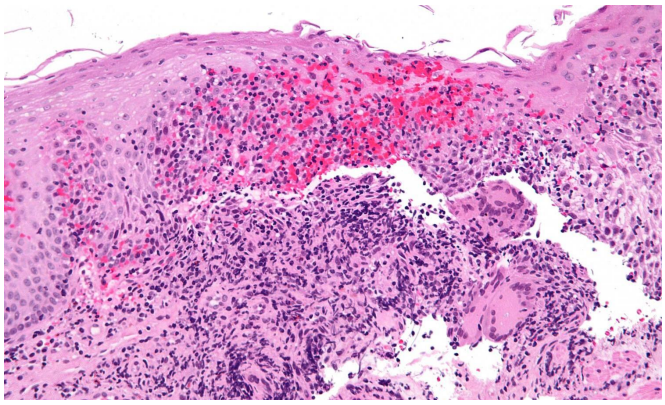

High magnification micrograph of Crohn's disease. Biopsy of esophagus. H&E stain. Credit: Nephron/Wikipedia

Mount Sinai researchers have identified genetic and cellular mechanisms of Crohn's disease, providing new insights for future treatments that could offer a tailored approach to patients with the chronic inflammatory disease, according to a study published in *Nature* on March 31.

The researchers found that blocking the common cytokine receptor subunit gp130 may benefit some patients with Crohn's disease and could complement a standard treatment for moderate to severe Crohn's disease known as anti-tumor necrosis factor (TNF) treatment. This treatment uses medications known as TNF inhibitors to block white blood cells producing the protein TNF, which causes the inflammation.

Crohn's disease is a chronic inflammatory intestinal disease with frequent abnormal healing and complications that narrow or constrict passage through the digestive tract. Complications associated with Crohn's disease are driven by communication between cells called macrophages that detect and destroy harmful bacteria or organisms, and cells known as fibroblasts that aid with wound healing. Mount Sinai researchers analyzed inflamed and normal tissues of the small intestine in humans, and zebrafish models of intestinal injury, and showed that a dysregulated macrophage-fibroblast niche can be driven by Crohn's disease-associated mutations in the gene *NOD2*.

These findings are reported on the 20th anniversary of the discovery by Judy H. Cho, MD, Dean of Translational Genetics and Director of The Charles Bronfman Institute for Personalized Medicine at the Icahn School of Medicine at Mount Sinai, her colleagues, and others that genetic variants that cause the protein produced by *NOD2* to lose function are associated with increased risk for Crohn's disease. *NOD2* recognizes bacterial components, and the intestinal immune system is exposed to high bacterial concentrations in both healthy and diseased states. However, the reasons why mutations in *NOD2* cause increased risk for Crohn's disease and why some patients do not respond to anti-TNF medications remained incompletely defined until now. Patients carrying *NOD2* mutations have increased activated fibroblast and macrophage gene expression, and in particular, elevated gp130-related gene expression. Given this finding, the researchers believe that blocking the protein gp130 may help patients who are nonresponsive to the treatment of anti-TNF medications.

"Our work defines a completely new mechanism whereby *NOD2* mutations confer risk, namely through altered differentiation of newly recruited blood monocytes over time," says Dr. Cho. "It sharpens current research efforts involved in serial tissue and blood analyses to define how non-response or loss-of-response to anti-TNF therapies may be improved."

Shikha Nayar, the study's first author and a Ph.D. candidate in Dr. Cho's lab at Icahn Mount Sinai,

said the findings could provide a more custom-made approach to future patient care. "We've developed novel in vivo and in vitro models to define mechanisms and timing of disease progression," she says. "These studies may help tailor treatments more effectively for Crohn's disease patients carrying *NOD2* mutations and elevated signatures we have described."

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