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Immune system malfunction may trigger inflammatory bowel disease

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In a finding that could have implications for the prevention and treatment of inflammatory bowel disease (IBD), Yale University researchers have identified a previously unknown sensor regulating the composition of certain intestinal bacterial microflora (the microbes that live in our gut). They also found the absence of this regulating sensor results in a dramatic alteration of the microbial environment of the intestines – increasing the risk of developing IBD. The study is available online in *Cell* on May 12, and will appear in the May 27 print edition.

The team's research focused on the protein NLRP6. It forms a multi-protein complex called an inflammasome, which regulates the function of many cell types during normal states and inflammation. The action of NLRP6 or the NLRP6 inflammasome were previously not known. Working with genetically-altered mice, the Yale team showed how a deficiency of this protein complex in the epithelial cells that line the the colon resulted in distinct alterations in the normally balanced microbial community in the intestines, allowing the growth of defined bacteria that set the stage for colitis and other forms of IBD.

Further, researchers found that the altered microbial environment was transmissible to genetically unaltered mice that were bred or housed together with the defective mice, causing severe IBD in these mice as well. According to lead author Richard A. Flavell, professor and chair of the Department of Immunology at Yale School of Medicine and a Howard Hughes Medical Institute investigator, "The finding could have profound implications in our understanding on how IBD is initiated and

the involvement of the microflora in its pathogenesis, and may direct novel therapies for the prevention and treatment of IBD."

Moreover, Flavell said, “The unexpected transmissibility of the flora, resulting in such dramatic alteration in the host immune response, will challenge the interpretation of disease phenotypes developing in gene knock-out mice and may become a new standard for similar studies in the future. Furthermore, the fact that IBD may be transmitted from a susceptible mouse to an ostensibly normal one has potentially profound implications for IBD and other human diseases in which the microbiota contribute.

In recent years, the intestinal microbiota (microbial environment of the gut) has been recognized as an important regulator of immune functions even at locations far from the intestine itself. “This study highlights how malfunction in one pathway may lead to development of IBD in mice through its effects on environmental factors such as the composition of the gut microflora,” Flavell said. “We are conducting studies to investigate more examples of such effects in other diseases and whether similar mutations may be found in humans as well.”

The lead researchers and authors in this project are Eran Elinav and Till Strowig, postdoctoral researchers at the Flavell lab from Israel and Germany, respectively. Other authors are Jorge Henao-Mejia, Christoph A. Thaiss, Stephanie C. Eisenbarth, Carmen J. Booth and David R. Peaper of Yale School of Medicine; Andrew L. Kau and Jeffrey I. Gordon of Washington University School of Medicine; and John Bertin of GlaxoSmithKline.

Provided by Yale University

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