Medical Xpress

Study identifies a genetic link to susceptibility and resistance to inflammatory bowel disease

April 13 2017

Inflammatory bowel disease (IBD), characterized by chronic relapsing inflammation of the gut, is a common problem in the industrialized world. However, how IBD develops remains unknown. There is currently no cure and treatment options are costly and limited to alleviating symptoms. A new study in *The American Journal of Pathology* reveals that the Cd14 gene is a protective factor in experimental inflammatory bowel disease by enhancing the intestinal barrier function.

It is well known that patients' genetics as well as microbial factors contribute to IBD. Researchers identified Cd14 in a genetic screen in a mouse model system for IBD. They showed that the Cd14 molecule plays a protective role in their model system of intestinal function in mice. Mice with Cd14 deficiency developed more severe inflammation

of the gut with destabilization of the intestinal barrier compared to controls, whereas stimulation of Cd14 expression strengthened the barrier's integrity.

"Our understanding of the microbiome and its interaction with host genetic factors is increasing dramatically, especially in the pathogenesis of IBD. Cd14 is involved in the detection of bacterial factors and has been identified as a candidate gene in genetic screens. Our study helps to understand the link between genetic susceptibility and microbial alterations in the gut in IBD," explained lead investigator André Bleich, PhD, Professor and Director, Institute for Laboratory Animal Science, Hannover Medical School, Hannover (Germany).

As a part of the innate immune system, Cd14 helps the body respond to bacterial infections by producing a protein that binds to lipopolysaccharides within the outer membranes of some bacteria. The protein can be found attached to cell surfaces or secreted in soluble form. The Cd14 protein is found among different cell types, including epithelia, blood, and dendritic cells. In mice, Cd14 levels can depend upon the strain of mice and the location of the tissue, with the highest concentration found in the furthest portions of the intestine, which contain the greatest number of bacteria.

Investigators examined the effects of Cd14 deficiency on intestinal function and studied both an acute and chronic model of colitis. In the acute model, the Cd14-deficient mice showed greater weight reduction and intestinal barrier disruption than controls, including more severe intestinal lesions and ulcerations. They also secreted higher amounts of inflammatory cytokines—interferon-? and tumor necrosis factor-α. "Cd14 seems to play a pivotal role in the maintenance of barrier integrity. Further analyses suggested that the presence of Cd14 becomes even more important when the epithelial layer is disturbed rather than during steady-state conditions," commented Dr. Bleich.

In contrast, stimulation of Cd14 expression played a protective role on the intestine. After administration of zinc, which increases Cd14 levels in a transgenic mouse model, the investigators found less inflammation in the colon and reduced levels of pro-inflammatory cytokines.

According to Dr. Bleich and his co-investigators, "Epithelial barrier function is predominantly dependent on tight junction proteins, which regulate transport into and between cells. Loss of gut barrier integrity, initiated by bacteria or by treatment with a chemical, can result in bacterial invasion and inflammation. Pro-inflammatory cytokines also cause dysregulation of barrier permeability during inflammation. Our work provides evidence that Cd14 is pivotal for regulating tight junction proteins by reducing the expression of pro-inflammatory cytokine. Our findings suggest that soluble Cd14 could be an interesting new therapeutic target for future clinical research."

More information: Stephanie Buchheister et al, CD14 Plays a Protective Role in Experimental Inflammatory Bowel Disease by Enhancing Intestinal Barrier Function, *The American Journal of Pathology* (2017). DOI: 10.1016/j.ajpath.2017.01.012

Provided by Elsevier

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