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Two genes linked to inflammatory bowel disease

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Inflammatory Bowel Disease (IBD), a group of chronic inflammatory disorders of the intestine that result in painful and debilitating complications, affects over 1.4 million people in the U.S., and while there are treatments to reduce inflammation for patients, there is no cure.

Now, Cincinnati Cancer Center and University of Cincinnati (UC) Cancer Institute researcher Susan Waltz, PhD, and scientists in her lab have done what is believed to be the first direct genetic study to document the important function for the Ron receptor, a cell surface protein often found in certain cancers, and its genetic growth factor, responsible for stimulating cell growth, in the development and progression of IBD.

These results are published in the advance online edition of the *American Journal of Physiology-Gastrointestinal and Liver Physiology*.

"Genome-wide linkage studies have identified the Ron receptor tyrosine kinase and its hepatocyte growth factor-like protein (HGFL) as genes highly associated with IBD," says Waltz, professor in the department of cancer biology at UC. "However, only scant information exists on the role of Ron or HGFL in IBD. Based on the linkage of Ron to IBD, we examined the biological role of Ron in colitis."

Colitis is swelling of the large intestine (colon) and is a potentially pre-cancerous condition.

Waltz says that due to her lab's cancer-related expertise with studying Ron and HGFL, she and her colleagues had all of the tools to translate their knowledge of the study of these proteins in IBD.

In the study, Waltz and Rishikesh Kulkarni, PhD, a postdoctoral fellow in UC's department of cancer biology, used animal models with colitis. A genetic knockout group did not have Ron; the other did.

"We found that genetic loss of Ron led to aggressive inflammation and damage to the colon of models with IBD," she says.

Loss of Ron also led to significantly reduced body weight and a dramatic reduction in colon tissue cell growth as well as increased pro-inflammatory cytokine (proteins important in cell signaling) production, which was associated with changes in important signaling pathways known to regulate IBD.

"In addition, there are a number of small changes called single nucleotide polymorphisms (SNP) in humans which map to both the Ron and HGFL gene and have been identified to strongly associate IBD disease in humans," Waltz says. "Our studies suggest that these SNPs may reduce the function of Ron and HGFL leading to chronic intestinal inflammation and damage.

"With the knowledge that we've gained in studying these proteins in cancer biology, we hope this information may be translated to help patients with Crohn's disease and ulcerative colitis. Further studies on the Ron signaling pathway are needed and could reveal an important new target for these conditions."

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