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Enzyme involved in inflammatory bowel disease discovered

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Researchers at Penn State College of Medicine, working with biochemists, geneticists and clinicians at the University of Bern, Switzerland and in the United Kingdom, have discovered an enzyme that has a key role in inflammatory bowel disease (IBD). The team, co-led by Judith Bond, Ph.D., Distinguished Professor and Chair of Biochemistry and Molecular Biology at Penn State College of Medicine, and Daniel Lottaz, Department of Rheumatology and Clinical Immunology at the University of Bern, Switzerland, could potentially lead to therapies to help the half-a-million Americans affected by ulcerative colitis and Crohn's disease, collectively referred to as IBD.

The enzyme, coded for by the MEP1A gene, is a zinc-containing metalloprotease called meprin, and is abundant in the intestine. A protease is an enzyme that breaks down proteins in the body.

Researchers at Penn State College of Medicine studied the role of meprin in IBD using genetically altered mice lacking the ability to produce the enzyme in collaboration with colleagues in Switzerland who studied the enzyme in IBD patients. Meprin is abundant in the latter part of the small intestine, or terminal ileum, and is also present in the large intestine at a lower level. The European researchers found an alteration in the meprin gene that correlated with IBD. They then compared the levels of meprin in affected and unaffected sections of colons from IBD patients and from healthy people. The amount of enzyme in the IBD patient's inflamed colon was significantly lower than that in normal colon sections. The researchers concluded that their findings strongly

correlate the severity of inflammation associated with both Crohn's disease and ulcerative colitis with low meprin levels.

"This discovery is a major advance in understanding the genetic control of inflammation, and of ulcerative colitis and Crohn's disease in particular," Bond said. She discovered meprin more than 25 years ago while at the Medical College of Virginia Commonwealth University. Since then, she has studied the structure and activities of the meprins and has located the genes for the subunits in both the mouse and human chromosomes. After coming to Penn State Hershey in 1992, her studies have focused on the biomedical significance of the meprin proteases. With colleagues from the National Institutes of Health, she found a linkage between the meprin gene and vulnerability to diabetic nephropathy in Pima Indians in the southwestern United States.

"These types of transitional research that provide sound basic understanding of a disease process, coupled with detailed examination and critical interpretation of clinical findings, are dependent upon sustained collaborations based upon trust and respect," Bond said. Before this international effort, she teamed up with kidney specialists at Albert Einstein College of Medicine in New York and with W. Brian Reeves, M.D., at Penn State Hershey to demonstrate that meprin influences the outcome of acute renal failure in mice.

The Penn State researchers used a mouse model of IBD, replicating inflammation in the intestine like that in human ulcerative colitis. Mice lacking meprin had more severe intestinal damage after drinking a solution to induce inflammation, than did the wild-type mice that have meprin. These results indicate that meprin reduces the level of inflammation in the injured intestine.

In the mouse model, it is possible to make detailed measurements on a number of consequences of inflammation. Nitric oxide in the blood is an

important host defense against bacterial infection, but its power as an oxidant also damages host tissue. A nitric oxide level in the blood of mice lacking meprin was much higher than the level in wild-type mice. The Penn State team also discovered that meprin is able to activate an inflammatory serum factor produced by white blood cells, and this factor is elevated in both the mouse model of IBD and in humans with active IBD. Bond explained, "The defect in the human meprin gene most associated with ulcerative colitis is in a region that regulates production of the meprin protein."

The researchers concluded that a particular defect in the MEP1A gene is an indicator of vulnerability to IBD, particularly ulcerative colitis. The association of the meprin gene with Crohn's disease remains to be characterized but disruption of the meprin gene affects the severity of both ulcerative colitis and Crohn's disease. Bond summarized the findings by saying, "There's the possibility of predicting who will be susceptible to IBD, and diagnosing the disease with this information. If we could increase meprin production, or replace it with an equivalent enzyme, there are therapeutic possibilities. More studies are needed to understand how meprin influences inflammation, but this is the first association of meprin levels as a key factor in the severity of IBD."

Source: Penn State Hershey Medical Center