

## Pro-Inflammatory Protein Contributes To Crohn's Disease According To Study

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A pro-inflammatory protein activated by bacteria in the colon plays a key role in the development of experimental colitis in mice - a mouse-version of human Crohn's disease - according to research by scientists at the UCSD School of Medicine.

The study, published in the February 4, 2005 issue of the journal *Science*, identified interleukin-1Beta (IL-1 $\beta$ ) as a major cause of severe inflammation in the mouse model of Crohn's disease, which is a painful, chronic and little-understood inflammatory bowel disease (IBD) in humans, affecting more than 500,000 Americans. These individuals are considered at high risk for colon cancer.

The identification of IL-1 $\beta$  offers a potential target for drug development, said the study's senior author, Michael Karin, Ph.D., UCSD professor of pharmacology and an American Cancer Society Research Professor. Although there is currently an IL-1 $\beta$  inhibitor on the market for other, non-Crohn's chronic inflammatory conditions such as rheumatoid arthritis, this drug is not a very potent IL-1 $\beta$  inhibitor.

"Now that we've identified IL-1 $\beta$  as an important target for Crohn's disease therapy, we hope that a better, more effective IL-1 $\beta$  inhibiting drug can be developed for testing its efficacy in these patients," Karin said.

Crohn's disease is thought to involve an interaction between a genetic defect and environmental factors such as bacterial infections that trigger the disorder. Recently, scientists identified mutations in a gene called NOD2 as leading to 50 percent of Crohn's cases in patients of Northern European descent, but they haven't known just how NOD2 causes the severe inflammation associated with the disorder. An intracellular sensor for bacterial infection, normal NOD2 activates a protein called nuclear factor-kappaB (NF-kB), which is involved in the immune system's rapid response to bacterial infection. It has been observed that many of the drugs currently used to help Crohn's disease patients may also act as weak and nonspecific NF-kB inhibitors in addition to having many other activities. Given the new results in the study, drugs that are more potent and more specific inhibitors of NF-kB also need to be tested for their therapeutic effects on Crohn's disease patients.

Karin, who has conducted extensive research over the years on NF-kB and related genes, developed mice with mutant NOD2, that is identical to what is found in many Crohn's disease patients, and then introduced a bacterial infection into the walls of their colons. One-third of the mice bearing the mutation developed very severe colon inflammation and died, while the surviving animals had large lesions in their colons and lost a considerable amount of weight. His research team found that the mice bearing the NOD2 mutation also had markedly high levels of active NF-kB in the inflammatory cells (macrophages) that were present within their colons. Interestingly these mice also had high levels of mature IL-1 $\beta$ , a pro-inflammatory protein.

"The unique thing about IL-1 $\beta$  is that it is first made as a larger precursor that accumulates within the inflammatory cells but is usually very poorly secreted," Karin said, "only under certain circumstances, an enzyme called IL1 converting enzyme (ICE) is activated, the IL-1 $\beta$  precursors, whose synthesis is stimulated by NF-kB, are cleaved and the mature protein can be secreted. Therefore finding high levels of IL-1 $\beta$  secretion in the mutant

mice suggested that in addition to activating the NF- $\kappa$ B, that mutant NOD2 also stimulated the processing of the IL-1 $\beta$  precursor into its mature form."

The Karin team then gave an IL-1 $\beta$  inhibitor to mice and it abolished the experimental colitis (Crohn's Disease) in the mutant mice; none of the animals died and inflammation was considerably reduced.

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