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Protein May Have a Good Side in Preventing Inflammation

New research shows that a protein often accused of sparking autoimmune disease can actually tamp down inflammation and suppress the onset of inflammatory bowel disease. Experiments by Howard Hughes Medical Institute researchers at Yale University reveal that the immune protein interleukin 17A, or IL-17A, can take on the characteristics of Dr. Jekyll or Mr. Hyde – depending on the time and place.

The two faces of IL-17A suggest to Richard Flavell, a Howard Hughes Medical Institute investigator at Yale University, that he and other researchers may want to think carefully about reducing autoimmune-triggered inflammation by using drugs that target IL-17A. If administered at the wrong time or in the wrong place, the drugs may backfire and block IL-17A's beneficial effects, he said.

Flavell's team collaborated on the studies with scientists at the University of Tokyo and Children's Hospital of Pittsburgh. The research was reported in an advance online publication in *Nature Immunology* on May 17, 2009.

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IL-17A is one of many cytokines produced when the immune system rallies to fend off infection. Normally, immune cells that produce IL-17A and other cytokines migrate to sites of infection or injury, where they launch attacks against invading microbes. Cytokines recruit other immune cells to the site of injury and amplify the inflammatory response. But the downside can be collateral damage: the cytokines can harm the very tissue they are meant to protect.

IL-17A, produced by a specific type of immune cell called a T helper 17 (T_H-17) cell, as well as other specialized cells of the immune system, guards exposed areas like the skin, airways, and intestines from bacterial and viral invasion. Although proteins in the IL-17 cytokine family can be beneficial defenders, that role is often overshadowed by their reputation for promoting autoimmune conditions such as inflammatory bowel disease, rheumatoid arthritis, and multiple sclerosis.

Flavell's team's new research suggests that scientists may want to reconsider this pro-inflammatory label for IL-17A -- at least for inflammatory bowel disease. "IL-17A is pro-inflammatory in the chronic stage of inflammatory bowel disease, but our model indicates that it is protective at the outset of the condition," said Flavell. Its benefits have apparently been masked by damage caused by its sibling cytokines, he added.

William O'Connor, a postdoctoral fellow in Flavell's lab and lead author of the *Nature Immunology* paper, began the experiments by looking at how colitis – a form of bowel inflammation – progressed in mice. One way of inducing colitis in these animals is by introducing new T cells into their immune system. For these experiments, the researchers induced colitis with genetically modified T cells, and found that inflammation was more severe in mice whose T cells could not produce IL-17A. Another set of experiments showed that colitis was aggravated in mice whose T cells were deficient in the receptor for IL-17, preventing those cells from responding to IL-17A.

The researchers also found that IL-17A slows T-cells' maturation into the more specialized T helper 1 (T_H1) cells. These more mature immune cells are known to cause colitis. "The subtle effects of IL-17A in slowing T_H1 differentiation seem to produce a significant protective effect in the animal," O'Connor said.

"But eventually the T_H1 program takes over, and likely drives this disease." This apparently explains why the beneficial effects of IL-17A occur primarily during the early stages of the disease, he says.

A number of clinical researchers are interested in treating inflammatory disorders by using drugs that would block IL-17A systemically. But the experiments by Flavell's group suggest that this strategy could have unintended effects. Since IL-17A can both promote and deter inflammation, depending on the tissue involved and the stage of the disease, Flavell and his colleagues urge caution in targeting IL-17A during the early stages of chronic inflammatory disease.

The scientists said that further research will help sort out why IL-17A suppresses the onset of inflammatory bowel disease. Those studies should lead to a better understanding of what causes autoimmune pathology, and how the balance between pathology and protection is normally maintained, Flavell said.

