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Targeting Molecule Could Keep Immune System in Check

By knocking out a molecule that is found on the surface of activated T cells, researchers may have found a way to dampen the runaway immune response that causes a variety of allergic reactions and autoimmune diseases.

The findings indicate that the inducible co-stimulatory molecule (ICOS) may become an important target for new drugs to treat asthma, inflammation associated with multiple sclerosis and other immune-related disorders. In an article published in the January 4, 2001, issue of *Nature*, Howard Hughes Medical Institute investigators Richard Flavell at Yale University and James P. Allison at the University of California, Berkeley, and their colleagues describe experiments in which they knocked out the ICOS gene in mice.

"ICOS appears to do much more than help B cells make antibodies; it also plays an important regulatory role in controlling the immune response in general."

— Richard A. Flavell

When cells of the immune system encounter a foreign invader, they chop it into fragments, called antigens, which are displayed on the surface of antigen-presenting cells (APCs), such as macrophages and dendritic cells. T cells become partially activated when APCs present them with a foreign protein fragment. In order for full activation to occur, however, T cells must receive additional signals from "co-stimulatory" molecules on the APC. When the co-stimulatory signal is received, T cells proliferate and secrete cytokines, which are intracellular signaling molecules.

During the process of T-cell activation, ICOS molecules appear on the surface of T cells. ICOS is a highly specific receptor for the protein, B7H/B7RP-1, that is expressed on the surface of B cells and macrophages. Stimulation of the B cell and subsequent antibody production takes place after the ICOS receptor attaches to its partner B7RP-1 molecule. Thus, the co-stimulatory molecules, ICOS and B7H/B7RP-1, provide important specificity for the immune-system activation process.

Before these studies, little was known about how ICOS worked in the immune system. "ICOS was known to exist; it was known to be present on activated T cells; and it was known to stimulate the production of certain cytokines, but its biological role wasn't very clear," said Flavell.

To begin probing the biological role of ICOS, the scientists first examined how T cells developed in mice in which the ICOS gene had been inactivated. They found that the absence of ICOS did not appear to affect T cell development in the thymus. Next, they looked at ICOS-deficient T cells in culture and found that those cells failed to proliferate or to function normally when stimulated by molecules including B7H/B7RP-1. Also, the deficient T cells produced abnormally low levels or complete absence of cytokines necessary for triggering T-cell proliferation and differentiation. Those absent included the "effector" cytokines, interleukin-4 and interleukin-13, that are critical in amplifying the immune response.

The scientists next looked more closely at the ICOS-deficient mice to see if they could find deficits in immune system function. "When we immunized the ICOS-knockout mice to activate their immune systems, we found the same deficiency in interleukin-4 production we found in cell culture. And, we also found that antibody responses dependent on interleukin-4 were also deficient."

Importantly, the scientists noticed that the immunized knockout mice failed to produce the antibody immunoglobulin E, which is important in asthma and allergic reactions. This finding, said Flavell, suggests that drugs that block ICOS might prove to be potent asthma medications.

Additional studies of the ICOS-knockout-mice revealed that they showed greatly reduced numbers and sizes of germinal centers—the areas in spleens where antibody-producing B cells develop.

In another set of experiments, the scientists triggered the immune systems of the knockout mice by injecting a protein called MOG, which is the protein that is expressed on the sheaths of neurons. Stimulating an immune response against MOG mimics the autoimmune reaction caused by multiple sclerosis.

"When we immunized normal mice with MOG, they developed a mild autoimmune reaction," said Flavell. "To our great surprise, however, the ICOS-deficient mice developed an extremely aggressive disease. Their tissues showed much more drastic infiltration of activated T cells that then produce more cytokines associated with autoimmune disease."

The normal mice appeared to be protected from the development of inflammatory disease by interleukin-13, said Flavell. Other researchers had shown that interleukin-13 protects against autoimmune reactions. Interleukin-13 was absent in the ICOS-deficient mice after immunization with MOG.

"So, we found that ICOS plays a protective role in preventing extremely strong inflammatory immune responses — a function which no one had

anticipated."

The explanation for this protective function, said Flavell, appears to be that cytokines triggered by immunization can induce tissues to express ICOS's partner, B7H/B7RP-1. Once this molecular partner of ICOS appears, it stimulates activated T cells to produce an inflammatory response.

Flavell and his colleagues also believe that ICOS may ameliorate this inflammatory response. "If you don't have ICOS you cannot ameliorate the response; you can't shut the system down," said Flavell. "And so it goes out of control and develops into an extremely aggressive disease. Thus, ICOS appears to do much more than help B cells make antibodies; it also plays an important regulatory role in controlling the immune response in general."

Flavell said that additional studies are needed to determine whether blocking ICOS could be an effective treatment for asthma. Likewise, there's much more work ahead to find out whether ICOS plays a more general role in autoimmune diseases, and whether drugs that switch on ICOS production might prove useful treatments for autoimmune diseases.