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UCSD Medical Researchers Are First To Demonstrate Molecular Link Between Inflammation And Cancer

Inactivation of Pro-Inflammatory Gene Dramatically Reduces Tumor Development

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First evidence of the molecular link between inflammation and cancer has been shown by researchers at the University of California, San Diego (UCSD) School of Medicine. Featured as the cover article in the August 6, 2004 issue of the journal *Cell*, the study also demonstrated that inactivation of a gene involved in the inflammatory process can dramatically reduce tumor development in mice with a gastrointestinal form of cancer.

The investigators found that a gene called I-kappa-B kinase (IKK beta), a pro-inflammatory gene, acts differently in two cell types to cause cancer. When IKK beta was deleted, the cancer incidence and tumor growth in mice was decreased by nearly 80 percent.

IKK beta is required for activation of a protein called nuclear factor kappa B (NF-kB), that acts as a master switch to turn on inflammation in response to bacterial or viral infections. In epithelial cells, NF-kB promotes the development of cancer not through inflammation, but through inhibition of a cell-killing process called apoptosis. In myeloid cells, NF-kB causes the expression of pro-inflammatory molecules that stimulate the division of genetically altered epithelial cells and thereby increase tumor size.

Because recurrent inflammation and chronic infections contribute to a large number of different cancers, the researchers chose one of these cancers - colitis associated cancer (CAC) - as their model for study. CAC occurs in people suffering from chronic colitis, which puts them at very high risk for cancer.

"We've shown how tumors arise from chronic inflammation that acts together with chemical carcinogens," said the study's senior author, Michael Karin, Ph.D., UCSD professor of pharmacology, American Cancer Society Research Professor, and a member of the Rebecca and John Moores UCSD Cancer Center.

"In response to chronic infection, the interplay between immune cells and the epithelial cells of the intestinal tract, which become genetically transformed to give rise to malignant cells by the carcinogen, results in increased tumor growth and suppression of apoptosis, whose role is to reduce cancer incidence," Karin added. "Our studies show how NF-kB acts very early in the carcinogenesis process, in two different ways."

The relationship between cancer and inflammation due to chronic infection has been suspected, but not proven, for many years. In a 1986 study, for example, one researcher compared the inflammatory response to a wound healing response, saying tumors were wounds that do not heal. Even without proof of the inflammation-cancer link, cancer therapies have been developed that utilize non-steroidal anti-inflammatory drugs (NSAIDs) to inhibit NF-kB and other mediators of inflammation, and to act as chemo-preventive agents that reduce the risk of gastrointestinal cancers. Some of these therapies, however, have been only partially effective because the precise molecular pathway targeted by the treatment has not been known.

In their study of NF-kB, the researchers began by administering two compounds to mice. The first was a pro-carcinogen called azoxymethane (AOM), which is commonly used to induce colorectal cancer in experimental animals. The second compound was a pro-inflammatory irritant called dextran sulfate sodium salt (DSS), that eroded the intestinal-tract epithelial cells, allowing the entrance of enteric bacteria, with resulting inflammation generated by the body to fight the infection.

In normal mice, these two compounds trigger both inflammation and, a few months later, tumors called adenocarcinomas. In this study, DSS and AOM were given to two additional groups of mice - one group bred without IKK beta in the epithelial cells of the intestine; the second group without IKK beta in myeloid cells, which play an important role in the immune system by generating white blood cells called macrophages to induce inflammation and fight infection.

Focusing on the epithelial cells deficient in IKK beta, the researchers found that DSS induced inflammation in the mice, even without NF-kB activation. And yet, the incidence of tumor development decreased by 80 percent as compared to normal mice. Using biochemical analysis of the tissue without IKK beta, the scientists determined that stimulation of a process called apoptosis had decreased cancer development.

A form of cell suicide, apoptosis prevents the growth of unwanted cells. It is a normal process the body uses to kill mutated or chemically transformed cells, as well as useful cells that have outlived their purpose. Evading apoptosis is one of the hallmarks of cancer.

In their study, the UCSD team found that apoptosis was increased in mice bred without IKK beta. Specifically, without NF-kB activation, there was an increase of pro-apoptotic proteins Bak and Bax, and a decrease in a protein called Bcl-xL, known to inhibit apoptosis.

Turning their focus to myeloid cells, the team found that inactivation of IKK beta reduced the expression of many genes that contribute to the inflammatory process. When NF-kB was not activated, there was a 50 percent reduction in tumors caused by DSS/AOM. The tumors that grew were significantly smaller in size than those in the normal mice that had received the two compounds.

To understand how IKK beta in myeloid cells affects tumor development, the researchers first examined the affect of IKK beta deletion on apoptosis and found none. What they discovered, instead, was that IKK beta deletion in myeloid cells decreased the expression of pro-inflammatory molecules such as cyclooxygenase, also known as COX-2, and interleukins 1 and 6, which are expressed at sites of inflammation.

"Our findings establish for the first time the role of myeloid cells in inflammation-associated tumor promotion in addition to their role in tumor progression and invasiveness," the authors stated in the *Cell* paper.

The authors added that "in addition to identifying a key molecular mechanism connecting inflammation and cancer, our results suggest that specific pharmacological inhibition of IKK beta may be very effective in prevention of colitis associated cancer."

In addition to Karin, the study's authors were first author Florian R. Greten, M.D., UCSD Department of Pharmacology; and Lars Eckmann, M.D., UCSD Department of Medicine; Jin Mo Park, Ph.D., UCSD Department of Pharmacology; Zhi-Wei Li, Ph.D., UCSD Department of Pharmacology and the Moffit Cancer Center and Research Institute, Tampa, Florida; Laurence J. Egan, M.D., UCSD Department of Medicine and the Gastroenterology Research Unit, Mayo Clinic, Rochester, Minnesota; and Martin F. Kagnoff, M.D., UCSD Department of Medicine.

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