New Anti-Inflammatory Strategy For Cancer Therapy Identified By UCSD Medical Researchers

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A new strategy for cancer therapy, which converts the tumor-promoting effect of the immune system's inflammatory response into a cancer-killing outcome, is suggested in research findings by investigators at the University of California, San Diego (UCSD) School of Medicine.

The findings provide new insight into the immune system's response to inflammation, the connection between inflammation and malignancy, and how the delicate balance between cancer promotion and inhibition can be manipulated in the patient's favor, according to 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.

The studies in mice with colon or breast cancer showed that cancer metastasis, the growth of malignant tumors beyond the original site, was halted with inhibition of either one of two naturally occurring substances, a pro-inflammatory protein called nuclear factor-kappa B (NF-kB) or an inflammatory mediator called tumor necrosis factor alpha (TNFa). The result, published in the September 20, 2004 issue of the journal *Cancer Cell*, was increased effectiveness of a cancer-killing protein called TNF-related apoptosis-inducing ligand (TRAIL), leading to a decrease in cancer cells and increase in the life span of tumor-bearing mice.

The study's first author, Jun-Li Luo, M.D., Ph.D., a member of the Karin team in the UCSD Laboratory of Gene Regulation and Signal Transduction, explained that normally, inflammation associated with malignancy activates NF-kB, TNFa and TRAIL, all at the same time. However, NF-kB has the upper hand, and with TNFa, stimulates tumor growth faster than TRAIL can inhibit it.

"Our results suggest that is it possible to use NF-kB or TNFa inhibitors to prevent inflammation-induced tumor growth, thus destroying their advantage, and allowing TRAIL to tip the balance in its favor," Luo said.

The study builds upon previous work in the Karin lab recently featured as the cover article in the August 6, 2004 issue of the journal *Cell* *. In that study, the researchers provided the first evidence of the molecular link between inflammation and cancer. They determined that an enzyme called I-kappa-B kinase beta (IKKb) is required for the activation of NF-kB, which acts as a master switch to turn on inflammation in response to bacterial or viral infections. In turn, NF-kB sets off a chain of reactions that lead to cancer.

Mice used in the new study were given colon or breast tumor cells which metastasized to the lung. Some of these cancer cells served as "controls," while other cells were given a protein that specifically inhibited activation of NF-kB, only in cancer cells. The different cells were injected into mice and all were able to establish metastatic growth in the lung, regardless of their ability or inability to activate NF-kB. After a week, all mice were injected with bacterial lipopolysaccchide (LPS), which induced inflammation. A post-mortum inspection of the mice showed that following inflammation, the control cells formed more numerous and larger tumor nodules, while the tumors formed by cells in which NF-kB was inhibited, had shrunk or partially disappeared after the LPS injection. As a

result, mice injected with cancer cells lacking NF-kB activity exhibited much better survival than mice inoculated with control cells.

In further tests to determine how NF-kB activation mediates inflammation-induced tumor growth, the team studied mouse lung tissue as well as tumor nodules for expression of specific proteins known to modulate the body's normal cell-killing process. Death-inhibiting proteins were abundant in tumors formed by cancer cells with normal NF-kB, but were absent in the tumors formed by cancer cells where NF-kB was inhibited.

While NF-kB is known to convert inflammatory stimuli into tumor growth signals, it is also known to activate TNFa, a major proinflammatory protein initially thought to play a role in the death of cancer cells. Investigators first reasoned that TNFa might be responsible for the death of cancer cells in which NF-kB was inhibited, seen in this study, since previous experiments have shown that high doses of TNFa can kill tumor cells when NF-kB activity is inhibited.

However, further experiments proved otherwise. When inflammation-inducing LPS was administered to tumor-bearing mice with normal NF-kB, the result was a rapid and robust induction of circulating TNFa and eventual acceleration of cancer growth. However, administration of an anti-TNFa antibody five minutes after LPS challenge neutralized most of the circulating TNFa, inhibited NF-kB activation in cancer cells, and prevented the inflammation-induced acceleration of tumor growth.

Rather than TNFa, the team found that TRAIL, a member of the TNF superfamily and a relative of TNFa, was the specific protein responsible for the tumor death response. While both NF-kB and TRAIL are activated in response to inflammation, NF-kB takes control, inhibits cell death and promotes cancer growth. When NF-kB or TNFa were inhibited, however, TRAIL was able to strongly assert its ability to reduce tumor growth by killing cancer cells. The role of TRAIL was further illustrated in additional experiments where a neutralizing anti-TRAIL antibody was injected into the mice following the LPS challenge. The result was tumor growth.

In their summary, the researchers said that since TNFa does not make a major contribution to tumor killing and instead may promote tumor growth, it may be advisable to develop drugs which reduce inflammation-associated toxicities, block inflammation-induced tumor growth and clear the way for TRAIL to initiate tumor killing. The latter approach can be accomplished by the use of NF-kB inhibitors, together with anti-TNFa drugs, the researchers contend. These drugs should be used in combination with TRAIL or TRAIL-inducing cytokines, such as beta interferon.

In addition to Luo and Karin, the study authors were Shin Maeda, Ph.D. and Li-Chung Hsu, Ph.D., members of the UCSD Laboratory of Gene Regulation and Signal Transduction, and Hideo Yagita, Department of Immunology, Juntendo University School of Medicine, Tokyo, Japan.

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* http://health.ucsd.edu/news/2004/08_05_Karin.html

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