Two Immune-System Proteins Linked to Colitis-Associated Cancer

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Recent research from the laboratory of Michael Karin, PhD, at the University of California, San Diego School of Medicine – the first researcher to demonstrate a molecular link between inflammation and cancer – has identified two potential targets for the prevention and treatment of colitis-associated cancer (CAC), the most serious complication of inflammatory bowel disease.

Karin, Distinguished Professor of Pharmacology and Pathology and member of the Moores UCSD Cancer Center, and his team used genetic tools to demonstrate in mice that a cytokine called Interleukin 6 (IL-6), is an important regulator of tumor production during CAC development, and that its molecular effects are largely mediated by the transcription factor STAT3 in cancer cells. Their latest study – which is also the first to establish the cancer-promoting function of STAT3 in a validated mouse model of human cancer – will be published in the February 3 on-line edition of the journal *Cancer Cell*.

Recurrent inflammation and chronic infections contribute to a large number of different cancers including CAC which occurs in people suffering from chronic colitis, a common inflammatory bowel disease, putting them at very high risk for cancer. Cytokines – small proteins released by immune-system cells – have been suggested to drive early tumor growth by stimulating the growth and survival of pre-malignant cells.

In previous work, Karin's team showed that activation of a pro-inflammatory protein called NF-kB stimulates the proliferation of premalignant epithelial cells in CAC, giving rise to malignant growths in the colon. Interestingly, NF-kB in colonic epithelial cells promotes the development of cancer, not through inflammation, but through inhibition of apoptosis or cell death. On the other hand, NF-kB in the immune cells promotes cancer by enhancing inflammation, mostly by controlling the expression of pro-inflammatory cytokine expression. One of these cytokines was thought to be IL-6.

"IL-6 fosters chronic inflammation by its effect on immune cells and it also regulates malignant cell survival," Karin said.

The proliferative and survival effects of IL-6 are largely mediated by the transcription factor STAT3, first suggested to have a cancer-promoting function by James Darnell at Rockefeller University in New York. The new work, which provides the first genetic evidence for the critical role of STAT3 in cancer using a mouse model of human cancer, also suggests that IL-6 and Stat3 constitute useful targets for the prevention and treatment of CAC, Karin added. The researchers showed that ablation of STAT3 in intestinal epithelial cells effectively inhibited CAC induction and growth in mice.

Colorectal cancer is one of the most common fatal malignancies worldwide, and almost half of all affected individuals die from the disease. Patients with inflammatory bowel disease, such as ulcerative colitis, are at a higher risk of developing colorectal cancer.

Additional contributors to this study include UC San Diego School of Medicine researchers Sergei Grivennikov; Eliad Karin (currently at Tel Aviv University Israel), Janos Terzic (currently at the University of Split, Croatia), Guann-Yi Yu; Sivakumar Vallabhapurapu and Lars Eckmann; La Jolla Institute for Allergy and Immunology scientists Hilde Cheroutre and Daniel Mucida; and researchers from Kiel University (Germany) Jurgen Scheller and Stefan Rose-John.

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Rose-John holds a patent describing the function of sgp130Fc and is a shareholder of the CONARIS Research Institute (Kiel, Germany).

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