Study finds key link responsible for colon cancer initiation and metastasis

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Chronic inflammation has long been known as a key risk factor for cancer—-particularly colon cancer—-but the exact mechanisms of how inflammation heightens the immune response, and ultimately influences the initiation and progression of cancer have remained elusive. It is well established that anti-inflammatory drugs, like aspirin, reduce the risk of colorectal cancer.

Now, an ASU research team led by Biodesign Institute executive director Dr. Ray DuBois, M.D., PhD, has shown that a key genetic culprit, called CXCR2, is implicated in the tumor formation, growth and progression in a mouse model of colon cancer.

"We have been trying for the past several years to understand the precise molecular links between inflammation and cancer, said DuBois. "We have demonstrated that CXCR2 mediates a critical step in the setup of the blood circulatory machinery that feeds tumor tissue. This provides an important new clue for the development of therapeutic targets to neutralize the effect of CXCR2 on colon cancer."

The DuBois' Laboratory for Inflammation and Cancer, which includes lead author Hiroshi Katoh, and colleagues Dingzhi Wang, Takiko Daikoku, Haiyan Sun, and Sudhansu K. Dey, published the results in the November 11 issue of *Cancer Cell*.

The results provide critical new clues toward the prevention of colorectal cancer, the second leading cause of cancer deaths in the U.S. Despite the availability of colonoscopy screening, the 5-year survival rate remains low, due to a large number patients presenting with advanced stages of the disease. Currently, there are no clinically available blood tests for the early detection of sporadic colon cancer.

Inflammation has long been associated with increasing one's risk for colon cancer. For instance, more than 20 percent of patients with a form of inflammatory bowel disease (IBD) develop colorectal cancer within 30 years of diagnosis. This colitis-associated cancer has a slow progression, but a very poor response to treatment and a high mortality rate.

Researchers have known that the broad mechanisms of cancer involve an interplay with the immune system response that includes: recruiting immune cells that influence the tumor microenvironment, escaping from host immunosurveillance and suppression, shifting of the host immune response, and tumor-associated angiogenesis to establish the blood supply.

For the study, the research team first "knocked-out" or removed the CXCR2 gene in mice, and found that the signs typically associated with inflammation were prevented. Furthermore, they demonstrated that CXCR2 dramatically suppressed colonic inflammation and the colitis associated tumor formation, growth and progression in mice.

CXCR2 decorates the outer part of immune cells called myeloid-derived suppressor cells, or MDSCs, that work to block the immune response of killer CD8+ T cells. In the knockout mice, without CXCR2 present, the MDSC cells could no longer migrate from the circulatory system to the colon, dodge the killer CD8+ T cell immune response, and feed the blood supply of the tumor environment. Furthermore, when they transplanted normal MDSC cells (with normal CXCR2) into the knockout mice, tumor formation was restored.

"These results provide the first genetic evidence that CXCR2 is required for recruitment of MDSCs into inflamed colonic mucosa and colitis-associated tumors," said DuBois.

For DuBois, who has devoted his career to unraveling the inflammatory circuitry responsible for colon cancer, the results help connect the dots between the immune system, inflammation and

tumor formation and metastasis.

DuBois' team was the first to show that colorectal tumors contained high levels of the enzyme cyclo-oxygenase-2 (COX-2), a key step in the production of pro-inflammatory mediators such as prostaglandin E2 (PGE2). PGE2 triggers production of a CXCR2 molecule that fits into CXCR2 like a baseball into a glove's pocket and activates it. CXCR2, like the pied piper, recruits MDSCs from the bloodstream to sites of inflammation, causing the colon cancer tumors to evade the immune killer CD8+ T immune response.

"Our findings reveal not only how MDSCs are recruited to local inflamed tissues and tumor microenvironment and how local MDSCs contribute to colorectal cancer progression, but now also provide a rationale for developing new therapeutic approaches to subvert chronic inflammation- and tumor-induced immunosuppression by using CXCR2 antagonists and neutralizing antibodies," said DuBois.

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