Researchers discover colorectal cancer biomarker, potential personalized treatment

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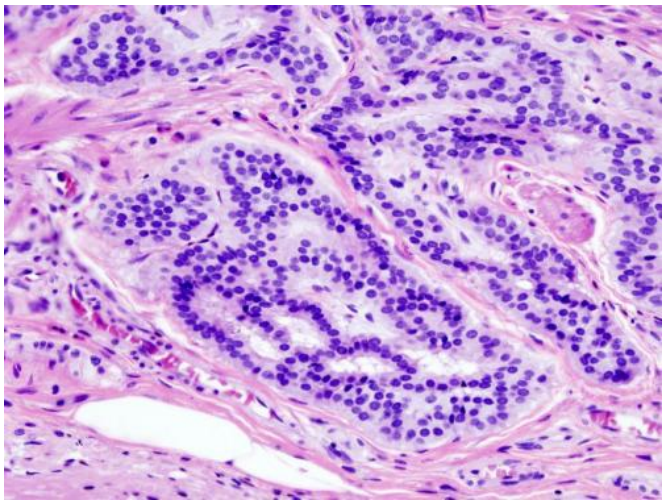

Cancer — Histopathologic image of colonic carcinoid. Credit: Wikipedia/CC BY-SA 3.0

UNC Lineberger Comprehensive Cancer Center researchers have discovered that a deficiency in a key protein that regulates immune system warning signals could be a new biomarker for colorectal cancer, the second largest cancer killer in the United States. They believe the marker could be used to gauge response to a potential new treatment for the disease.

In the journal *Cell Reports*, researchers reported they found markedly low levels of the protein NLRX1 in multiple laboratory models of colorectal cancer, and in samples of human tissue. Studies have shown that the protein is known to be involved in regulating immune system signals in order to prevent hyperactive inflammatory responses by the immune system. The UNC Lineberger researchers believe their finding also points to a role for the protein in preventing colorectal cancer growth. Based on their findings, they believe they've identified a potential treatment for colorectal cancer with low NLRX1.

"What we're proposing is, if you can profile people with low NLRX1 in their colorectal cancer, you could consider using this therapy that we identified," said the paper's senior author Jenny P. Ting, PhD, a University of North Carolina Lineberger member and the William R. Kenan Jr. Professor of Microbiology and Immunology at the UNC School of Medicine. "We have identified a critical biomarker for this disease."

The protein NLRX1 helps keep immune system responses in-check by downregulating signals that help trigger a wider immune response. A. Alicia Koblansky, PhD, the paper's first author and a postdoctoral research fellow at UNC Lineberger, said they believe the protein is involved in dampening immune signals that could harm the host.

In the UNC Lineberger-led study, researchers studied the effect of deleting NLRX1 in preclinical models of sporadically-growing colorectal cancer. They tested the effect in an animal model with mutations in the APC (Adenomatous polyposis coli) gene. Koblansky said about 80 percent of human colon cancer tumors have a mutation in this gene. The mutation is known to lead to spontaneous growth of colon cancer tumors. The loss of NLRX1 revealed a dramatic increase in tumor growth as well as an increase in activation of signaling pathways known to help drive cancer.

Additionally, they found significantly lower expression of NLRX1 in human colon cancer cell samples compared to normal cells. They also studied multiple public databases of colon cancer samples, finding decreased expression of NLRX1 in each. The findings reinforced their belief that NLRX1 normally helps to keep a check on colorectal cancer.

The researchers believe the findings can have treatment implications, since they know that NLRX1 limits activation of signals that help trigger other

cancer-driving growth signals.

To that end, they tested a drug, already approved as a treatment for arthritis, that's designed to block one of the downstream pathways normally down-regulated by NLRX1. They found that the drug, which blocked a small signaling protein called IL-6, decreased tumor growth and activation of downstream cancer-causing signals. Based on these findings, they believe IL-6 blockers could be redirected against colorectal cancers with low NLRX1 expression.

"We're arguing that clinicians could analyze NLRX1 expression, and provide them with a more targeted treatment based on that finding," Koblansky said. "We want to help clinicians to drive precision medicine for patients as much as possible."

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