Genomic makeup of colorectal cancers predicts immune system ability to fight tumors

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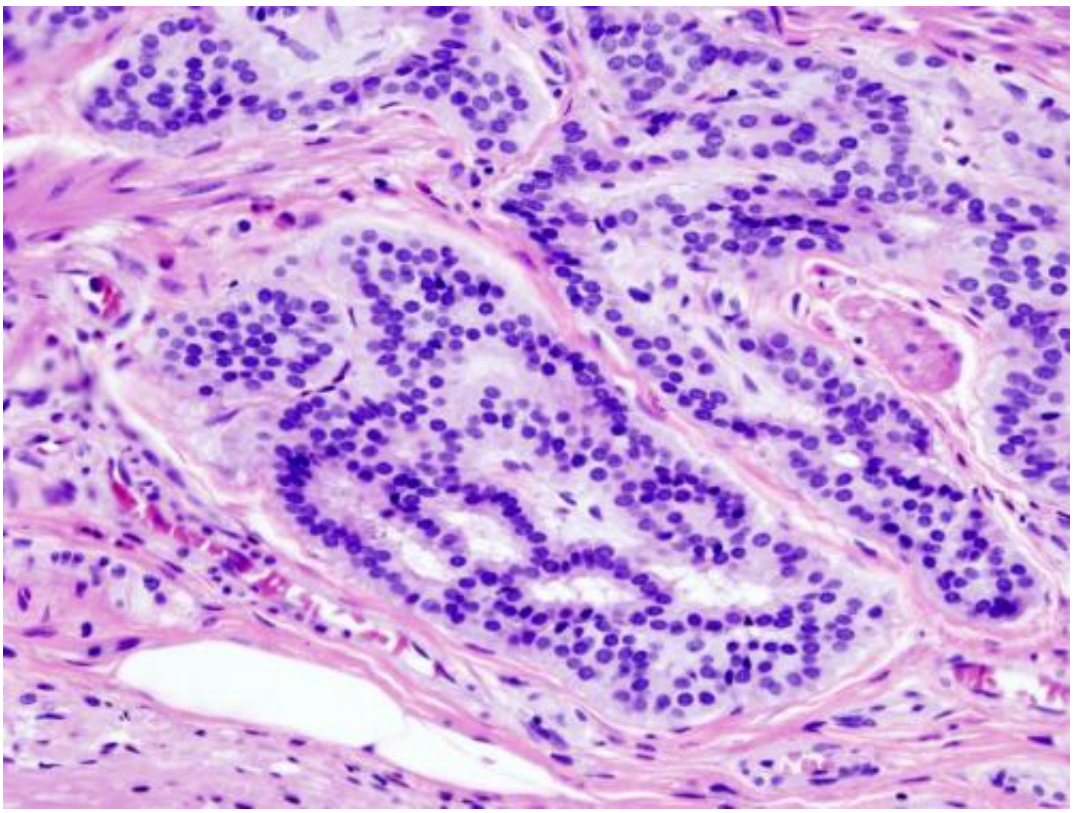

Cancer—Histopathologic image of colonic carcinoid. Credit: Wikipedia/CC BY-SA 3.0

Colorectal cancers heavily bedecked with tumor-related proteins called neoantigens are likely to be permeated with disease-fighting white blood

cells, researchers at Dana-Farber Cancer Institute and the Broad Institute of MIT and Harvard report in a new study. Because such an influx of white blood cells often signifies an immune system attack on cancer, the discovery will sharpen research into therapies that make tumors more vulnerable to such an attack.

The discovery is being published in a study today in the journal *Cell Reports*. It was made by combining several data sets from patients in two large health-tracking studies, the Nurses' Health Study and the Health Professionals Follow-up Study. Researchers first performed whole-exome sequencing on colorectal tumor samples from 619 patients - itemizing each letter of DNA that specifies how cell proteins are to be constructed. This information was merged with data from tests of the immune system's response to the tumors and with patient clinical data, including length of survival.

"We were looking for genetic features that predict how extensively a tumor is infiltrated by lymphocytes [certain white blood cells] and which types of lymphocytes are present," said study co-lead author, Marios Giannakis, MD, PhD, medical oncologist and clinical investigator at the Dana-Farber Gastrointestinal Cancer Treatment Center, and researcher at the Broad Institute of MIT and Harvard. "We found that tumors with a high 'neoantigen load' - which carry large quantities of neoantigens - tended to be infiltrated by a large number of lymphocytes, including memory T cells, which provide protection against previously encountered infections and diseases. Patients whose tumors had high numbers of neoantigens also survived longer than those with lower neoantigen loads."

Neoantigens are deviant forms of protein antigens, which are found on normal cells. Genetic mutations often cause cancer cells to produce abnormal proteins, some of which get lifted to the cell surface, where they serve as a red flag to the immune system that something is amiss

with the cell.

"There can be hundreds or thousands of neoantigens on tumor cells," Giannakis explained. "Only a few of these may actually provoke T cells to infiltrate a tumor. But the more neoantigens on display, the greater the chance that some of them will spark an immune system response."

Therapies known as immune checkpoint inhibitors work by removing some of the barriers to an immune system attack on cancer. Although these agents have produced astonishing results in some cases, they're generally effective only in patients whose immune system has already launched an immune response to cancer. By showing that tumors with high antigen loads are apt to be laced with T cells - and therefore to have provoked an immune response - the study may help investigators identify which patients are most likely to benefit in new clinical trials of immune checkpoint inhibitors.

The study's genomic analysis of colorectal tumor samples also found several often-mutated genes that had not previously been strongly associated with the disease, including BCL9L, RBM10, CTCF, and KLF5. The discovery of their prevalence in colorectal cancer suggests that they may be valuable targets for new therapies.

"Our study helps shed light on the overall development of colorectal cancer," Giannakis remarked. "It also shows the insights that can be gained by integrating molecular research with findings from other areas such as epidemiology and immunology."

Provided by Dana-Farber Cancer Institute

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