

Researchers discover how colon cancer mutates to escape the immune system

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Dr. Antoni Ribas, Catherine Grasso and colleagues found that more mutated cancers have more alterations of genes that interact with the immune system. Credit: Milo Mitchell/UCLA Jonsson Comprehensive Cancer Center

A UCLA-led study has found how colon cancer alters its genes during development in order to avoid detection by the immune system, creating

a specific genetic imprint in the process.

This ability of cancer to change its genes—a process called immunoediting—had never been described in [colon cancer](#) before, and the new understanding could help researchers develop new immunotherapies that target those genetic changes.

"By identifying the evolution of changes needed to escape the immune system, researchers should be able to design treatments that empower the immune system to outsmart the cancer," said lead author Catherine Grasso, assistant professor of medicine at the David Geffen School of Medicine at UCLA. "We expect that in the future, we'll be testing new immunotherapies to prevent the development of colon cancer, while also using combinations of different agents to treat advanced cancers."

The research appears in the journal *Cancer Discovery*, published by the American Association for Cancer Research.

Investigators from the UCLA Jonsson Comprehensive Cancer Center, the Broad Institute, the Parker Institute for Cancer Immunotherapy and the Fred Hutchinson Cancer Institute used the genetic analyses of more than 1,200 colon cancers from the Cancer Genome Atlas, the Nurses' Health Study and the Health Professionals Follow-up Study. Because the cancers were sequenced at the DNA and RNA level, researchers were able to make highly detailed assessments of the changes made to evade the immune system.

Among their findings was that more mutated cancers, called MSI-high (for high microsatellite instability), have more alterations of genes that interact with the immune system. That's significant because the 15 percent of colon cancers in this category can currently be treated with a type of immunotherapy that acts on a specific receptor, known as PD-1, located on [cells](#) in the immune system. This receptor normally functions

as a brake to the immune system.

Immunotherapy releases this brake, allowing the immune system to attack cancer cells when it recognizes their high frequency of mutations as abnormal. Knowing how cancer cells change could help scientists further refine immunotherapy treatments for such cancers.

The study also shed light on the 85 percent of colon cancers that are not MSI-high. These cancers have fewer mutations and are not usually attacked by the immune system; instead, they have alterations in Wnt signaling, a pathway important in cell development. The study documents the extent to which Wnt-activating mutations were associated with the lack of an [immune response](#) in the tumor.

"The genetic data show that colon cancer is being attacked by the immune system from the start, even before immunotherapies based on immune-checkpoint blockade have been given to patients," said Dr. Antoni Ribas, co-senior author of the study and a professor of medicine, surgery, and molecular and medical pharmacology at Geffen School of Medicine and director of the cancer center's Tumor Immunology Program.

Added Grasso: "There are many ways for the immune system to fail in recognizing and attacking a cancer cell due to mutations in the tumor cells and we found examples of them. Our data suggest that the number of mutations is not the sole predictor of infiltration of the cancer by [immune cells](#), which has been reported frequently in the literature."

For example, Grasso and colleagues showed that as WNT signaling increases, immune infiltration in colon [cancer](#) decreases. This suggested that inhibitors of WNT signaling could potentially stimulate immune infiltration, so that the tumors could respond to immunotherapy.

More information: Catherine S. Grasso et al. Genetic Mechanisms of Immune Evasion in Colorectal Cancer, *Cancer Discovery* (2018). [DOI: 10.1158/2159-8290.CD-17-1327](https://doi.org/10.1158/2159-8290.CD-17-1327)

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