

# Colorectal cancers may mutate to escape immune system detection in many ways

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Whole exome sequencing revealed that colorectal cancers with high mutational load (MSI-H) predominantly use "immunoediting" to escape immune surveillance while colorectal cancers with low mutational load (MSS) use oncogenic signaling to escape from the immune response, according to data presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, held Oct. 26-30. The data suggest that promoting immune-cell infiltration into MSS colorectal tumors by blocking certain cancer genes could potentially make them respond to immunotherapies.

"Immunoediting is the evolution of mutations in the tumor to knock out the immune system before treatment because there is selection pressure in place between the T cells and the tumor," explained Catherine Grasso, PhD, assistant professor in the Department of Hematology and Oncology at University of California, Los Angeles. "The tumor and the immune system are at an impasse, but the tumor evolves to develop resistance to the immune system by knocking out surveillance."

It is important to study colorectal tumors prior to treatment to assess whether the tumor is being attacked by the immune system, because immunotherapies based on immune checkpoint blockade will not work if the tumor is not being attacked, explained Grasso. The researchers sought to identify novel immunotherapeutic opportunities in colorectal [cancer](#) by comparing cancers from the subtypes that respond to immunotherapy and those that do not respond.

Grasso and colleagues used colorectal tumor exome data from 592 cases from The Cancer Genome Atlas (TCGA), and 619 cases from the Nurses' Health Study and the Health Professionals Follow-up Study to examine immunoediting in MSI-H (179 cases) and MSS (1,032 cases) tumors. They used the MutSigCV algorithm and identified highly mutated [genes](#) that are unique for MSI-H (40 genes) and MSS (nine genes) tumors, and those that were present in both types of tumors (13 genes).

The researchers found that mutations in some genes that were specific for MSI-high were novel, involved in modulating the immune system and the antigen presenting machinery. "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," noted Grasso. Some of the immune pathways that the tumors evade, through gene mutations, were those involving trafficking of the immune cells around the body, infiltration of immune cells, antigen presentation, signaling between the tumor and the T cells, and signaling methods of the T [cells](#) to kill the [tumor cells](#).

"For MSI-H colorectal cancers, these mutation data suggest the need for targeted sequencing to monitor immune competence before anti-PD1 treatment, which will ensure that people do not get treatments to which they may not respond," Grasso said.

"Our data suggest that mutation load is not the sole predictor of [tumor](#) infiltration, which has been reported frequently in the literature," she added. For example, Grasso and colleagues showed that WNT signaling correlated negatively with immune infiltration in colorectal cancer, like melanoma. This suggested that inhibitors of WNT signaling could potentially stimulate immune infiltration, so that the tumors could respond to anti-PD1 therapy. This is important because it indicates that tumors with low mutational load, such as MSS [colorectal cancers](#), may

be stimulated to be attacked by [immune cells](#) prior to anti-PD1 treatment, Grasso noted.

A limitation of the study is that the researchers only looked at the genetic and molecular predictors of T-cell infiltration and did not study the responses to immune checkpoint blockade, because response data was not available. "We have just scratched the surface of what is possible in immunotherapy. Funding for large genomics studies will continue to provide deep insights," Grasso said, "especially as we accrue and study samples before and after treatment."

Provided by American Association for Cancer Research

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