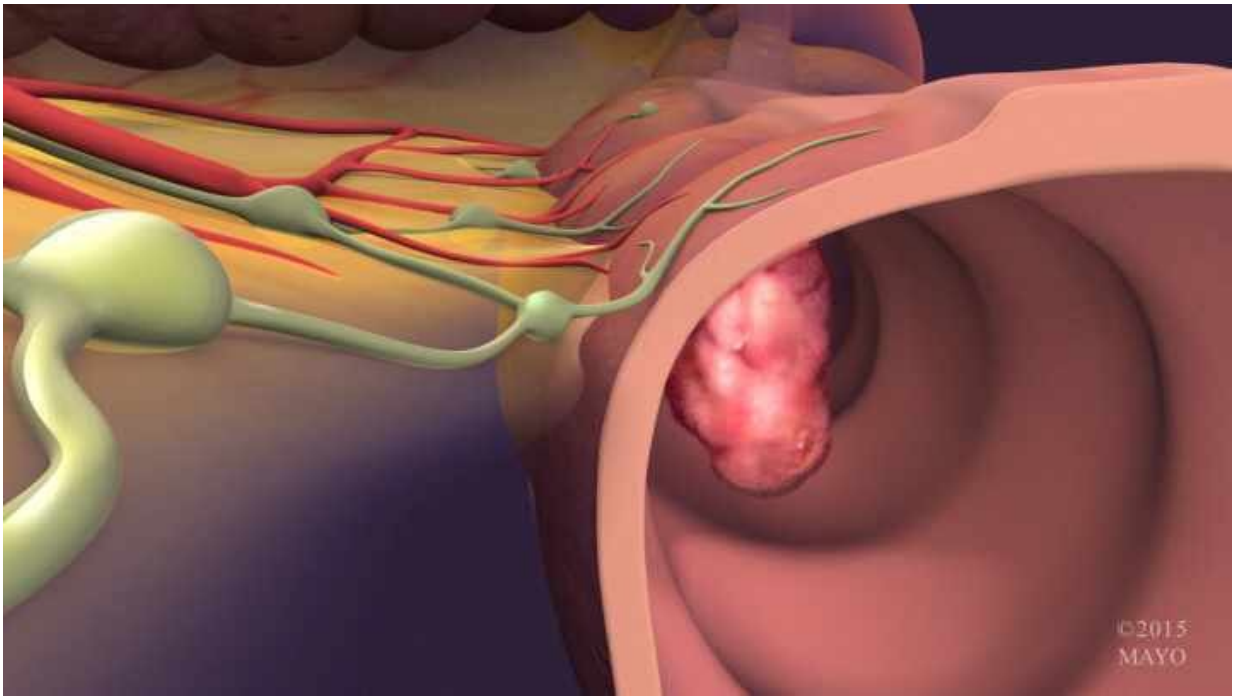
Genetically manipulating protein level in colon cancer cells can improve chemotherapy

August 26 2019



Credit: Mayo Clinic

Colorectal cancer outcomes may improve by genetically altering an immune-regulatory protein in cancer cells, making the cells more vulnerable to chemotherapy. That's according to new Mayo Clinic research.

The findings, published this month in *Oncogene*, indicate that increasing

the expression of the PD-L1 protein in colorectal cancer cells can improve the effectiveness of chemotherapy.

"These findings, if verified by subsequent research, suggest that the level of tumor cell PD-L1 may be important in drug sensitivity and suggest that enhancing PD-L1 expression may be a potential strategy to improve treatment outcomes in this malignancy," says Frank Sinicrope, M.D., a Mayo Clinic medical oncologist and gastroenterologist. Dr. Sinicrope is co-director of the Gastrointestinal Cancer Program at Mayo Clinic and corresponding author of the study.

PD-L1 is an immune checkpoint protein that interacts with another protein, PD-1, to negatively affect cell functions and enable tumor cells to evade the body's immune system. Research has shown that interrupting the PD-L1/PD-1 interaction can enhance attacks on anti-tumor immunity.

However, the Mayo Clinic study describes another function of PD-L1: its effect on proteins that regulate tumor cell death. Deleting the PD-L1 gene suppressed two proteins that are associated with increased chemotherapy-induced cell death. In contrast, restoring PD-L1 expression reversed the suppression of these proteins.

"We sought to determine the relevance of our findings for PD-L1 in patients with colorectal cancer," Dr. Sinicrope says. "To do so, we utilized the Cancer Genome Atlas database of the National Cancer Institute to examine the association of PD-L1 expression with the survival of patients with colon cancer."

The study found that increased tumor cell PD-L1 expression was associated with better survival among patients expected to have received chemotherapy, which is the standard of care for patients with stage 3 and stage 4 cancers, according to Dr. Sinicrope.

"This suggests a broader role for PD-L1 as a possible predictive biomarker for how patients will respond to cancer treatment, though more research is needed to address this issue," he says.

The study also found that the BRAF oncogene, a gene that can transform a cell into a cancer cell, can regulate the expression of PD-L1. When the BRAF oncogene is mutated, it can increase PD-L1 expression in colorectal cancer cells, according to the study.

"Current therapies targeting PD-L1 are mainly focused on blocking or disrupting its function in tumor cells," says Haidong Dong, M.D., Ph.D., a Mayo Clinic tumor immunologist and co-author of the study. "This work suggests that enhancement of PD-L1 expression in tumor cells may promote the efficacy of chemotherapy, at least in colon cancer. It is an idea-changing discovery that, if validated in clinical trials, would bring more benefit to patients with colon cancer that is resistant to current chemotherapy."

More information: Daofu Feng et al. BRAFV600E-induced, tumor intrinsic PD-L1 can regulate chemotherapy-induced apoptosis in human colon cancer cells and in tumor xenografts, *Oncogene* (2019). DOI: 10.1038/s41388-019-0919-y

Provided by Mayo Clinic