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Subgroup of colorectal cancer patients ID'd: Do poorly, could benefit from immunotherapy

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While the medical community agrees that immune cells inside a tumor leads to improved health outcome, for a subset of colorectal cancer patients, having too much of a good thing—too many immune cells—is a strong predictor of disease recurrence and reduced chances of survival, according to new research from City of Hope, a world-renowned independent research and treatment center for cancer, diabetes and other life-threatening diseases.

"Having immune cells in tumors is widely recognized as a good thing, but we found that too much of a good thing is actually bad," said Peter P. Lee, M.D., chair of the Department of Immuno-Oncology at City of Hope and senior author of a study published in the *Journal of Clinical Investigation* on Sept. 16.

The researchers examined colorectal cancer, the third-leading cause of cancer-related deaths in the United States.

"This study is the first report of immune infiltrated tumors with poor health outcomes and is counter to the standard belief in the field," said Lee, the Billy and Audrey L. Wilder Professor in Cancer Immunotherapeutics. "This is a new way to look at colorectal tumors and is a reminder that physicians cannot base treatment merely on established, one-size-fits all treatment templates."

City of Hope physician-scientists are working on precision medicine research so that their patients can receive more bespoke treatment. They analyzed public genomic data sets from The Cancer Genome Atlas and NCBI Gene Expression Omnibus and validated their findings with data from 71 City of Hope patients diagnosed with Stage 3 colorectal cancer.

About 10% of these City of Hope colorectal cancer patients had a cornucopia of immune cells turned on, including CD8+ T cells. However, this group of patients all relapsed. In fact, they relapsed even earlier than patients with little or no immune cells in their tumors. The problem appeared to be that their immune system was on overdrive; they also had their immune checkpoint inhibitors—the proteins that put the immune system in neutral—in overdrive. The result is like two trains colliding: No one going anywhere fast.

Based on a series of analyses and cross-validation tests, the researchers were able to stratify the patients into four categories. Patients with high levels of immune cell infiltration and high levels of the checkpoint inhibitor PD-L1 were two to three times more likely to die from colorectal cancer compared to their peers who had tons of immune cell infiltration and low levels of checkpoint inhibitors.

Although the study needs to be duplicated in a prospective study with a larger sample size, the researchers propose that PD-L1 expression and CD8 combined score could be used as a biomarker to identify colorectal cancer patients who may require more aggressive monitoring and treatment.

"Patients in this subgroup may be good candidates for immunotherapy to reduce the chances of disease recurrence," said Marwan Fakih, M.D., co-director of the Gastrointestinal Cancer Program at City of Hope and lead author of the study.

About 60% of the patients in this subgroup had tumors that are "microsatellite instable," a disease category that points to people who typically have had positive responses to an immunotherapy that uses immune checkpoint inhibitors.

"Those in this subgroup who have high immune cell infiltration and a high immune-suppressive tumor microenvironment should be considered for enrollment in clinical trials that use immune checkpoint inhibitors," Fakih said. "If we continue to treat these patients with standard of care, they will continue to have a poor prognosis. We should use what we learned in this study to improve their chances of survival."

The study provides a more nuanced understanding of Immunoscore, a recent benchmark used to predict risk of colorectal cancer recurrence. Most colorectal patients who have tumors with high CD8+ T-cell infiltration still have favorable outcomes. However, City of Hope researchers found that if those patients also have high levels of PD-L1 expression, they may be mislabeled as having a good prognosis by Immunoscore, which relies solely on expression of CD3 and CD8 immune T cells.

City of Hope scientists are beginning to apply the same techniques used in this study to examine data on breast cancer patients. They plan to use the same process to analyze other cancers such as melanoma and lung cancer.

Provided by City of Hope