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Number of mutations in a tumor varies by age and type of cancer

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A team of investigators led by researchers at Georgetown Lombardi Comprehensive Cancer Center has found that the tumor mutation load, or TML, in a patient's cancer biopsy varied by age and the type of cancer, along with several other factors.

Researchers say the findings are some of the most comprehensive analyses of TML to date as they include 14 types of solid tumors. Over 8,000 tissue samples were included in the study making this one of the larger collections of tumors examined for TML. The abstract describing the work was released today. Additional details will be presented at the American Society of Clinical Oncology annual meeting next month in Chicago.

TML is a measurement of the number of mutations in DNA. Mutated DNA can be subsequently translated to harmful changes in proteins. Mutated proteins often appear foreign to the immune system and can therefore activate a robust immune response that can be boosted by immunotherapeutic agents.

"One of our more interesting findings was the fact that mutation load increased with age in many cancers," says the study's principal investigator, Mohamed E. Salem, M.D., assistant professor of medicine at Georgetown Lombardi. "Older age correlated closely with TML in most of the cancers we examined, but in some cancers, such as bladder cancer, there was no correlation by age, which also makes for an important observation in a difficult to treat type of cancer."

Looking for high levels of mutations in tumor may seem to be a contrary way of looking for what therapies might be most effective to fight cancer. Because immunotherapies work by taking the brakes off the immune system, and hence allowing immune-fighting cells to go after cancer cells, the more mutations a cancer cell has may make it appear more alien to the immune-fighting cells and therefore, a more focused object of attack. If a cell's TML is high, an immunotherapy could be more effective and hence Salem's interest in quantifying TML. Tumor mutation load also could be used as a marker to determine which types of cancer and which patients, or subsets of patients, could most benefit from immunotherapy.

"We found that, as expected, melanoma had the highest TML as we know clinically that this type of cancer responds best to immunotherapy," says Salem, also a member of Georgetown Lombardi's Ruesch Center for the Cure of GI Cancer. "Indeed, the mean TML for melanoma was nearly double that of the next highest mean, non-small cell lung cancer. In addition, we see that high TML often occurs in tumors lacking well-known cancer-related genes, like BRAF or NRAS genes in melanoma and EGFR or ALK genes in non-small cell lung cancer. This suggests that immune checkpoint inhibitors may be particularly effective in patients who are not candidates for common targeted therapies in these types of cancer."

"Our next step is to validate and correlate TML levels with outcomes in patients who have received immunotherapy. We'll look to see if patients had high TML levels before they started therapy and then determine if those with the highest levels had the best clinical outcome, which is what we might expect," he says.

"If validation studies prove helpful, they could be very useful in designing clinical trials for many types of cancer," Salem concludes.

More information: Paper title: Characterization of tumor mutation load (TML) in solid tumors

Provided by Georgetown University Medical Center