Tumor mutations may predict response to immunotherapy

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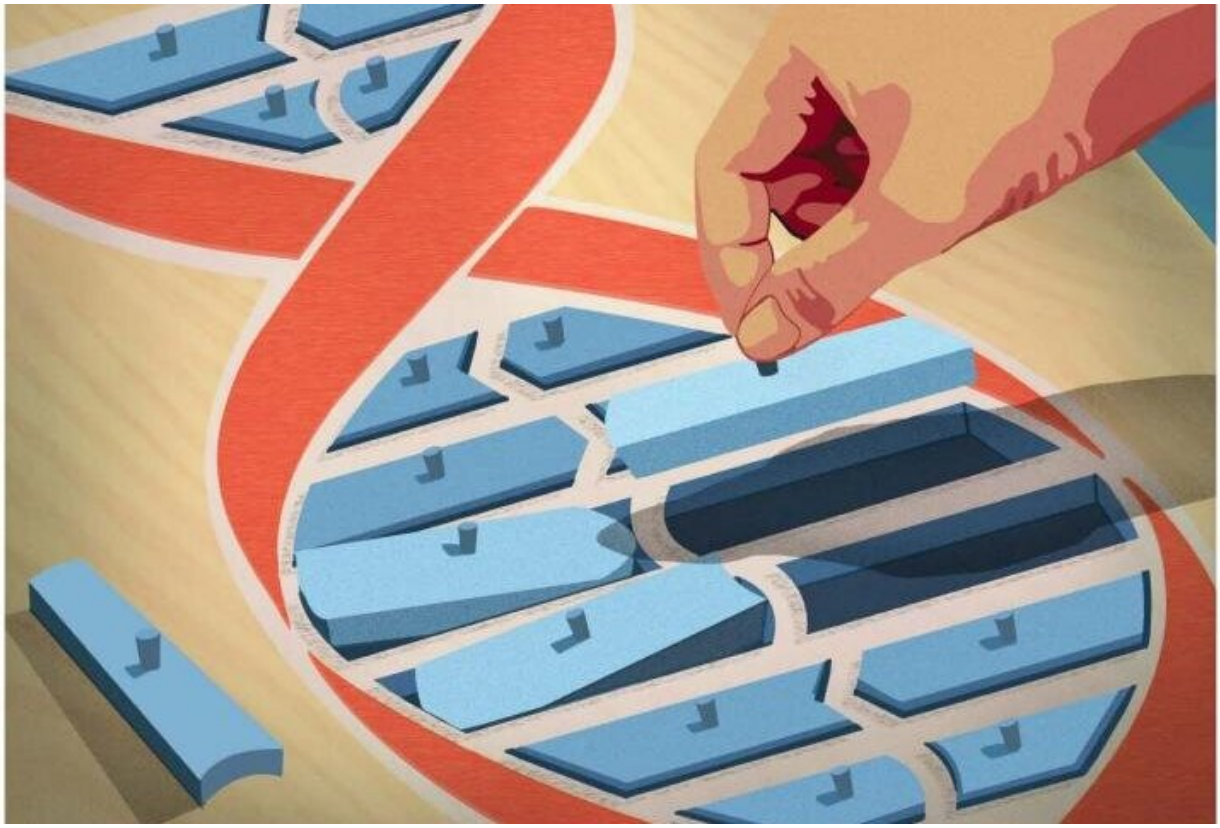

Mismatch repair deficiency refers to a characteristic of some cancer cells that create a large number of mutations, or changes, in certain genes when their mismatch repair proteins are unable to correct mistakes made when DNA is copied and passed on to daughter cells. Credit: Andrew H. Lee

Mismatch repair deficiency refers to a characteristic of some cancer

cells that create a large number of mutations, or changes, in certain genes when their mismatch repair proteins are unable to correct mistakes made when DNA is copied and passed on to daughter cells. Tumor cells with many such mutations create what is known as microsatellite instability and a worsening inability to correct those DNA mistakes. And, because defective genes can cause both inherited and noninherited (or sporadic) forms of cancer, they are used as biomarkers for diagnostic screening and chemotherapy treatment planning.

In a new study of such tumors in mice and humans, the investigators say they discovered that the tumors most likely to respond to immunotherapy have a higher degree or intensity of microsatellite instability (MSI) than tumors with lower MSI, meaning the former tumors possess a higher degree of DNA alterations after repeated cell divisions over time.

In particular, the researchers report, they have a higher amount of insertion/deletion, or indel, mutations of the DNA building blocks compared to other tumors. Indel mutations involve a series of nucleotides, or genetic "letters," either inserted into the genetic code or removed during cell division. They can potentially generate neoantigens, or new proteins in cancer cells that the immune system can recognize and destroy.

A description of the new work is published in the May 3 issue of the journal *Science*.

One anticipated outcome of the new findings is that by taking a biopsy and sequencing the DNA of one of these tumors, clinicians could look for the degree of MSI intensity when forming a treatment plan for patients, says lead study author Rajarsi Mandal, M.D., director of the Head and Neck Cancer Immunotherapy Research Program at the Bloomberg~Kimmel Institute for Cancer Immunotherapy. Mandal is also

an assistant professor of otolaryngology-head and neck surgery at the Johns Hopkins University School of Medicine.

"This genetic 'signature' potentially could serve as a novel biomarker, akin to a crystal ball, to see which cancer patients may respond to immunotherapy," Mandal says. He cautions that the new results need to be validated in a larger study. "We're not making any definitive claims at this time," he says, "but we believe this is the first evidence that it might be possible to use such sequencing data for patients with advanced mismatch repair deficient tumors."

At least 14 cancers types have this genetic characteristic, Mandal says. It's most common in colorectal, stomach, uterine and endometrial cancers, but it is also seen, to a lesser degree, in other types such as lung cancer and head and neck cancer.

Mandal and colleagues performed several experiments to tease out immunotherapy response in mismatch repair deficient tumors. First, they took mouse melanoma and mouse colorectal cancer cell lines and used gene-editing tools (CRISPR-Cas9) to create tumors with mismatch repair deficiency akin to those found in human tumor cells, and grew them over several weeks.

Those grown for four weeks were termed MSI-intermediate cell lines, whereas those grown for four months were termed MSI-high cell lines. On analysis using whole exome sequencing they found that the MSI-high cell lines had more indel mutations, and more of another type of mutation called missense (in which just one genetic letter is replaced during cell division) than the MSI-intermediate cell lines or the original parent cell lines created for the experiment.

Investigators then implanted these cell lines into the flanks of living mice and treated the mice with either immunotherapy drugs called anti-PD-1

checkpoint inhibitors or a sham treatment. Anti-PD-1 checkpoint inhibitors release the brakes on immune cells that would otherwise shut down the immune response against cancer cells.

Mice implanted with the MSI-high lines and treated with anti-PD-1 had a much more pronounced decrease in tumor volume than mice with MSI-intermediate lines and the parent lines. This suggested that the variable response the team saw was due to variations in the genetic characteristic of these tumors, says Mandal.

Then, 24 days after implantation, researchers analyzed the amount of tumor-infiltrating lymphocytes (immune system white blood cells that attack and destroy tumor cells) in the mouse tumors. They found a statistically significant and highly pronounced increase in these cells in the MSI-high tumors after anti-PD-1 therapy compared to the other samples, suggesting the response is related to the immune system.

Next, the team sequenced the DNA of the MSI-high tumors and found a reduction in missense and indel mutations in those treated with anti-PD-1. This suggested that these mutations were responsible for creating neoantigens recognized and eliminated by the immune system, Mandal says.

Building on these findings, the team looked at clinical data drawn from three independent cohorts of cancer patients to see what the relationship might be between MSI intensity and response to anti-PD-1 therapy in people. The researchers first examined baseline immune activity as measured by a previously reported and standardized immune activity score, known as CYT, measured across 14 human cancers, finding a general trend toward increased immune activity in MSI-high tumors compared to MSI-low tumors.

The researchers also say they observed a statistically significant

difference—meaning the findings were not by chance—between the immune activity in MSI-high and MSI-low cancers frequently detected to have mismatch repair deficiency, such as uterine, endometrial, stomach and colorectal cancers.

The team also analyzed DNA sequences from two separate groups of patients with mismatch repair deficient tumors treated with anti-PD-1 immunotherapy. Among the first group of 15 patients from Johns Hopkins, from the nine with mismatch repair deficiency they noted that patients with higher levels of genetic MSI generally were the ones who had complete or very good responses to immunotherapy compared to patients with lower levels.

In a second group of 33 patients from Memorial Sloan Kettering, the team noted that patient MSI levels in the top 80th percentile were associated with improved survival after treatment with immune checkpoint inhibitors, mostly compared to those in the bottom 20th percentile.

"Together, our data demonstrate that a range of MSI types exist, and may help identify patients who will benefit from immunotherapy," says Mandal. "It may be possible to classify responders and nonresponders to anti-PD-1 therapy across mismatch repair deficient cancers by using precise, next-generation sequencing measures of MSI intensity."

Mandal says the team's next steps will explore the role of the innate immune system in the MSI-related immune response and confirm whether the baseline or the continuously generated mutations, particularly insertion-deletions mutations, are responsible for the therapeutic response observed.

More information: Rajarsi Mandal et al. Genetic diversity of tumors with mismatch repair deficiency influences anti–PD-1 immunotherapy