Absent tumor-suppressors allow melanoma to thwart immunotherapy

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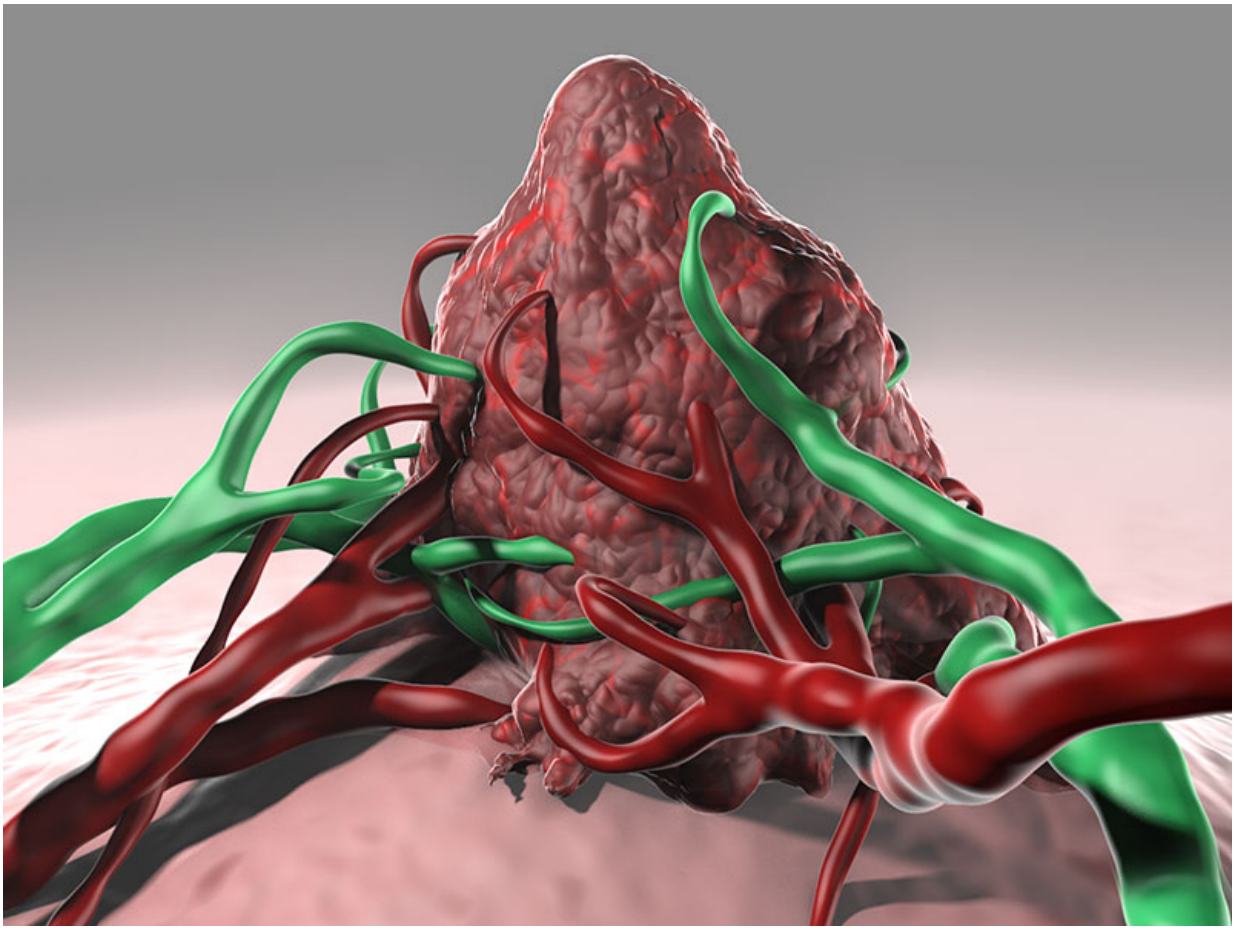

Researchers identified a set of genetic changes that predict whether melanoma patients will respond to checkpoint inhibitor therapies. Credit: Chris Bickel / Science Translational Medicine (2017)

It's what's missing in the tumor genome, not what's mutated, that thwarts treatment of metastatic melanoma with immune checkpoint blockade drugs, researchers at The University of Texas MD Anderson Cancer Center report in *Science Translational Medicine*.

Whole exome sequencing of tumor biopsies taken before, during and after treatment of 56 patients showed that outright loss of a variety of tumor-suppressing genes with influence on immune response leads to resistance of treatment with both CTLA4 and PD1 inhibitors.

The team's research focuses on why these treatments help 20-30 percent of patients—with some complete responses that last for years - but don't work for others. Their findings indicate that analyzing loss of blocks of the genome could provide a new predictive indicator.

"Is there a trivial or simple (genomic) explanation? There doesn't seem to be one," said co-senior author Andrew Futreal, Ph.D., professor and chair of Genomic Medicine and co-leader of MD Anderson's Moon Shots Program. "There's no obvious correlation between mutations in cancer genes or other genes and immune response in these patients."

"There are, however, pretty strong genomic copy loss correlates of resistance to sequential checkpoint blockade that also pan out for single-agent treatment," Futreal said. Doctoral candidate Whijae Roh, co-lead author, Futreal, and co-senior author Jennifer Wargo, M.D., associate professor of Surgical Oncology and Genomic Medicine, and colleagues analyzed the genomic data for non-mutational effects.

"We found a higher burden of copy number loss correlated to response to immune checkpoint blockade and to lower immune scores, a measure of immune activation in the tumor's microenvironment," said Roh, a graduate student in the University of Texas MD Anderson UTHealth Graduate School of Biomedical Sciences. "We also found copy loss has

an effect that is independent of mutational load in the tumors."

Mutational load + copy loss tells a story

Melanoma tumors with larger volumes of genetic alterations, called mutational load, provide more targets for the immune system to detect and are more susceptible to checkpoint blockade, although that measure is not conclusive alone. "Combining mutational load and copy number loss could improve prediction of patient response," Wargo said.When the team stratified patients in another data set of patients by whether they had high or low copy loss or high or low mutational load, they found that 11 of 26 patients with high mutational load and low copy loss had a clinical benefit, while only 4 or 26 with low mutational load and high copy loss benefited from treatment.

In the trial, patients were treated first with the immune checkpoint inhibitor ipilimumab, which blocks a brake called CTLA4 on T cells, the immune system's specialized warriors, freeing them to attack.

Patients whose melanoma did not react then went on to anti-PD1 treatment (nivolumab), which blocks a second checkpoint on T cells. Biopsies were taken, when feasible, before, during and after treatment for molecular analysis to understand response and resistance.

To better understand the mechanisms at work, the team analyzed tumor genomes for recurrent copy loss among 9 tumor biopsies from patients who did not respond to either drug and had high burden of copy number loss. They found repeated loss of blocks of chromosomes 6, 10 and 11, which harbor 13 known tumor-suppressing genes.

Analysis of a second cohort of patients confirmed the findings, with no recurrent tumor-suppressor loss found among any of the patients who had a clinical benefit or long-term survival after treatment.

Ipilimumab sometimes wins when it fails

The researchers also found a hint that treatment with ipilimumab, even if it fails, might prime the patient's immune system for successful anti-PD1 treatment.

The team analyzed the genetic variability of a region of the T cell receptors, a feature of T cells that allows them to identify, attack and remember an antigen target found on an abnormal cell or an invading microbe. They looked for evidence of T cell "clonality," an indicator of active T cell response.

Among eight patients with longitudinal samples taken before treatment with both checkpoint types, all three who responded to anti-PD1 therapy had shown signs of T cell activation after anti-CTLA treatment. Only one of the five non-responders had similar indicators of T cell clonality.

"That's evidence that anti-CTLA4 in some cases primes T cells for the next step, anti-PD1 immunotherapy. It's well known that if you don't have T cells in the tumor, anti-PD1 won't do anything, it doesn't bring T cells into the tumor," Futreal says.

Overall, they found that T cell clonality predicts response to PD1 blockade but not to CTLA-4 blockade.

"Developing an assay to predict response will take an integrated analysis, thinking about genomic signatures and pathways, to understand the patient when you start therapy and what happens as they begin to receive therapy," Wargo said. "Changes from pretreatment to on-therapy activity will be important as well."

APOLLO tracks response over time

The *Science Translational Medicine* paper is the third set of findings either published or presented at scientific meetings by the team, which is led by Futreal and Wargo, who also is co-leader of the Melanoma Moon Shot.

Immune-monitoring analysis showed that presence of immune infiltrates in a tumor after anti-PD1 treatment begins is a strong predictor of success. They also presented evidence that the diversity and composition of a patient's gut bacteria also affects response to anti-PD1 therapy.

The serial biopsy approach is a hallmark of the Adaptive Patient-Oriented Longitudinal Learning and Optimization (APOLLO) platform of the Moon Shots Program, co-led by Futreal that systematically gathers samples and data to understand tumor response and resistance to treatment over time.

The Moon Shots Program is designed to reduce cancer deaths by accelerating development of therapies, prevention and early detection from scientific discoveries.

More information: "Integrated molecular analysis of tumor biopsies on sequential CTLA-4 and PD-1 blockade reveals markers of response and resistance," *Science Translational Medicine*, stm.sciencemag.org/lookup/doi/ … scitranslmed.aah3560

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