Study finds melanoma biomarkers predicting checkpoint blocker response

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Melanoma. Credit: Wikimedia Commons/National Cancer Institute

Scientists at Dana-Farber/Brigham and Women's Cancer Center (DF/BWCC) have identified biomarkers in melanoma that could help tailor immunotherapy treatments to maximize the benefits for patients while reducing the likelihood of severe side effects.

While the utility of these biomarkers needs to be validated in future clinical trials, the findings reported in *Science Translational Medicine* suggest that the current practice of combining two different types of immune checkpoint blocker drugs in advanced melanoma patients may be the best course in some instances, but not in others, because the immune makeup of some melanoma tumors may cause them to be resistant to one class of checkpoint inhibitors.

"By looking at how melanoma is avoiding immune detection, we may be able to identify patients who may do just as well with a single agent, with no loss of efficacy, but improved tolerability," said Scott Rodig, MD, Ph.D., an oncologic pathologist at DF/BWCC and first author on the report. The study revealed that some patients, whose tumors are deficient in a protein needed for the immune system to recognize cancer cells, are unlikely to benefit from ipilimumab, an immunotherapy drug that blocks the CTLA-4 checkpoint, but which has potentially severe side effects. Therefore, identifying such patients with a biomarker test prior to treatment could spare them the adverse effects.

The outlook for patients with advanced melanoma has dramatically improved in recent years because of drugs known as immune checkpoint inhibitors, which mobilize the immune system to attack cancer. These drugs block checkpoint molecules that act as brakes on the immune system; by removing these brakes, checkpoint inhibitors unleash immune defenders such as T cells to recognize and attack cancer.

Typically, patients with advanced melanoma receive a combination of two different checkpoint inhibitor types: one, such as ipilimumab, targets the CTLA-4 checkpoint, while the other, including nivolumab and pembrolizumab, targets the PD-1 checkpoint.

In general, patients with advanced melanoma have better outcomes when they receive drugs that block both the CTLA-4 checkpoint and the PD-1

or PD-L1 checkpoints, said F. Stephen Hodi, MD, director of the Melanoma Disease Center at Dana-Farber and senior author of the report. Treated with the combination, more than 50 percent of patients will have tumor shrinkage and some of the responses will be quite prolonged, he said. But this benefit can come at a steep cost—around 50 percent of patients will have severe side effects, such as inflammation of the gut causing diarrhea; rash, or inflammation of the liver and pancreas.

The new study was inspired by recent research by Margaret Shipp, MD, at Dana-Farber showing that Hodgkin lymphomas frequently avoid immune detection by eliminating their MHC class I proteins. MHC class I proteins are found on the surface of most cells in the body. Their function is to bind fragments of foreign proteins, including those stemming from cancer cells, and present them to T cells, which then mount a mass attack on the invader. But if cancer manages to somehow dial down the abundance of MHC class I proteins, the immune system won't recognize the cancer as foreign and respond against it. In Hodgkin lymphoma, the tumor cells accomplish this feat by deleting a key gene required for expression of the MHC class I proteins.

Speculating that something similar might occur in melanoma, the authors of the new study used data from two clinical trials of immunotherapy for advanced melanoma that included measurements of MHC class I proteins and other immune cells and immune regulators. The investigators found that partial or complete loss of MHC class I proteins was common in untreated melanoma patients, and those patients had poor responses to treatment with ipilimumab—the drug that blocks the CTLA-4 checkpoint. "CTLA-4 is exquisitely sensitive to even partial loss of these MHC class I proteins," said Rodig. The result was the melanoma was highly resistant to ipilimumab treatment and the cancer continued to grow, because even though the immunotherapy drug was releasing the CTLA-4 brake on the immune system, the melanoma cells weren't recognized due to the lack of MHC class I proteins to "present"

the cancer fragments to the T cells. These findings may explain why most melanoma patients don't respond to single-agent ipilimumab.

However, the researchers also observed that the deficiency of MHC class 1 proteins did not make melanoma tumors resistant to the other type of checkpoint inhibitor, drugs like nivolumab, a PD-1 inhibitor. That is because responses to those drugs activate an immune substance known as interferon-gamma, which in turn activates both MHC class I-dependent and MHC class I-independent immune pathways and thereby promotes anti-tumor activity when MHC class I levels are reduced by the tumor. Indeed, the data from the clinical trials showed that patients whose tumors had higher pre-treatment levels of interferon-gamma had better outcomes when treated with nivolumab or a combination of nivolumab and ipilimumab but not ipilimumab alone.

These results, the authors conclude, reveal that the clinical efficacy of anti-CTLA-4 drugs like ipilimumab is "dependent on robust, pre-existing expression of MHC class I proteins by tumor cells." By contrast, efficacy of anti-PD1 checkpoint blockers like nivolumab depends on "pre-existing interferon-gamma-mediated inflammation within the tumor microenvironment." Combining the two types of checkpoint blockers "provides a further immune stimulus over individual therapies alone and, in addition, overcomes the limitations of each," they said.

Going forward, the researchers said, it would be ideal to have clinical trials in which treatment options are determined in accordance with the results of tissue-based biomarker studies."

  More information: S.J. Rodig el al., "MHC proteins confer differential sensitivity to CTLA-4 and PD-1 blockade in untreated metastatic melanoma," *Science Translational Medicine* (2018). stm.sciencemag.org/lookup/doi/ … scitranslmed.aar3342