Team pinpoints immune changes in blood of melanoma patients on PD-1 drugs

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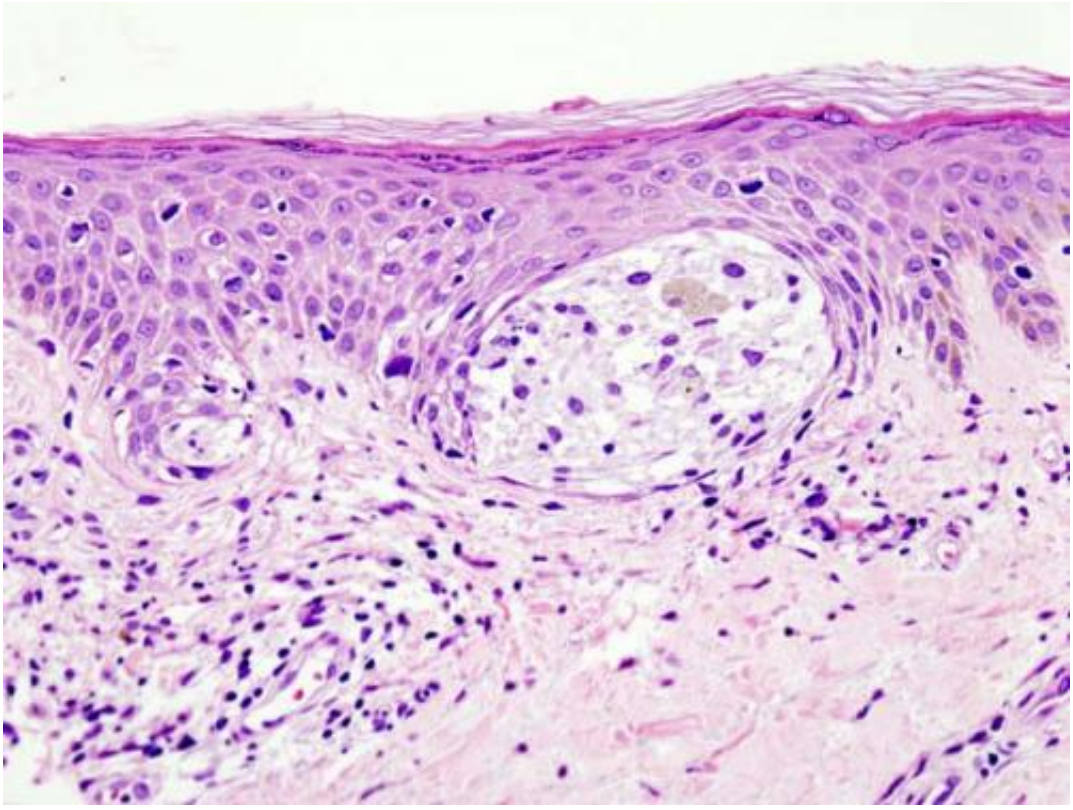

Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

A simple blood test can detect early markers of "reinvigorated" T cells and track immune responses in metastatic melanoma patients after initial treatment with the anti-PD-1 drug pembrolizumab, researchers from the Abramson Cancer Center of the University of Pennsylvania report in

new research being presented at the inaugural CRI-CIMT-EATI-AACR International Cancer Immunotherapy Conference. The new findings give more insight into how the anti-PD-1 therapy, approved last year by the U.S. Food and Drug Administration to treat metastatic melanoma, goes to work inside patients' bodies, and potentially form the basis of a biomarker to predict which patients are most apt to respond to the immunotherapy.

Pembrolizumab, approved by the FDA for treating metastatic melanoma a year ago, is a PD-1 inhibitor, a class of drug which stimulates the immune system to attack tumors. Preclinical mouse studies have shown that in cases of metastatic melanoma, certain immune cells called CD8+ T cells have high levels of a protein called PD-1, which inhibits or prevents the CD8+ T cells from attacking the cancer. Pembrolizumab in effect, takes the brake off, helping reinvigorate the CD8+ T cells.

However, only about 40 percent of patients respond to anti-PD1 therapy, and there is currently no way to determine who will benefit from the immunotherapy. Therefore a biomarker to predict efficacy of anti-PD1 therapy is needed for early escalation of therapy in non-responders and minimizing toxicity for those who do respond, since many take the drug in combination with other therapies, like radiation and checkpoint inhibitors.

"Anti-PD-1 therapies have changed the melanoma treatment landscape, and shown impressive responses in groups of patients; however, there is still more information about its effects on the human immune system that need to be uncovered," said the study's lead author, Alexander Huang, MD, a clinical fellow in the division of Hematology/Oncology at Penn's Perelman School of Medicine and Abramson Cancer Center "As a result of our study, we are encouraged to see changes suggesting reinvigoration in CD8+ T cells following treatment with pembrolizumab."

"We are able to track clear immune changes in the blood, which means that finding a noninvasive biomarker to predict who might respond to the immunotherapy is potentially in reach," he added.

In a phase I clinical trial, Huang and colleagues analyzed blood samples from 39 patients with metastatic melanoma over 12 weeks. For each patient, blood samples were obtained immediately before the every-three-week pembrolizumab treatment began. What's surprising is that the majority of patients treated by anti-PD-1 therapy had a significant immune response.

The researchers focused on changes in levels of proteins characteristic of reinvigoration in CD8+ T cells positive for PD-1 (CD8+PD-1+ T cells). They found increased levels of the protein granzyme B, which is a marker of the killing capacity of a CD8+ T cell, and the protein Ki67, which is a marker of cell proliferation, in blood samples obtained after pembrolizumab treatment had started.

In addition, the frequency of CD8+ T cells positive for granzyme B was greater in blood samples obtained after pembrolizumab treatment had started compared with blood samples obtained before pembrolizumab treatment started.

"Our next step is to examine the blood-based data for each patient in context with their clinical profiles. We want to see if the magnitude of changes we found is linked to clinical response, in particular, objective measures such as tumor burden, progression-free survival and tumor shrinkage," Huang said. "This will be crucial for determining if our data could serve as the basis of a noninvasive biomarker test for predicting which patients could be helped by pembrolizumab."

In previous trials, pembrolizumab was shown to be twice as effective as chemotherapy, halting and occasionally shrinking tumor growth in 34

percent of patients with advanced malignant melanomas, compared to only 16 percent of patients receiving chemotherapy alone. Until recently, patients with advanced melanomas were typically told they should not expect to live for more than six to nine months. But in one trial, 60 percent of patients who received pembrolizumab survived for at least 12 months. The drug is so new that longer-term survival data do not yet exist.

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