MedicalXpress

New imaging method may predict immunotherapy response early

May 1 2017

A noninvasive PET imaging method that measures granzyme B, a protein released by immune cells to kill cancer cells, was able to distinguish mouse and human tumors that responded to immune checkpoint inhibitors from those that did not respond early in the course of treatment.

The study was published in *Cancer Research*, a journal of the American Association for Cancer Research, by Umar Mahmood, MD, PhD, professor of radiology at Harvard Medical School and director of the Division of Precision Medicine at Athinoula A. Martinos Center for Biomedical Imaging in Massachusetts General Hospital (MGH), Boston.

Although immunotherapies, such as checkpoint inhibitors, have revolutionized cancer treatment, they only work in a minority of patients, which means that most patients receiving this treatment will not benefit but still have the increased risk of side effects, besides losing time that they could spend on other therapies, Mahmood explained.

Response to immunotherapy often cannot be measured effectively at early time points by traditional imaging techniques that measure tumor size, such as CT and MRI scans, or those that measure tumor glucose uptake, such as FDG PET, because these techniques cannot distinguish a nonresponding tumor from a tumor that is responding to immunotherapy but appears to grow in size because it is filled with immune cells and accompanied by increased glucose uptake, Mahmood noted. Tissue biopsies can be unreliable because of tumor heterogeneity and constant

changes in the levels of the biomarker proteins measured.

Mahmood and colleagues designed a probe that binds to granzyme B—a protein that immune cells release to kill their target—after it is released from the immune cells, so they could directly measure tumor cell killing. The researchers attached the probe to a radioactive atom and used PET scanning to noninvasively image the entire body and see where immune cells are actively releasing tumor-killing granzyme B.

The team tested their probe in tumor-bearing mice before and after treatment with immune checkpoint inhibitors and found that one group of mice had high PET signal, meaning high levels of granzyme B in the tumors, while the other group had low levels of PET signal in the tumors. When the two groups of mice were followed, all mice with high PET signal responded to the therapy and their tumors subsequently regressed, whereas those with low PET signal did not respond to the therapy, and their tumors continued to grow.

"Because PET imaging is quantitative, we could measure the degree of effectiveness and put a number on it," Mahmood added. When they compared the data from monotherapy and combination therapy, they saw a significant increase in tumor granzyme B PET signal in the combination group.

The researchers then collaborated with Keith Flaherty, MD, and Genevieve Boland, MD, PhD, from MGH, and tested their probe on nine human melanoma biopsy samples, six from patients treated with nivolumab (Opdivo) and three from those treated with pembrolizumab (Keytruda). They detected high levels of granzyme B in the samples from responders and much lower levels in the samples from nonresponders.

"The ability to differentiate early in the course of treatment patients who

are likely to benefit from immunotherapy from those who will not can greatly improve individual patient care and help accelerate the development of new therapies," Mahmood said.

"In our study, we found a marker that was highly predictive of response to immunotherapy at a very early time after starting treatment, and we were able to design an imaging probe to detect this marker and accurately predict response noninvasively," said Mahmood.

"These findings could have a significant impact on drug development, as different combinations could be imaged at very early time points in patients and the levels of tumor granzyme B used to compare treatments and rank effectiveness," Mahmood said. "Further, therapeutics that achieve high levels of granzyme B release can be advanced faster and those leading to low granzyme B release can be altered or eliminated."

Provided by American Association for Cancer Research