Gene expression profile may ID renal cell carcinoma pts unlikely to benefit from nivolumab

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Renal cell carcinomas positive for the protein PD-L1 from patients who did not respond to treatment with the anti-PD-1 therapeutic nivolumab (Opdivo) had significantly higher expression of genes associated with metabolism, compared with PD-L1-positive tumors from patients who did respond to nivolumab.

The study was published in *Cancer Immunology Research*, a journal of the American Association for Cancer Research, by Suzanne L. Topalian, MD, professor of surgery and oncology at the Johns Hopkins University School of Medicine, director of the Melanoma Program at the Sidney Kimmel Comprehensive Cancer Center, and associate director of the Bloomberg~Kimmel Institute for Cancer Immunotherapy at Johns Hopkins in Baltimore, Maryland.

Between 15 and 30 percent of patients with renal cell carcinoma, the most common type of kidney cancer, have substantial and durable responses to immunotherapeutics that target the PD-1/PD-L1 pathway, such as nivolumab, according to Topalian.

Researchers are now trying to identify markers that can predict whether or not a patient is likely to respond to these treatments, so that those who are unlikely to respond are saved the time and can avoid the potential adverse effects of a treatment unlikely to benefit them, added Topalian.

Evidence from some studies suggests that renal cell carcinomas positive for PD-L1 are more likely to respond to PD-1 pathway blockers compared to those negative for PD-L1, but not all PD-L1-positive renal cell carcinomas respond to these immunotherapies, she noted.

Topalian, Maria Libera Ascierto, PhD—a postdoctoral fellow working in Topalian's laboratory—and colleagues analyzed archived pretreatment tumor samples from 13 patients with metastatic renal cell carcinoma positive for PD-L1 who had gone on to receive nivolumab through clinical trials. Four of these patients were classified as having responded to nivolumab treatment and nine were classified as having not responded.

Whole-genome expression profiling, covering 29,377 genes, identified significantly elevated levels of 110 genes in tumors from nonresponding patients. Further analysis showed that genes expressed at elevated levels in tumors from nonresponding patients were predominantly associated with metabolism, the chemical processes that generate energy and eliminate waste products in cells. These genes were also found to be expressed in cultured kidney cancer cells.

"In this study, we found high expression levels of metabolic genes in PD-L1-positive renal cell carcinomas from patients who did not respond to nivolumab," said Topalian. "If these data are reproduced in larger groups of patients, we could potentially use the information to guide treatment decisions for patients with renal cell carcinoma.

"Given that nivolumab works by releasing the brakes on the immune system, most studies of treatment resistance so far have focused on looking for immune system-related mechanisms," continued Topalian. "Our data suggest that resistance can also be caused by tumor-specific mechanisms.

"Given the success of our unbiased whole-genome expression profiling approach, we are looking to extend these studies to analyze other types of cancer, as well as to confirm our current results in additional renal cell carcinomas from patients receiving anti-PD-1 therapies," she added. "Such studies may also reveal new drug targets for combination therapies with anti-PD-1."

According to Topalian, the main limitation of the study is that it was a retrospective analysis of samples from a small number of patients. However, she explained that the research team is hopeful that these preliminary but statistically significant results will provide a starting point for further exploration in larger cohorts of patients at Johns Hopkins and other institutions.

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