Risk of side effects from cancer immunotherapy linked to genetics

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Even as they've revolutionized cancer treatment, drugs known as immune checkpoint inhibitors can produce a range of adverse, immune-related side effects. In a new study, scientists at Dana-Farber Cancer Institute identify, for the first time, inherited genetic variations that place patients at high risk for these complications.

The discovery, reported online today in the journal *Nature Medicine*, was made with a mathematical model that allowed investigators to make an extraordinary analytical leap: using data about cancer-related mutations in tumor tissue, researchers were able to infer features of patients' genetic inheritance. They found that patients with specific germline variants—common inherited alterations in genes—had an increased likelihood of developing autoimmune-like side effects from checkpoint inhibitor treatment.

By identifying such patients prior to treatment—using the model and tumor-profiling technology already available at many U.S. cancer centers—doctors may be able to modify therapy to minimize side effects, the study authors say.

"Immune checkpoint inhibitors are remarkably effective across a variety of cancer types, but patients often experience immune-related toxicities, some of which can be quite severe," says co-senior author Alexander Gusev, Ph.D., of Dana-Farber, the Broad Institute of MIT and Harvard, and Brigham and Women's Hospital.

"Efforts to identify patients at high risk for toxicities have largely focused on genetic aspects of tumor tissue. Our hypothesis in this study was that the germline genetics of the patient influence the risk of

developing these toxicities."

Roughly 20% of patients treated with checkpoint inhibitors develop moderate to severe side effects—a figure that's consistent all cancer types for which the drugs are approved. The side effects mirror those associated with autoimmune diseases: skin problems, fatigue, joint pain, recurring fever, colitis, and, in severe cases, myocarditis, inflammation of the heart muscle.

These symptoms are the result of an overaggressive immune system attack. Checkpoint inhibitors work by lowering the barriers to an immune system assault on cancer cells, but because normal cells deploy some of the same barriers, they, too, may come under fire.

To see if patients' germline DNA—the genetic material within their cells—holds clues about their susceptibility to such events, researchers conducted a genome-wide association study (GWAS) of 1,715 patients being treated with checkpoint inhibitors across 12 cancer types. GWASs canvas the genome to see whether sections that often vary from person to person are associated with a particular disease.

Normally, this involves technology that reads each letter of DNA, in order, in a patient's normal cells (often, blood cells). For the new study, however, Gusev and his colleagues devised a way to do a GWAS study with data already on hand from a genomic analysis of patients' tumor tissue.

As part of the Profile program at Dana-Farber, the 1,715 patients in the study had had their tumor tissue scanned for mutations in about 500 genes linked to cancer. While this helped identify genetic vulnerabilities within these tumors, it didn't exhaust the genomic data collected for each one. Gusev created a mathematical model that uses raw data from Profile to generate readouts of the patients' genomes—and to identify

any variations within them.

"We went from 500 genes that were targeted in the tumor to, now, common variations genome-wide in this group of patients," Gusev remarks.

With the genomic data in hand, the researchers analyzed patients' medical records to see if those who experienced moderate to severe side effects from checkpoint inhibitors carried any common genomic variations. They found a connection to three such variations, the most prominent of which was near the gene IL7. They then confirmed these findings in a group of 196 patients treated at Massachusetts General Hospital and in 2,275 patients who took part in clinical trials of the checkpoint inhibitor atezolizumab.

"In our initial cohort of patients, we found that the rate of checkpoint inhibitor-related toxicities was three times higher in patients who had a genomic alteration near IL7," says study co-senior author Toni Choueiri, MD, of Dana-Farber. "In the two other groups of patients, the toxicity rate was five time higher in the IL7 group."

"The IL7 gene is known to help stabilize lymphocytes [white blood cells that help fight disease]," notes Matthew Freedman, MD, of Dana-Farber, also a co-senior author of the study. Researchers found that patients harboring the IL7 germline variant had greater lymphocyte stability during and after checkpoint inhibitor treatment, and that this stability was linked to a higher risk of adverse events and improved survival.

It makes biological sense that stable, vigorous lymphocytes could be responsible both for autoimmune-like side effects and a fiercer attack on tumors, extending patient survival, researchers say.

The study provides the first evidence that inherited genetic variations

can be a marker for increased susceptibility to immune-related side effects from checkpoint inhibitor therapy. The finding may ultimately help oncologists further personalize treatment for patients: those found likely to experience harsh side effects may be recommended for less intense or shorter courses of treatment, while those at low risk for toxicity may benefit from higher doses or more aggressive treatment, the study authors say.

More information: Groha, S. et al, Germline variants associated with toxicity to immune checkpoint blockade, *Nature Medicine* (2022). DOI: 10.1038/s41591-022-02094-6

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