Response to cancer immunotherapy may be affected by genes we carry from birth

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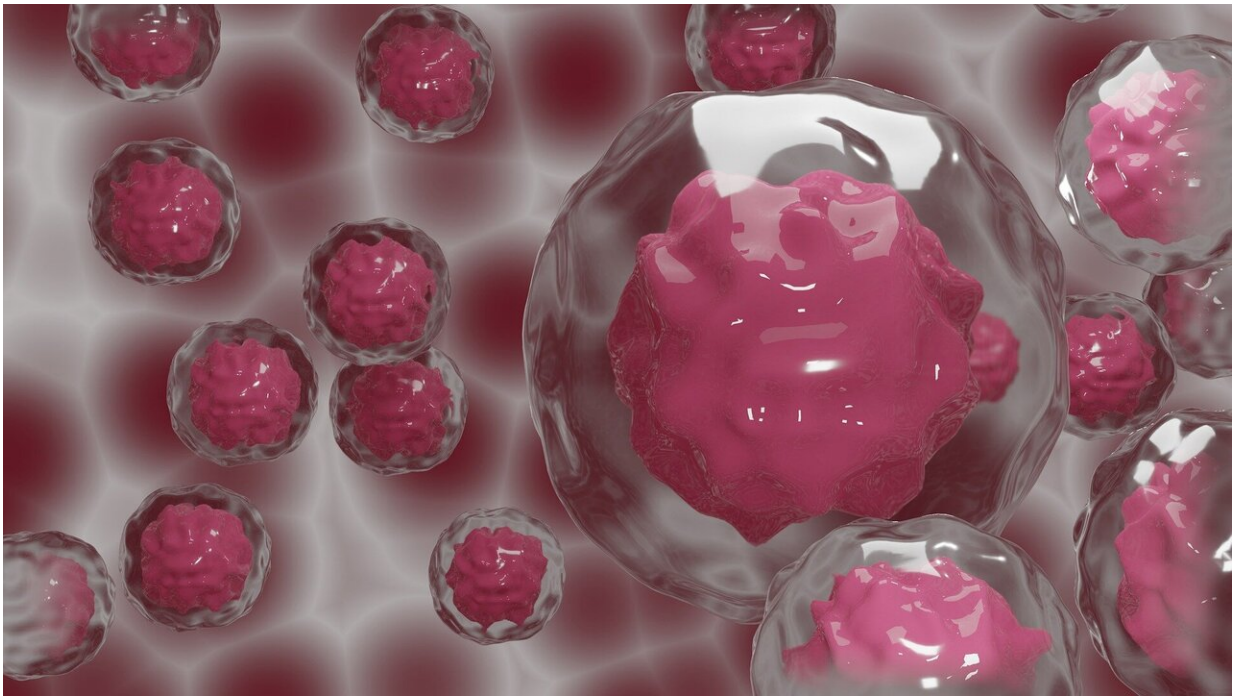

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For all their importance as a breakthrough treatment, the cancer immunotherapies known as checkpoint inhibitors still only benefit a small minority of patients, perhaps 15 percent across different types of cancer. Moreover, doctors cannot accurately predict which of their patients will respond.

A new study finds that inherited genetic variation plays a role in who is likely to benefit from checkpoint inhibitors, which release the immune system's brakes so it can attack cancer. The study also points to potential new targets that could help even more patients unleash their immune system's natural power to fight off malignant cells.

People who respond best to immunotherapy tend to have 'inflamed' tumors that have been infiltrated by immune cells that are capable of killing both viruses and cancer. This inflammation is also driven by the immune signaling molecule interferon.

"There are some factors that are already associated with how well the immune system responds to tumors," said Elad Ziv, MD, professor of medicine at UCSF and co-senior author of the paper, published Feb. 9, 2021, by an international team in *Immunity*. "But what's been less studied is how well your genetic background predicts your immune system's response to the cancer. That's what is being filled in by this work: How much is the immune response to cancer affected by your inherited genetic variation?"

The study suggests that, for a range of important immune functions, as much as 20 percent of the variation in how different people's immune systems are able to attack cancer is due to the kind of genes they were born with, which are known as germline genetic variations.

That is a significant effect, similar to the size of the genetic contribution to traits like high blood sugar levels or obesity.

"Rather than testing selected genes, we analyzed all the genetic variants we could detect across the entire genome. Among all of them, the ones with the greatest effect on the immune system's response to the tumor were related to interferon signaling. Some of these variants are known to affect our response to viruses and our risk of autoimmune disorders,"

said Davide Bedognetti, MD, Ph.D., director of the Cancer Program at the Sidra Medicine Research Branch in Doha, Qatar, and co-senior author of the paper. "As observed with other diseases, we demonstrated that specific genes can also predispose someone to have a more effective anti-cancer immunity."

The team identified variants in 22 regions in the genome, or in individual genes, with significant effects—including one gene, IFIH1, that is already well known for the role its variants play in autoimmune diseases as varied as type 1 diabetes, psoriasis, vitiligo, systemic lupus erythematosus, ulcerative colitis and Crohn's disease.

The IFIH1 variants act on cancer immunity in different ways. For instance, people with the variant that confers risk of type 1 diabetes had a more inflamed tumor, which suggests they would respond better to cancer immunotherapy. But the researchers saw the opposite effect for patients with the variant associated with Crohn's, indicating they might not benefit.

Another gene, STING1, was already thought to play a role in how patients respond to immunotherapy, and drug companies are looking for ways to boost its effects. But the team discovered that some people carry a variant that makes them less likely to respond, which may require further stratification of patients to know who could benefit most from those efforts.

The study required a huge amount of data that could only be found in a dataset as large as The Cancer Genome Atlas (TCGA), and from which they analyzed the genes and immune responses of 9,000 patients with 30 different kinds of cancer.

All told, the scientific team, which includes members from the United States, Qatar, Canada, and Europe, examined nearly 11 million gene

variants to see how they matched with 139 immune parameters measured in patient tumor samples.

But the 22 regions or genes identified in the new study are just the tip of the iceberg, the researchers said, and they suspect many more germline genes likely play a role in how the immune system responds to cancer.

The next step, Ziv said, is to use the data to formulate "polygenic" approaches—taking a large number of genes into account to predict which cancer patients will benefit from current therapies, and developing new drugs for those who will not.

"It's further off," he said, "but it's a big part of what we hope will come out of this work."

More information: Rosalyn W. Sayaman et al, Germline genetic contribution to the immune landscape of cancer, *Immunity* (2021). DOI: 10.1016/j.immuni.2021.01.011

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