Algorithm offers new way to spot patients likely to respond to immunotherapy

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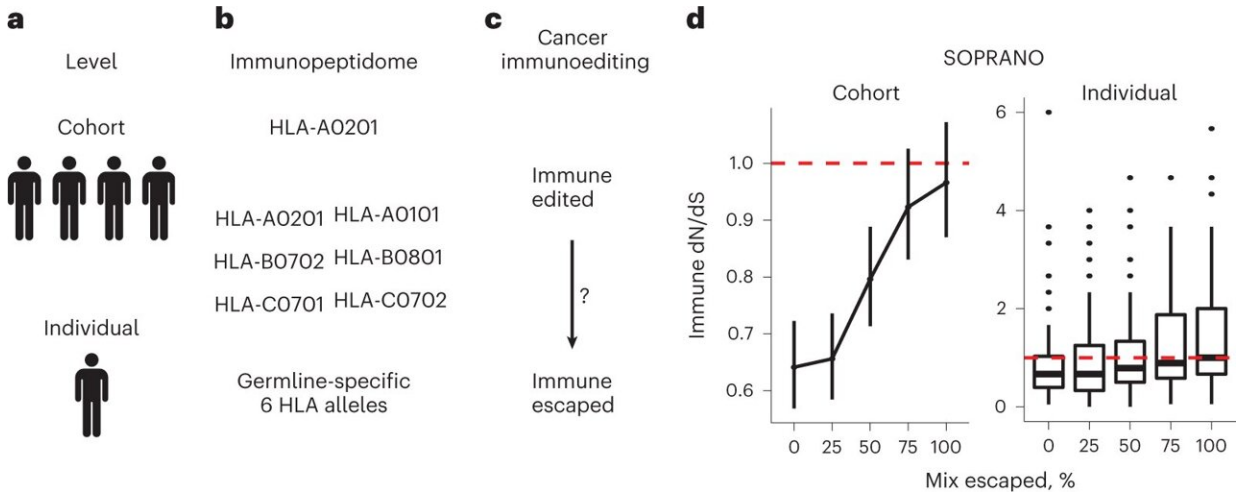

Overview of immune selection calculation using SOPRANO. a, Estimates can be performed at the cohort or at the single individual level. b, In each case, it is possible to estimate immune selection on a single HLA allele (that is, HLA-A0201), a generic combination of HLA alleles (proto-HLA) or the germline-specific HLA-immunopeptidome. c, Immune selection determines the evolutionary trajectories of clonal growth; fully immune-edited tumors with strong immune selection signals can transit towards fully immune-escaped tumors where signals are absent. d, Toy model of mixing immune-edited and immune-escaped tumors. It is possible to estimate immune dN/dS by aggregating all mutations and generate a single cohort estimate or to estimate a distribution of values per patient. In both cases, we hypothesize that mixing escaped with edited tumors leads to loss of immune selection signals reflected by immune dN/dS values closer to one (depicted as red dashed lines in the figure). Credit: *Nature Genetics* (2023). DOI: 10.1038/s41588-023-01313-1

Scientists have developed a new way of using cancers' DNA to spot cancer patients who may benefit from immunotherapy.

Researchers developed a computer algorithm to tell the difference between two different strategies that tumors use to hide from the immune system—one of which is better at dodging the effects of immunotherapy than the other. The team, led by scientists at The Institute of Cancer Research, London and the Human Technopole in Milan, found that the algorithm could help guide treatment by predicting whether immunotherapy is likely to work. It also tells us more about the evolutionary arms race between cancer and the immune system, potentially supporting efforts to diagnosis and treat cancers earlier.

The study was published in the journal *Nature Genetics* on March 9.

'Hiding' from the immune system

The body's immune system can recognize cells as being foreign by detecting "molecular flags" on their surface, known as neoantigens.

But cancer can adopt two different strategies to hide from the immune system. Some cancer cells use a "cloaking" mechanism to escape the immune response even though they have these neoantigens on their surface, while others "edit" the number of neoantigens on their surface to suppress the immune response.

Using genomic data from 10,000 cancer samples across 33 cancer types available from the Cancer Genome Atlas, researchers developed a computer algorithm that works out which strategy cancer cells are using to evade the immune system.

By looking at the excess number of neoantigens present in a tumor compared with the number of mutations, the model can differentiate

between the two strategies, known as immune escape and immune edited.

The team applied their algorithm to 308 cancers from the Hartwig Medical Foundation that had spread to other parts of the body and had been treated with immunotherapy, including skin, lung, and head and neck cancers. Of these, 26% responded well to immunotherapy. These cancers tended to be immune-escaped tumors, as they had a greater average excess of neoantigens than the cancers that did not respond as well.

Removing cancer's 'invisibility cloak'

Immunotherapy removes the "invisibility cloak" placed on cancer cells by these immune-escape strategies, revealing them to the immune system.

The researchers are now working to apply their algorithm to healthy cells and other tumor types. Using this information, they hope to identify at what point initial cloaking by cells triggers the development of cancer—opening up potential opportunities to detect cancer earlier.

In the future, their algorithm could be used to identify which patients would best respond to immunotherapy based on if their tumor cells are immune-escaped or immune-edited. This could save patients from potentially harmful side-effects while being more cost-effective for the NHS.

The ICR scientists who led the study are based in the ICR's Center for Evolution and Cancer, which has pioneered the understanding of cancer through the lens of evolution. The ICR is seeking philanthropic support for the Center, which will play a key role in the search for new cancer treatments.

Personalizing treatment

Study first author, Dr. Luis Zapata Ortiz, Fellow in Evolutionary Genomics and Modeling at The Institute of Cancer Research, London, said, "Cancers can play a 'hide-and-seek' game against the immune system by either hiding all their neoantigens that can be detected by the immune system, or by depleting the pool of neoantigens needed for a successful immune response.

"We have developed an algorithm, using Darwin's principles of evolution, to identify which patients will benefit from immunotherapy based on the interactions between their cancer and immune cells. Our algorithm has the potential to personalize patient treatment using the latest genomic technologies available in the clinic. It could also save some cancer patients unnecessary side effects and be more cost-effective for the NHS.

"We hope to now apply our algorithm to healthy cells to see at what point a seemingly healthy cell turns cancerous. This could pave the way for a new method of early cancer detection, helping us to target cancer when the disease is at its most treatable."

Study co-leader, Professor Trevor Graham, Director of the Center for Evolution and Cancer at The Institute of Cancer Research, London, said, "To survive in our body, cancer cells will need to find a way to hide from our immune system—either by adopting a kind of cloaking mechanism, or by reducing the number of neoantigens they produce on the cell surface.

"Our algorithm can tell the difference between the different strategies cancer cells use to evade the immune system, and so make a prediction of the likelihood that immunotherapy will be effective. It can spot cancer cells which still have high numbers of neoantigens, and which

therefore could be recognized by the immune system with a helping hand from immunotherapy."

Study co-leader Professor Andrea Sottoriva, Head of the Computational Biology Research Center at Human Technopole in Milan, said, "Immunotherapy is an incredibly effective treatment that works by harnessing the body's own immune system to fight cancer. However, until now, it has been difficult to understand why some patients respond to immunotherapy better than others.

"Our algorithm could predict which patients will respond best to immunotherapy based on the type of avoidance strategy used by their tumor. Those whose cancers possess immune-escape strategies will respond better to immunotherapy than those with immune-edited strategies. This is because this treatment removes the 'invisibility cloak' used by immune-escaped cancer cells, making them now visible to the immune system.

"We hope that our algorithm can be used as a tool to help devise better treatment strategies for patients in the future."

More information: Luis Zapata et al, Immune selection determines tumor antigenicity and influences response to checkpoint inhibitors, *Nature Genetics* (2023). DOI: 10.1038/s41588-023-01313-1

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