Experimental test promises to predict side-effects and cancer's return in patients treated with immunotherapy

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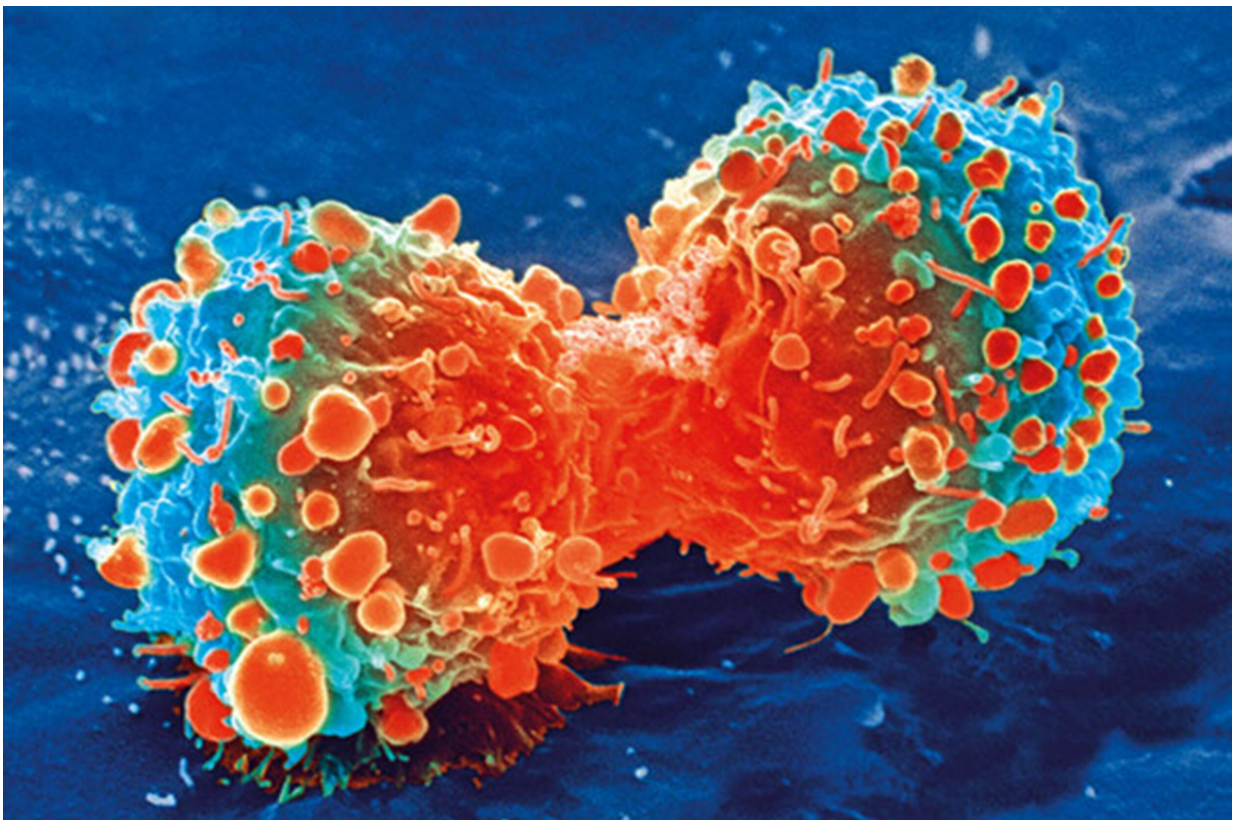

Cancer cell during cell division. Credit: National Institutes of Health

A single research test has the potential to predict which patients treated with immunotherapies—which harness the immune system to attack

cancer cells—are likely to have their cancer recur or have severe side effects, a new study found.

Published online September 15 in *Clinical Cancer Research*, the study revolved around the set of immune system signaling proteins called antibodies that recognize invading bacteria, viruses, and fungi. These blood proteins are designed to glom onto and inactivate specific bacterial and viral proteins, but in some cases "autoantibodies" also react to the body's "self" proteins to cause autoimmune disease.

Led by researchers at NYU Grossman School of Medicine and its Perlmutter Cancer Center, the new study generated data suggesting that a newly identified a panel of autoantibodies, if found in patients' blood before immunotherapy, has the potential to accurately predict whether a patient's cancer would recur and if they would experience autoimmune side effects because of the treatment itself. The study patients had received adjuvant immunotherapy, where the aim is to keep cancer from returning after prior treatment.

To spare normal cells from autoimmune attack, immune cells have "checkpoint" sensors that turn them off when they receive an appropriate signal. The body recognizes tumors as abnormal, but cancer cells hijack checkpoints, including programmed death receptor 1 (PD-1), to turn off immune attack. As one type of immunotherapy, PD-1 inhibitors are effective against many cancers, and are used as adjuvant therapy in patients with resected melanoma. Nevertheless, some patients suffer recurrent disease or severe treatment-related side effects, researchers say

The research team theorized that certain patients might have higher levels of key autoantibodies prior to treatment but not enough to be detected as autoimmune disease. This hidden susceptibility, they hypothesized, would then be triggered by checkpoint inhibitors to cause

greater immune-based side effects.

In the current work, the team identified a panel of distinct autoantibody signatures that could predict immune-related adverse effects upon treatment with two leading checkpoint inhibitors, nivolumab and ipilimumab, and for the combination of the two agents. Although their data support the predictive utility of the autoantibody scores by comparing them with data from clinical trials, the researchers say, more research is needed to validate the value of such a test in the clinic, and to better understand the relationship between autoantibodies, recurrence, and toxicity.

"Our results show that the new research test, by predicting whether a patient will respond to a treatment or experience side effects, has the potential to help physicians make more precise treatment recommendations," says study first author Paul Johannet, MD. At the time of the study, Johannet was a postdoctoral fellow in the lab of senior study author Iman Osman, MD, the Rudolf L. Baer Professor of Dermatology in the Ronald O. Perelman Department of Dermatology and a member of Perlmutter Cancer Center. "With further validation, this composite panel might help patients to better balance the chances of treatment success against severe side effects."

The researchers obtained blood samples from more than 950 patients enrolled in one of two Phase 3 randomized controlled trials of adjuvant checkpoint inhibitors in patients with advanced melanoma. Tumors in these patients had been surgically removed and blood samples collected before they received any treatment. The new test employs a microchip with 20,000 proteins attached in specific spots. When an antibody recognizes any of the proteins present in a blood sample, those spots glow with the signal intensifying as the concentration of antibody increases.

Based on the newly identified panel of autoantibodies, and using statistical modeling, co-senior author Judy Zhong, Ph.D., and colleagues developed a score-based prediction system for each treatment used. Patients with a high autoantibody recurrence score were found to have quicker disease return than those with a lower score, says Zhong, a professor in the Department of Population Health and the Department of Environmental Medicine at NYU Grossman School of Medicine. Similarly, patients with higher pre-treatment autoantibody toxicity scores were significantly more likely to develop severe side effects than those with lower scores.

"That we identified 283 autoantibody signals shows that the biological phenomena underlying recurrence and toxicity are complex, and cannot be driven one or two biomarkers" says Osman, also director of the Interdisciplinary Melanoma Cooperative Group at NYU Langone Health.

Moving forward the researchers plan to test the predictive value of autoantibody signatures in patients with the other cancer types for which checkpoint inhibitors are currently approved for use.

Along with Osman and Zhong, other study authors from NYU Langone Health were Jeffrey S. Weber, MD, Ph.D., the Laura and Isaac Perlmutter Professor of Oncology in the Department of Medicine; David Fenyö, Ph.D., professor in the Department of Biochemistry and Molecular Pharmacology and faculty in the Institute for Systems Genetics; Wenke Liu, Ph.D.; Michelle Krogsgaard, Ph.D., associate professor in the Department of Pathology; and Janice Mehnert, MD, professor in the Department of Medicine and associate director for clinical research at Perlmutter Cancer Center.

More information: Baseline serum autoantibody signatures predict recurrence and toxicity in melanoma patients receiving adjuvant immune

checkpoint blockade, *Clinical Cancer Research* (2022). DOI: 10.1158/1078-0432.CCR-22-0404