Vulnerability found in immunotherapy-resistant triple-negative breast cancer

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Researchers at Vanderbilt-Ingram Cancer Center have discovered a drug target on natural killer cells that could potentially trigger a therapeutic response in patients with immunotherapy-resistant, triple-negative breast cancer.

Currently, only about 15% of early-stage, triple-negative breast cancer patients benefit from combining immunotherapy, drugs that target immune cells to attack the tumor, with chemotherapy. Identifying why most patients don't respond is critical for personalizing treatment plans and minimizing therapy side effects in patients.

The research, published in *Cancer Discovery*, highlighted NKG2A receptors as potential targets for overcoming immunotherapy resistance in breast cancer. These receptors exist on immune cells ("natural killers") capable of destroying cancer cells.

In this study, the researchers led by Justin Balko, PharmD, Ph.D., Ingram Associate Professor of Cancer Research, studied tumor-specific Major Histocompatibility Complex I (tsMHC-I), a molecule that is essential to the immune system's ability to recognize tumor cells.

Analyzing the variability of tsMHC-I in human breast cancers and in mouse models, they found high heterogeneity in the expression of this molecule. This variability was linked with a lack of benefit from the addition of immunotherapy. They then set about exploring how to overcome this therapeutic resistance in patients.

Their findings suggest that combining anti-NKG2A with anti-PD-L1 therapy may represent a promising, yet under-explored approach for treating triple-negative breast cancer. This study deepens the understanding of why immunotherapies are ineffective for many triple-negative breast cancer patients and how to overcome this drug resistance.

"These findings shed some light on at least one reason why only a small fraction of breast cancer patients benefit from immunotherapy—their tumors have already found a way to remove a critical component for immunotherapy response. However, understanding this gives us a potential biomarker for identifying those patients and, perhaps more importantly, exposes a new way to target the tumor cells that have escaped the immune system," said Balko, the study's corresponding author.

The lead authors of the study are Brandie C. Taylor, MS, and Xiaopeng Sun, who are graduate students in the Balko Lab.

"This study was the result of a collaborative effort between researchers and clinicians. We hope our findings will help determine which triple-negative breast cancer patients should receive immunotherapy and which patients may benefit from the addition of anti-NKG2A in clinical trials," the two lead authors stated.

Other Vanderbilt researchers who contributed to the study are Paula Gonzalez-Ericsson, MD, Melinda Sanders, MD, Elizabeth Wescott, Susan Opalenik, Ph.D., Ann Hanna, Ph.D., Brian Lehmann, Ph.D., Vandana Abramson, MD, and Jennifer Pietenpol, Ph.D.

More information: Brandie C. Taylor et al, NKG2A is a Therapeutic Vulnerability in Immunotherapy Resistant MHC-I Heterogeneous Triple Negative Breast Cancer, *Cancer Discovery* (2023). DOI: 10.1158/2159-8290.CD-23-0519 , aacrjournals.org/cancerdiscove … tic-Vulnerability-in

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