Cardiac antigen identified as mechanism for heart complication with immunotherapy-related myocarditis

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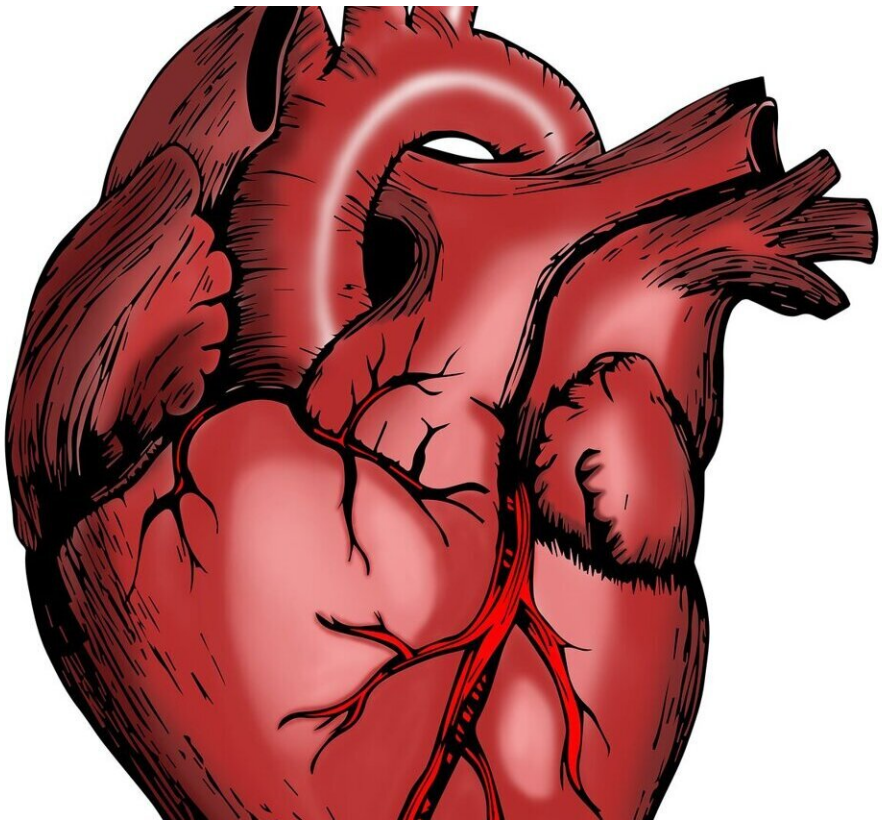

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Myocarditis is a complication that can occur in cancer patients treated with immune checkpoint inhibitors. Although the adverse event is

rare—affecting less than 1% of patients given the immunotherapy—the mortality rate is nearly 50%. Now, researchers from Vanderbilt-Ingram Cancer Center have identified the mechanism for the deadly heart inflammation.

The researchers discovered that T-cells recognizing the cardiac antigen α-myosin are the mechanism for this complication, setting the framework to identify biomarkers so at-risk patients can be recognized and medical strategies developed for them to tolerate the immunotherapy. Their findings are reported Nov. 16 in *Nature*.

"In 2016, our research group first described two melanoma patients treated with immunotherapy who developed myocarditis, and performed some early studies linking the activity of T cells in the heart to the condition, work which was published in *The New England Journal of Medicine*," said Justin Balko, PharmD, Ph.D., Ingram Associate Professor of Cancer Research, and a co-corresponding author of the study. "Subsequently, working the Nobel laureate James P. Allison, Ph.D. from MD Anderson Cancer Center in Houston, we helped characterize a mouse model that seemed to replicate what we had observed in patients (published in *Cancer Discovery* in 2020). Using that same model, together with oncologist Douglas Johnson, MD, MSCI at Vanderbilt and co-corresponding author Javid Moslehi, MD at UCSF, we were able to pinpoint the mechanism of why it occurs—and importantly—translate this back to patients. This discovery represents the next important step to making these often-effective therapies safer in patients."

The research team obtained cardiac samples and peripheral blood from three patients who had suffered severe myocarditis after being treated with immune checkpoint inhibitors. These samples were analyzed after the team replicated immunotherapy-related myocarditis in a mouse model. The researchers sequenced individual T cells invading the heart

during myocarditis in the mouse models to reconstruct their receptors. These T cell receptors were then screened against peptides to determine specificity. After determination of the specific peptide, the researchers analyzed the human samples and found that the three patients had reactive T cells to this same antigen source—a protein called α-myosin, which is expressed only in heart and skeletal muscles.

"The extension of our findings from the mouse model to human patients was a key part of our work. These results show how useful it is to have a mouse model where you can make an initial discovery and use that to understand something about human disease. Our data show that α-myosin is a disease-relevant autoantigen in patients with immunotherapy-related myocarditis. We hope this mechanistic understanding of this often-deadly complication can pave the way toward making immunotherapy safer for patients," said the study's lead author, Margaret Axelrod, Ph.D., a Vanderbilt Medical Scientist Training Program student who completed her Ph.D. in the Balko Lab.

Clinicians currently do not have a clear understanding for why immunotherapy-related myocarditis occurs in some patients. Although early treatment with steroids can improve survival chances, a more effective treatment is needed. The study is the first to identify the role of α-myosin in the mechanism of heart complications from immune checkpoint inhibitors. The study is also among the first to identify a candidate autoantigen for an immunotherapy toxicity in humans.

"While autoreactive T cells are the presumed mechanism for many toxicities to immunotherapies, tracing the condition back to a specific T cell receptor (often unique to each patient) and antigen source (drawing from tens- to hundreds- of thousands of potential antigens in the human body) is a daunting task," Balko said.

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More information: Justin Balko, T cells specific for α-myosin drive immunotherapy-related myocarditis, *Nature* (2022). DOI: 10.1038/s41586-022-05432-3.
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