Hormone therapy could lower risk of immunotherapy-associated myocarditis in women

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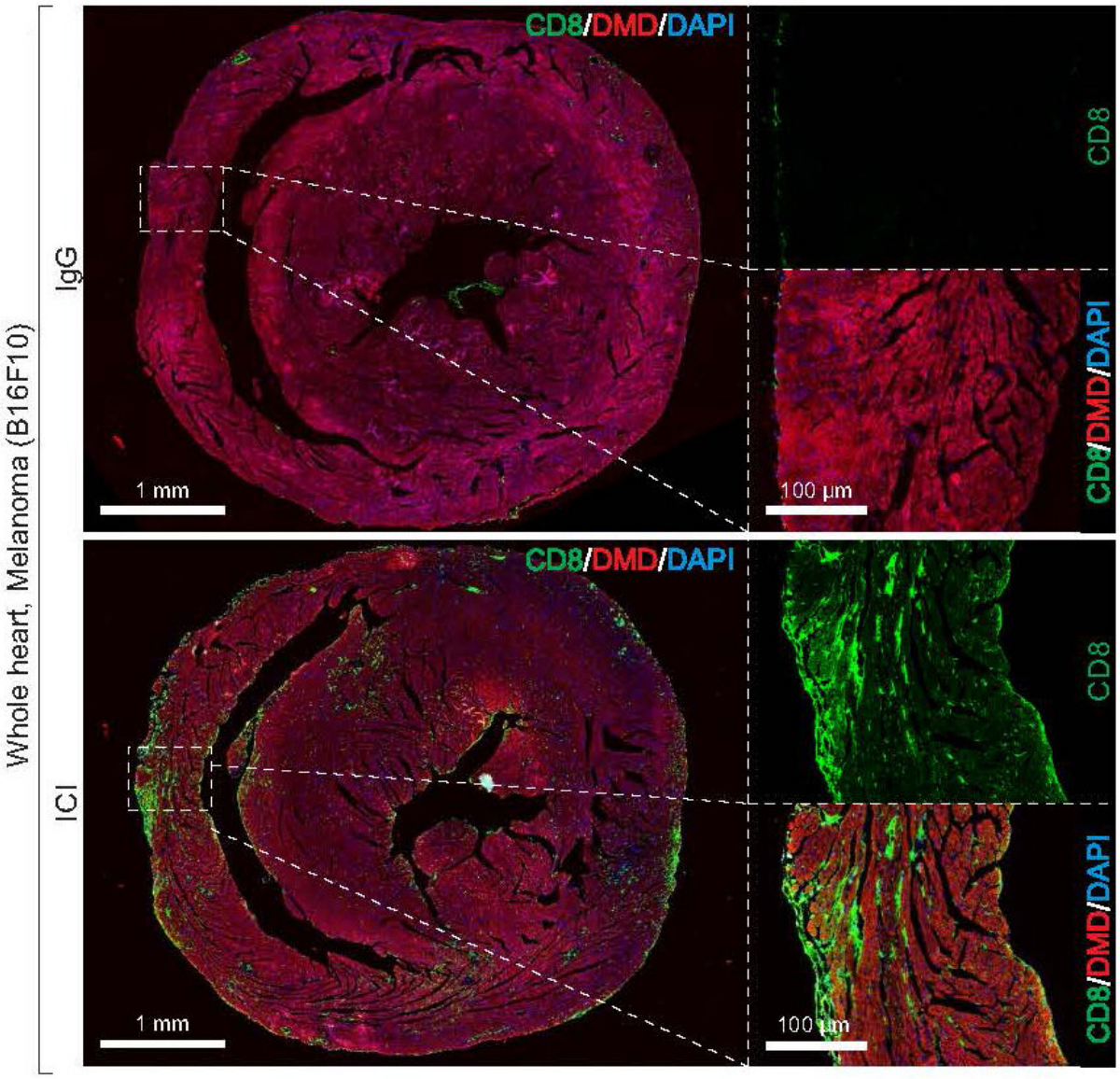


Stained images of heart tissues in female and male mice with melanoma, treated with IgG antibodies or immune checkpoint inhibitors (ICI). Credit: Y. Zhang, et al., *Science Translational Medicine* (2022)

A new preclinical study from researchers at The University of Texas MD Anderson Cancer Center and the University of California San Francisco (UCSF) has discovered the underlying cause of gender differences in immunotherapy-associated myocarditis after immune checkpoint inhibitor (ICI) treatment. Their findings point to possible treatment strategies for this side effect, which disproportionately affects female patients.

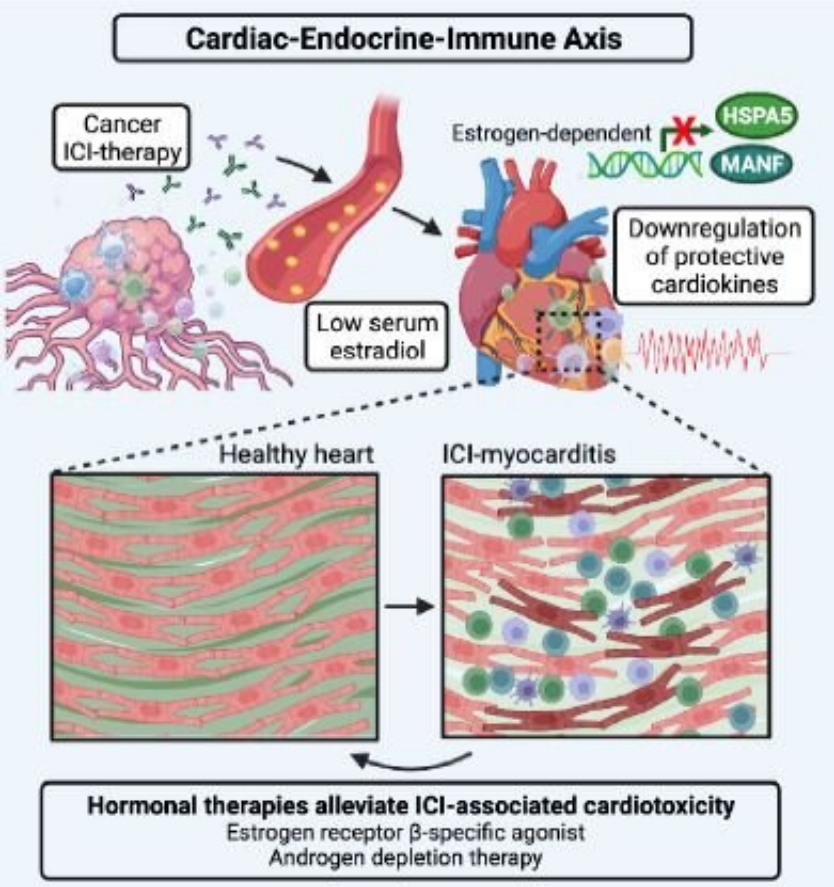
The study, published today in *Science Translational Medicine*, demonstrates how life-saving ICI treatment reduces levels of estrogen and important heart-protective proteins, sometimes leading to cardiovascular complications. The results suggest several treatment approaches, including hormone therapies, that could target this endocrine-cardiac-immune pathway without affecting treatment responses.

"Immune checkpoint inhibitors can be life-saving for many patients, but increasing the dose or combining with other therapies also increases the risk for myocarditis, particularly in women," said co-corresponding author Liuqing Yang, Ph.D., associate professor of Molecular and Cellular Oncology. "With this study, we now understand the mechanisms behind this, and we've found several potential ways to reduce this risk without compromising the antitumor effects of treatment."

Immune checkpoint inhibitors result in durable anti-tumor responses in many patients, but they are associated with an increased risk of

cardiovascular toxicities caused by immune cells that infiltrate heart tissue. While this occurs in only about 1% of patients, these side effects can significantly increase the mortality rate in women.

To better understand the mechanisms behind these gender differences, Yang worked with co-corresponding authors Chunru Lin, M.D., Ph.D., associate professor of Molecular and Cellular Oncology at MD Anderson, and Javid Moslehi, M.D., associate professor of Cardio-Oncology and Immunology for the UCSF Heart and Vascular Center.



Graphic illustration of the mechanism and management of ICI-associated myocarditis. Credit: Y. Zhang, et al., *Science Translational Medicine* (2022)

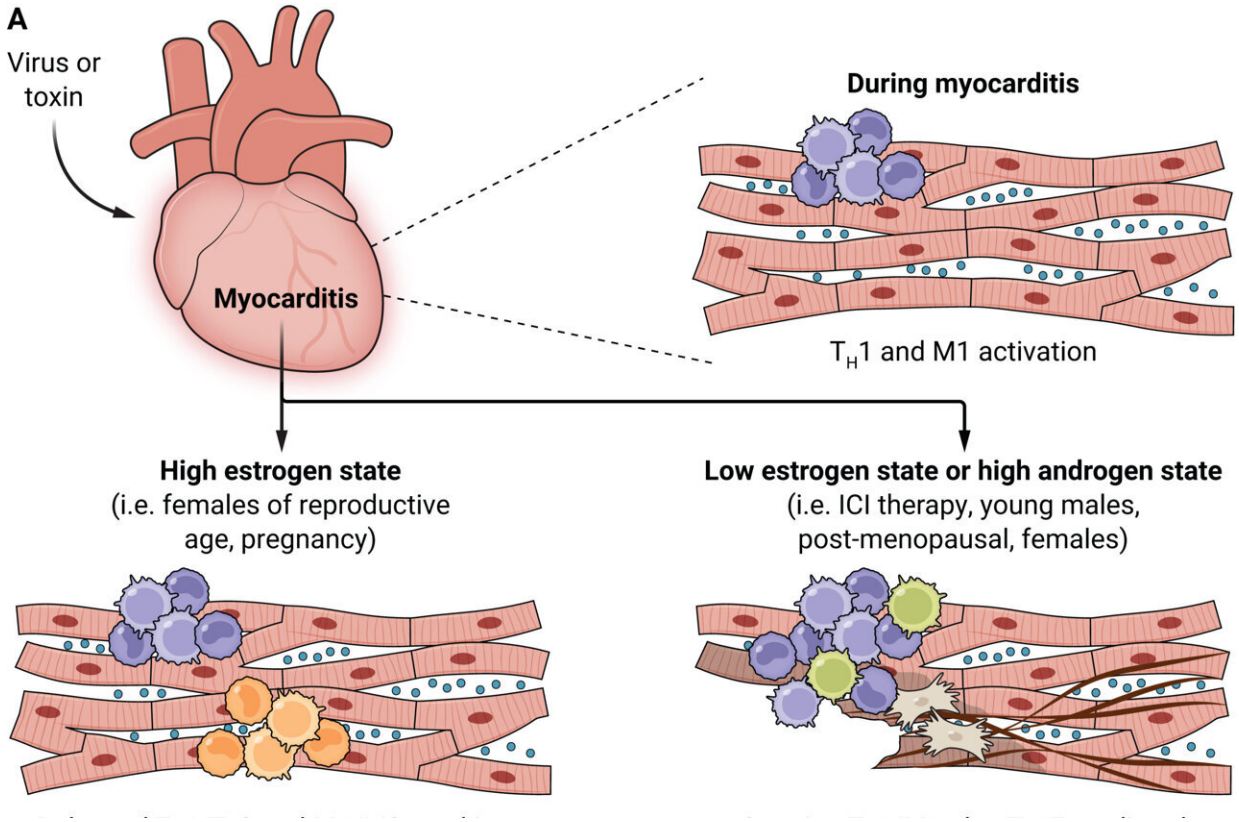
Checkpoint blockade reduces expression of heart-protective genes, particularly in females

MD Anderson researchers collaborated with Moslehi and his team at UCSF to develop laboratory models of melanoma, breast and colorectal cancer to study ICI-associated myocarditis. Treatment with commonly used ICIs (anti-PD-1 and anti-CTLA-4 antibodies) inhibited tumor growth but also increased immune cell infiltration, particularly in female hearts, causing electrocardiographic abnormalities and systolic dysfunction associated with myocarditis.

By studying these models, the team discovered that ICI treatment decreased expression of *Manf* and *Hspa5* genes in heart tissue, especially in females. Similarly, models lacking the immune checkpoint genes *Ctla4 and Pdcd1* also had a pronounced increase in heart-infiltrating immune cells and a lower expression of *Manf and Hspa5*.

Further investigation revealed the same pattern in patients with ICI-associated myocarditis, where MANF and HSPA5 proteins were decreased and immune cells were elevated compared to healthy donors. These findings suggest that MANF and HSPA5 are involved in regulating interactions between the cardiovascular and immune systems.

Infusions of recombinant MANF and HSPA5 proteins reversed these effects, improving cardiac function without affecting antitumor response after ICI, highlighting this as a possible therapeutic strategy.



Sex differences in ICI-myocarditis are mediated by hormone signaling patterns. Credit: P. Nguyen, et al., *Science Translational Medicine* (2022)

ICI treatment influences sex hormone levels, suggesting possible treatment approaches

"The sex differences observed in both ICI-myocarditis mouse models are especially intriguing because in non-ICI myocarditis (viral or autoimmune) in the general population, male sex is considered a risk factor and defines a more severe course," Moslehi said. "If such an opposite sex difference in ICI-myocarditis is true, it suggests a possible interaction of immune checkpoints and sex hormones."

Indeed, the researchers noted that serum concentrations of estrogen were significantly reduced in both males and females two weeks after ICI treatment, along with downregulation of *Manf* and *Hspa5*.

Using an estrogen receptor β (ERβ) agonist to increase estrogen-dependent expression of *Manf* and *Hspa5* resulted in tumor shrinkage and a decrease in heart-infiltrating immune cells following ICI treatment. Conversely, androgen deprivation therapy increased expression of these proteins and proved successful in laboratory models as an alternative strategy to lessen myocarditis.

"Based on these results, we can envision several potential treatment strategies. For example, we may consider monitoring estrogen levels in patients after ICI treatment and potentially infusing them with recombinant MANF and HSPA5 proteins to bring their levels back up and improve outcomes," Lin said. "Likewise, targeting with an ERβ agonist to increase expression of *Manf* and *Hspa5,* or blocking androgens to do the same, might reduce the risk of adverse events, allowing us to tailor these strategies to individual patient needs so we can optimize the use of immunotherapy and minimize cardiac toxicities."

While this is a preclinical study, the authors are planning clinical trials to evaluate these approaches using drugs already approved by the Federal Drug Administration (FDA).

More information: Yaohua Zhang et al, Hormonal therapies upregulate MANF and overcome female susceptibility to immune checkpoint inhibitor-myocarditis, *Science Translational Medicine* (2022). DOI: 10.1126/scitranslmed.abo1981.
www.science.org/doi/10.1126/scitranslmed.abo1981