JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 8, NO. 12, 2023

EDITORIAL COMMENT

PD-1 Checkmate and the 2-Edged Sword of the Immune System

What Next?*

Madeleine W. Cunningham, PhD,[a] Leslie T. Cooper, MD[b]

Oncological immunotherapies have revolutionized cancer treatment and improved survival in many cancers where programmed cell death protein (PD)-1 is blocked for its ability to dampen the immune response leading to immune tolerance. PD-1 is well known for protecting the body from autoimmune diseases, but what happens when the checks and balances go awry? Immune checkpoint inhibitor (ICI) therapy is associated with up to 1% risk of autoimmune myocarditis, with a case fatality rate approaching 50%. ICI myocarditis is commonly associated with a clinical syndrome of heart failure, conduction system disease, and arrhythmia with elevated cardiac troponin, and a significant minority of cases are associated with myasthenia gravis and skeletal myositis.[1] The experimental observation that α-myosin specific clonal CD8+ T cells are the dominant T cell subset in $Pdcd1^{-/-}Ctla4^{+/-}$ mice with myocarditis has directed attention towards specific T-cell subtypes in clinical disease.[2] Heart biopsy specimens from patients with ICI myocarditis have also revealed prominent $CD\text{-}8^{+}$ T cells in the inflammatory infiltrate.[3]

Little is known about risk factors that may suddenly trigger myocarditis and subsequent cardiomyopathy, a rare disease in humans. In this issue of *JACC: Basic to Translational Science*, Hayashi et al[4] report that recurrent beta adrenergic stress by isoproterenol, a well characterized beta adrenergic receptor agonist, provoked a persistent myocarditis in PD-1-deficient mice. PD-1 deficiency in their mouse model mimicked ICI treatment in humans. In ICI blockade, anti-PD-1 antibody blocks the activity of PD-1, which is considered to be the brakes of the immune system, and which is turned off so that the tumor can be destroyed or controlled by a more robust immune response. Hayashi et al[4] provide an exciting and very thorough dissection of the cellular pathways by which PD-1 holds back the immune response against the heart in normal wild type (WT) mice while the deletion mutant PD-1-deficient strain, lacking functional PD-1, develops a $CD8^{+}$ myocarditis, particularly in the female C57BL6 mouse model of the PD-1-deficient strain.

The model from Hayashi et al[4] uses isoproterenol treatment in a regimen in which the model receives 3 priming low doses and then 1 final high-dose intraperitoneally 7 days of isoproterenol after the last priming dose. This neurohormonal stressor leads to myocarditis in only the PD-1-deficient strain of mice which is then characterized vs the WT which does not develop myocarditis. In the PD-1-deficient mice, the $CD8^{+}$ T-cell myocarditis proves to be an important cellular infiltrate coming from the mediastinal lymph nodes. The WT mice show little effect and do not have any lethality compared to the PD-1-deficient strain which displays fulminant myocarditis similar to PD-1/ICI myocarditis in humans.

Their study investigated further the different immune cell types infiltrating the heart in the PD-1-deficient mouse model developing myocarditis, and they found that $CD8^{+}$ T cells were associated with and potentially causing the myocarditis and cardiomyopathy. Most importantly, the $CD8^{+}$ T-cell

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

From the [a]Department of Microbiology and Immunology, University of Oklahoma Health Sciences Center Oklahoma City, Oklahoma, USA; and the [b]Cardiovascular Division, Mayo Clinic, Jacksonville, Florida, USA.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2023.10.006

subset is usually dominant in human ICI myocarditis.[2] In male mice, $CD4^+$ T cells were significantly elevated and were also observed in the $CD8^+$ infiltrate; however, in females, the $CD4^+$ subset did not differ. Although speculative, the female specificity could be related to estrogen control of $CD8^+$ T-cell response to antigen with granzyme and perforin upregulation as has been recently found for $CD8^+$ T cells in rheumatic valve disease.[5]

Similar to human ICI-driven smoldering myocarditis, the persistent low level of $CD8^+$ myocarditis in the PD-1-deficient strain was associated with poor outcomes with lower left ventricular ejection fraction and increased systolic volume between baseline and weeks 2 and 5 of follow-up. The important finding in the study was that recurrent neurohormonal stressors triggered a persistent dysregulated $CD8^+$ myocardial inflammation and reduced cardiac function, which led to hypertrophy and increased lethality in PD-1-deficient mice. The mice were followed up to 35 days with echocardiogram results reporting effects of PD-1-deficiency and $CD8^+$ infiltrates in the myocardium similar to ICI myocarditis in humans.

PD-1 is somewhat ubiquitous on different cell types. Both innate immune cells and T cells express PD-1 to further limit T-cell activation and the adaptive immune response of T cells. The innate immune cells help to activate and recruit T cells and mediate an adaptive response such as potential autoantibody production and strong T-cell activation responses. Consequently, PD-1 on innate cells such as dendritic cells reduces their activity, limiting self-reactive responses to damage associated molecular antigens. These tolerance mechanisms are very important for controlling heart-specific T cells to prevent self-reactivity leading to heart disease. It has been shown by Li et al[6] that depletion of dendritic cells has an adverse effect on the outcome and development of myocarditis. When stimulated, dendritic cells can produce tolerizing interleukin-10 which is one way that dendritic cells control self-reactive T cells and promote protection against myocarditis.[6]

Thus, PD-1 checkpoint inhibitors play a role in the entire process where they affect the immune response including the role of dendritic cells and their potential expression of immune tolerizing cytokines such as interleukin-10 to protect against myocarditis and cardiomyopathy with γIFN potentially driving the disease process including the $CD8^+$ T-cell driven disease in this mouse model as well as in humans. Loss of PD-1-controlled immunity in ICI treatments can lead to a dendritic cell/$CD8^+$ T-cell-directed fulminant myocarditis leading to cardiomyopathy and in some cases death from loss of heart function.

Would these findings potentially impact clinical patient care? What does this mean for cancer patients using the checkpoint inhibitors to destroy their cancer or halt a persistent chronic infectious disease? Importantly, most people do not develop autoimmune heart disease in the presence of ICI treatments. Current management of ICI myocarditis consists of stopping the checkpoint inhibitor treatment which then places patients more at risk for progressive cancer, or starting treatment with high-dose corticosteroids often with a second immunosuppressive agent which then introduces significant risk of opportunistic infection. Clinical trials have focused on anti-T-cell strategies with agents such as abatacept, a CTLA4-Fc fusion protein that binds to CD80 and CD86 on antigen-presenting cells or the broader spectrum anti-CD52 agent alemtuzumab that can target both B and T cells causing disease to eliminate them from the blood. The present study raises the possibility that targeted therapy directed solely at $CD8^+$ T cells might provide less toxicity and possibly allow for the later reinstitution of effective antitumor treatments.

Questions remain about the underlying mechanisms and risk factors of susceptibility during PD-1 deficiency or ICI treatment where in rare instances autoimmune heart disease develops in humans. The report herein in mice suggests that there are other risk factors that play a role in tipping the scale toward autoimmune heart disease in addition to the PD-1 deficiency. This would be risk from beta-receptor stimulation and activation of the beta receptors as was instituted in the mouse model in Hayashi et al.[4] The data suggest that there are other risk factors leading to inflammatory activation in the heart with cellular infiltration and cardiomyopathy in humans in addition to the strong risk factor PD-1 deficiency or ICI treatment. What would these risk factors look like? Possibly bouts of excessive hypertension, recurrent episodes of ischemia, or incessant tachycardia might be sufficient to trigger ICI-induced myocarditis. Any of the beta adrenergic receptor stimulants from norepinephrine to autoantibodies signaling the beta receptors might also play a role. When ICI therapy is instituted in

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 8, NO. 12, 2023
DECEMBER 2023:1518–1520

humans, to be or not to be, that is the question, and whether the patient has these risk factors that may play a role in tipping the balance toward autoimmune heart disease.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Drs Cunningham and Cooper have been supported by grants RO1HL56267 and RO1HL135165 from the National Heart, Lung, and Blood Institute. Dr Cunningham is co-founder and CSO of Moleculera Labs, Research Park, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, where tests are offered in a CLIA and COLA certified laboratory to detect anti-neuronal autoantibodies in neuropsychiatric postinfectious sequelae and dopamine receptor encephalitis in chorea and other neurologic and neuropsychiatric states. Moleculera holds a license for testing of heart autoantibodies in myocarditis, cardiomyopathy and heart failure.

ADDRESS FOR CORRESPONDENCE: Dr Madeleine Cunningham, University of Oklahoma Health Sciences Center, 975 Northeast 10th Street, BRC 217, Stanton L Young Biomedical Research Center, Oklahoma City, Oklahoma 73104, USA. E-mail: madeleine-cunningham@ouhsc.edu.

REFERENCES

1. Moslehi JJ, Salem JE, Sosman JA, LeBrun-Vignes B, Johnson DB. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. *Lancet Child Adolesc Health*. 2018;391(10124):10–16.

2. Axelrod ML, Meijers WC, Screever EM, et al. T cells specific for a-myosin drive immunotherapy realted myocarditis. *Nature*. 2022;(611):818–826.

3. Imai R, Ono M, Nishimura N, Suzuki K, Komiyama N, Tamura T. Fulminant Myocarditis caused by an immune checkpoint inhibitor: a case report with pathologic findings. *J Thorac Oncol*. 2019;14(2):E36–E38.

4. Hayashi T, Lim KRQ, Kovacs A, Mann DL. Recurrent adrenergic stress provokes persistent myocarditis in PD1 deficient mice. *J Am Coll Cardiol Basic Trans Science*. 2023;8(12):1503–1517.

5. Passos LSA, Jha PK, Becker-Greene D, et al. Prothymosin alpha: a novel contributor to estradiol receptor alpha-mediated CD8+ T-cell pathogenic responses and recognition of type 1 collagen in rheumatic heart valve disease. *Circulation*. 2022;145(7):531–548.

6. Li Y, Heuser JS, Kosanke SD, Hemric M, Cunningham MW. Protection against experimental autoimmune myocarditis is mediated by IL-10 producing T cells that are controlled by dendritic cells. *Am J Pathol*. 2005;167:5–15.

KEY WORDS immune checkpoints, inflammation, myocarditis, tissue injury