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EDITORIAL COMMENT

Keeping the Failing Heart in Check

Can Modulating Immune Checkpoints Promote Myocardial Recovery?*

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Programmed cell death protein (PD)-1 is a protein identified on T cells, and when bound to programmed death-ligand 1 (PD-L1) protein, it prevents the killing of other cells by T cells. Immune checkpoint inhibitors (ICIs), in the form of antibodies against inhibitory proteins such as PD-1/PD-L1 expressed on immune cells, allow for increased stimulation of T cells to fight tumor cells. Over the past decade, ICIs have played a crucial role in the armamentarium of several types of cancers, and have been shown to be effective even in advanced stages. However, 10%-15% of patients suffer major immune-related adverse events, requiring cessation of therapy.[1] Of these, cardiotoxicity has emerged within a subset of patients undergoing ICI therapy, with manifestations such as perimyocarditis, stress cardiomyopathy, acute coronary syndromes, and arrhythmias. Whereas the prevalence of cardiotoxicity is relatively low, its mortality is high, especially with drugs inhibiting the PD-1/PD-L1 pathway.[1]

The exact role that immune checkpoints play in mediating cardiomyopathy is not well understood, although multiple mechanisms have been proposed.[1] The PD-1/PD-L1 pathway plays a critical role in attenuating cardiomyocyte autoimmunity and modulating autoreactive T-cell responses has long been established. In mouse models with intrinsic predisposition to autoimmune disease, a deficiency of PD-1 or PD-L1 allowed for spontaneous development of myocarditis within 8-10 weeks.[2] Moreover, a separate line of murine models, when made deficient in PD-1, developed dilated cardiomyopathy mediated by autoantibodies to cardiac troponin I.[3] On the other hand, early studies have also implicated PD-1/PD-L1 inhibition in promoting smooth muscle cell proliferation and accelerating graft arterial disease in cardiac allografts.[4] Recently, the PD-1/PD-L1 axis has been implicated in a wide range of vascular inflammatory diseases.[5]

Clinical manifestations of stress cardiomyopathy have been reported in a number of case studies with ICI therapy,[6] and these reports have prompted a new line of translational investigations into the potential contributions of the PD-1/PD-L1 pathway in this enigmatic condition that has been largely attributed to excessive catecholamine surge yet with great potential of myocardial recovery.[7] There is growing evidence to support the presence of myocardial inflammation in the acute phase of stress cardiomyopathy, with the main pathophysiology still attributed to maladaptive reactions toward a stressful trigger. Recent work has identified the temporal course of a chronic inflammatory response in stress cardiomyopathy, with an initial early influx of neutrophils into myocardial tissue followed by proinflammatory macrophages and increase in systemic inflammatory cytokines with activation of downstream signaling pathways.[8] In this issue of *JACC: Basic to Translational Science*, Hayashi et al[9] leveraged a similar approach by simulating cardiac injury using high-dose isoproterenol, a sympathomimetic stimulus previously shown to result in hemodynamic and ischemic stress. By simulating stress cardiomyopathy, these investigators introduced

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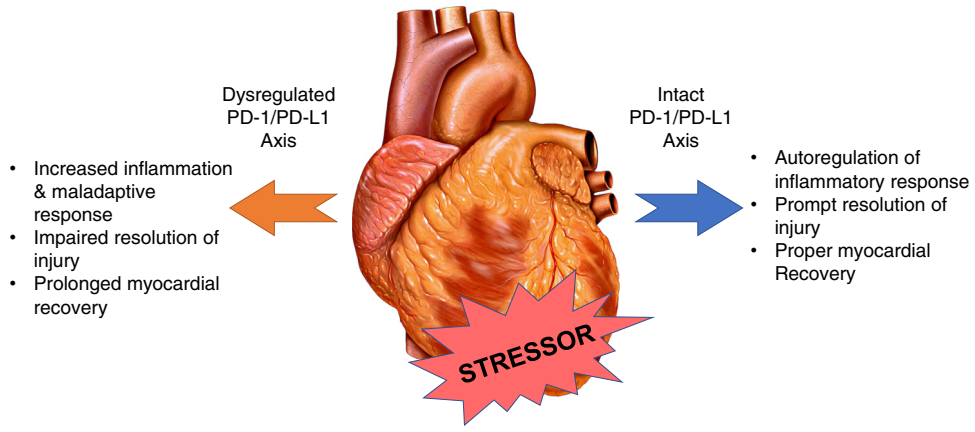
FIGURE 1 Intact vs Dysregulated PD-1/PD-L1 Axes in Response to Myocardial Stressors



Intact and dysregulated programmed cell death protein (PD)-1/programmed death-ligand 1 (PD-L1) axes are shown in response to myocardial stressors.

a process that is classically thought to be unrelated with the inflammatory milieu. Mice treated with PD-L1 inhibitor prior to isoproterenol had a higher mortality rate, as well as higher troponin elevation on isoproterenol injection, whereas PD-1-deficient mice were slower to recover from wall motion abnormalities and without full recovery to baseline at 7 days.[9] Indeed, this degree of additional cardiomyopathy was not shown with administration of programmed cell death protein (PD)-2 inhibitors in wild-type mice.[9] Taken together, these findings imply that the PD-1/PD-L1 pathway not only plays a role in suppressing autoreactive T-cell-mediated immune disease, but the pathway also engages the innate immune system in the autoregulation of the inflammatory response after tissue injury. It appears that inhibition of the pathway allows for prolonged and/or excessive inflammation and subsequent myocardial injury, resulting in the manifestations that would be judged clinically as stress cardiomyopathy or myocarditis. This is of considerable interest, because these observations may imply that immune checkpoint PD-1/PDL-1 may play an important role in mitigation and reversal of progressive cardiac damage related to unchecked inflammation.

Though employing previously established protocols, Hayashi et al[9] introduce several novel insights that may have implications in understand the protocols' roles promoting myocardial recovery. First, it is pertinent to consider the intersection between ICI-induced cardiotoxicity and other forms of immune-mediated cardiomyopathies with stress cardiomyopathy in a broader spectrum. Whereas the dysregulated PD-1/PD-L1 axis can promote myocardial inflammation and edema (but not necessarily extensive scarring or fibrosis) that may progress to myocarditis, more fulminant cases with hemodynamic consequences can be triggered by shared mechanisms with stress cardiomyopathy. Further studies can explore the nature of PD-L1 and whether there are PD-1-independent mechanisms involved. Second, it is apparent that immune checkpoints such as PD-1/PD-L1 may appear to have a larger role in resolution of cardiac tissue injury, possibly irrespective to the inciting cause. Without appropriate PD-1/PD-L1 axis function and its modulation of the innate immune responses, proper resolution of injury can be impaired (**Figure 1**). It is conceivable that the PD-1/PD-L1 axis may be involved in resolution of other forms of myocardial injuries such as myocardial infarction with nonobstructive coronary arteries or other forms of myocarditis as well. Indeed, unique patterns of myocardial PD-1/PD-L1 expression in has been observed in both ischemic and nonischemic failing heart tissues of noncancer patients that were not observed in patients without cardiovascular diseases.[10] If the PD-1/PD-L1 axis is active in maintaining endothelial and myocardial integrity, ensuring that the failing myocardial can recover appropriately from stressors, there may be promising therapeutic potential in modulating the immune checkpoint to promoting myocardial recovery—to keep the failing heart in check.

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REFERENCES

1. Rikhi R, Karnuta J, Hussain M, et al. Immune checkpoint inhibitors mediated lymphocytic and giant cell myocarditis: uncovering etiological mechanisms. *Front Cardiovasc Med*. 2021;8:721333.

2. Lucas JA, Menke J, Rabacal WA, Schoen FJ, Sharpe AH, Kelley VR. Programmed death ligand 1 regulates a critical checkpoint for autoimmune myocarditis and pneumonitis in MRL mice. *J Immunol*. 2008;181(4):2513–2521.

3. Okazaki T, Tanaka Y, Nishio R, et al. Autoantibodies against cardiac troponin I are responsible for dilated cardiomyopathy in PD-1-deficient mice. *Nat Med*. 2003;9(12):1477–1483.

4. Koga N, Suzuki J, Kosuge H, et al. Blockade of the interaction between PD-1 and PD-L1 accelerates graft arterial disease in cardiac allografts. *Arterioscler Thromb Vasc Biol*. 2004;24(11):2057–2062.

5. Veluswamy P, Wacker M, Scherner M, Wippermann J. Delicate role of PD-L1/PD-1 axis in blood vessel inflammatory diseases: current insight and future significance. *Int J Mol Sci*. 2020;21(21):8159.

6. Serzan M, Rapisuwon S, Krishnan J, Chang IC, Barac A. Takotsubo cardiomyopathy associated with checkpoint inhibitor therapy: endomyocardial biopsy provides pathological insights to dual diseases. *J Am Coll Cardiol CardioOnc*. 2021;3(2):330–334.

7. Singh T, Khan H, Gamble DT, Scally C, Newby DE, Dawson D. Takotsubo syndrome: pathophysiology, emerging concepts, and clinical implications. *Circulation*. 2022;145(13):1002–1019.

8. Wilson HM, Cheyne L, Brown PAJ, et al. Characterization of the myocardial inflammatory response in acute stress-induced (takotsubo) cardiomyopathy. *J Am Coll Cardiol Basic Trans Science*. 2018;3(6):766–778.

9. Hayashi T, Tiwary SK, Lavine KJ, et al. The programmed death-1 signaling axis modulates inflammation and structure/function in a stress-induced cardiomyopathy model. *J Am Coll Cardiol Basic Trans Science*. 2022;7(11):1120–1139.

10. Kushnareva E, Kushnarev V, Artemyeva A, Mitrofanova L, Moiseeva O. Myocardial PD-L1 expression in patients with ischemic and non-ischemic heart failure. *Front Cardiovasc Med*. 2021;8:759972.

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