Title

PD-1/PD-L1 in Myocarditis Transcriptional Signals, Functional Questions

Journal

JACC Basic to Translational Science, 11(8)

ISSN

2452-302X

Authors

Durai, Vivek
Moslehi, Javid J

Publication Date

2026-08-01

DOI

10.1016/j.jacbts.2026.101569

Peer reviewed

PD-1/PD-L1 in Myocarditis: Transcriptional Signals, Functional Questions

Vivek Durai[1,2], Javid J. Moslehi[1]

Author Affiliations:

[1]Section of Cardio-Oncology & Immunology; Cardiovascular Research Institute (CVRI), University of California San Francisco, School of Medicine, San Francisco, California,
[2]Gladstone Institutes, San Francisco, California

Words: 1311 (LIMIT: 1500 words, 10 references)

Immune checkpoint inhibitors (ICI) targeting the PD-1/PD-L1 axis have transformed oncology by providing the ability to restore T cell–mediated anti-tumor immunity. Under normal conditions, PD-1 on activated T cells engages PD-L1 on tissue or tumor cells to dampen immune responses and maintain peripheral tolerance. Blockade of the PD-1/PD-L1 axis releases inhibitory signaling to enhance tumor clearance, but at the cost of impaired self-tolerance and immune-related adverse events (IRAEs)[1]. Among the most severe is ICI myocarditis, in which activated immune cells infiltrate and damage the myocardium, leading to arrhythmias and high mortality[1,2]. Despite growing recognition of the function of PD-1/PD-L1 in immune homeostasis, its role in myocarditis pathogenesis remains incompletely defined, and it is unclear whether these functions are unique to ICI-myocarditis or shared with other forms such as myocarditis. The overlap in lymphocyte-driven inflammation and therapeutic pathways across these conditions suggests that disruption of PD-1/PD-L1 signaling may reveal broader principles governing cardiac immune tolerance and autoimmunity.

Into this context enters the present study by Yousif et al. published in this edition of JACC: BTS. The authors leveraged prior single-cell and single-nuclei RNA-seq datasets from murine models of viral (TL1 and CVB3) myocarditis, as well as from an autoimmune myocarditis model, which was induced by the adoptive transfer of T cells that react against the myocardial protein MYH6 into naïve mice. By applying a unified bioinformatic approach to identify differentially expressed inflammatory genes and infer ligand–receptor interactions across models, they observed broad upregulation of PD-1 and TNFα pathway genes, along with consistent predicted interactions between PD-1 on T cells and PD-L1 on endothelial cells. These findings were then evaluated in human single-nuclei RNA-seq data from biopsy-confirmed acute myocarditis, which similarly demonstrated enrichment of PD-1 pathway signatures, although ligand-receptor interactions were not detected, likely due to limited sample size. In follow-up studies, inflammatory gene expression peaked alongside CD8 T-cell infiltration, with PD-1 primarily expressed on proliferating and exhausted CD8 T cells. PD-L1-positive endothelial cells were enriched for antigen-processing pathways, whereas PD-L1-negative endothelial cells showed stress and cell death signatures. To validate these findings *in vitro*, the authors stimulated human endothelial

cells with TNF-α and found similar upregulation of PD-L1 in gene expression. Similar PD-L1-associated transcriptional upregulation was observed in cardiac fibroblasts.

This study provides novel insight into the role of the PD-1/PD-L1 signaling in non-ICI myocarditis, demonstrating that these pathways are active in both viral and by autoimmune forms of myocarditis and are conserved across humans and mice. A particular strength is the use of single-cell transcriptomics, which enables interrogation of less well-characterized populations, such as endothelial cells[3]. The prominent PD-L1 expression in this population and their possible interaction with PD-1 expressing CD8 T cells is intriguing and warrants further investigation. At the same time, the reliance on single cell transcriptomic analysis introduces important limitations. Such approaches are inherently associative and do not establish causality, and thus the observed transcriptional changes may reflect, rather than drive, myocardial inflammation. For example, the authors report an inverse relationship between PD-L1 expression and cell death pathway activation in endothelial cells; however, this inverse association may simply arise from loss of PD-L1 expression in dying cells rather than PD-L1 protecting cells from being killed as the authors surmised[4]. Similarly, the proposed roles of endothelial cells and fibroblasts as nonprofessional antigen-presenting cells should be interpreted with caution. While these conclusions are supported by increased expression of antigen-processing pathways, such changes are also a well-described, nonspecific response to inflammatory cytokines and may not indicate functional antigen presentation[5]. Definitive clarification of these possibilities will require careful *in vivo* studies capable of directly manipulating these cell populations during the initiation and promulgation of the immune response against the myocardium. Finally, although the inclusion of human data supports cross-species relevance, the small sample size limits statistical power, which may account for the lack of significant ligand–receptor interactions and tempers interpretation of the observed gene expression changes.

Building on these observations, several key questions emerge that will require a shift from descriptive to mechanistic investigation[6]. Foremost is whether PD-L1 expression in cardiac cell populations, particularly endothelial cells and fibroblasts, plays a causal role in restraining myocardial inflammation or instead reflects a secondary response to injury. This could be addressed through cell type–specific genetic manipulation of PD-L1 or MHC pathways in murine models of viral and autoimmune myocarditis, coupled with detailed phenotyping of immune infiltration, T cell activation, and cardiac function. Complementary spatial and functional approaches, including multiplex imaging to define physical interactions between PD-L1–expressing cardiac cells and PD-1–positive T cells, as well as ex vivo co-culture systems, will be necessary to establish whether these interactions actively modulate T cell effector function. Defining the antigenic drivers of these responses, through T cell receptor sequencing and immunopeptidomic profiling, will further clarify whether shared or distinct immune programs underlie different forms of myocarditis. Finally, larger-scale human studies integrating single-cell and spatial transcriptomics with clinical phenotyping will be essential to validate these pathways and assess their therapeutic relevance. Together, such efforts will be critical to determine

whether the PD-1/PD-L1 axis represents a viable target for modulating cardiac immune tolerance without compromising systemic immunity.

Overall, this study by Yousif et al extends the relevance of PD-1/PD-L1 signaling beyond ICI-myocarditis, demonstrating that this pathway is active across infectious and autoimmune forms of myocardial inflammation. These findings motivate future work to define how manipulation of this axis alters disease trajectory *in vivo*, how its activity evolves from acute injury to chronic remodeling, and how cell-cell interactions can be more precisely resolved using spatial approaches. Expanding this framework to include other checkpoint pathways such as CTLA-4 and LAG-3 will further refine our understanding of immune regulation in the heart[7]. Still, therapeutic manipulation of this pathway must balance its potential protective role in limiting myocardial inflammation against its known effects on impairing anti-tumor and antiviral immunity.

More broadly, these findings highlight that checkpoint pathways such as PD-1/PD-L1 are not solely therapeutic targets, but fundamental regulators of immune homeostasis. Continued investigation of these pathways within cardio-oncology offers a unique opportunity to uncover core principles of cardiovascular immunobiology. What began as an adverse effect of cancer therapy may ultimately redefine our understanding of immune homeostasis in the heart[8].

Funding

V.D. is supported by the UCSF CVRI T32 training grant (T32HL007731) and AHA postdoctoral fellowship 26POST1563550. J.J.M. is supported by NIH grant Nos. R01HL155990, R01HL156021, R01HL160688, R01HL170038, and P01HL141084.

Disclosures

J.J.M. has provided consulting or advisory roles for Deciphera, Takeda, AstraZeneca, Regeneron, Bayer, Kiniksa Pharmaceuticals, Daiichi Sankyo, BeiGene, Incyte, AskBio, Arcus Biosciences, Nektar Therapeutics, F. Hoffmann-La Roche Ltd, Skribe Medical, Inc, Verastem, ImmunoCore, Innovent Biologics, Shattuck Labs, Sobi, Sumitomo, Repare Therapeutics, Pin Therapeutics, and Cytokinetics. J.J.M. is a coinventor of a patent related to the use of abatacept in the treatment of immune checkpoint inhibitor–mediated myocarditis and has other patents pending related to diagnostics and therapeutics in inflammatory heart disease.

References

1. Munir AZ, Gutierrez A, Qin J, Lichtman AH, Moslehi JJ. Immune-checkpoint inhibitor-mediated myocarditis: CTLA4, PD1 and LAG3 in the heart. *Nat Rev Cancer.* 2024;24(8):540-553.
2. Johnson DB, Balko JM, Compton ML, et al. Fulminant Myocarditis with Combination Immune Checkpoint Blockade. *N Engl J Med.* 2016;375(18):1749-1755.

3. Gardner RS, Tucker NR, Amancherla K. Leveraging Single-Cell Technologies to Advance Understanding of Myocardial Disease. *Circ Res.* 2026;138(1):e326002.
4. Grabie N, Gotsman I, DaCosta R, et al. Endothelial programmed death-1 ligand 1 (PD-L1) regulates CD8+ T-cell mediated injury in the heart. *Circulation.* 2007;116(18):2062-2071.
5. Steimle V, Siegrist CA, Mottet A, Lisowska-Grospierre B, Mach B. Regulation of MHC class II expression by interferon-gamma mediated by the transactivator gene CIITA. *Science.* 1994;265(5168):106-109.
6. Kaelin WG, Jr. Publish houses of brick, not mansions of straw. *Nature.* 2017;545(7655):387.
7. Munir AZ, Gutierrez A, Krawiec CJ, et al. CXCR6(+) T Cells Drive Immune Checkpoint Inhibitor Myocarditis. *Circulation.* 2026.
8. Moslehi JJ. Cardio-Oncology: A New Clinical Frontier and Novel Platform for Cardiovascular Investigation. *Circulation.* 2024;150(7):513-515.