806 PD-1 BLOCKADE AFFECTS INFLAMMATION AND METABOLIC FLEXIBILITY TO POTENTIALLY MEDIATE CARDIAC IMMUNE-RELATED ADVERSE EVENTS

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Background Immune checkpoint blockade (ICB) is now a mainstay of cancer therapy with success in extending the survival time in several cancers, including melanoma. Still, these modalities result in immune-related adverse events (irAEs), with approximately 80% of melanoma patients experiencing toxicity. IrAEs can lead to treatment discontinuation, contributing to mortality. In addition, one uncommon irAE with a high mortality rate is ICB-related myocarditis. In addition to myocarditis, ICB can also cause arrhythmias and heart failure. Currently, early markers to predict cardiotoxicity are unknown. During cardiac insult, cardiomyocyte metabolic flexibility results in metabolic reprogramming from fatty acid oxidation to glycolysis to overcome injury; however prolonged metabolic remodeling precedes most pathological alterations in the heart, suggesting that changes in metabolism may contribute to immunotherapy-related cardiac damage.

Methods Male C57BL/6 mice were injected with B16 melanoma cells. Once tumors reached 100 mm^3, the animals were treated with three doses of anti-PD-1 antibody (200 µg IP). Echocardiograms were performed prior to necropsy using Vevo LAZR ultrasound to assess cardiac function. Bulk RNA sequencing (RNA-seq) and immunohistochemistry were performed on cardiac tissue. Single-cell RNA sequencing (scRNA-seq) was performed on human peripheral blood mononuclear cells (PMBCs) in patients treated with anti-PD-1 therapy.

Results Echocardiogram showed that anti-PD1 treatment attenuated stroke volume and increase heart rate compared to WT mice, suggesting that anti-PD1 treatment may be associated with changes in cardiac function. Histological examination showed no evidence of cardiac inflammation. RNA-seq was performed to further examine mechanisms of anti-PD1 therapy on the heart. Our data shows that over 230 genes were uniquely expressed in cardiac tissue of mice treated with anti-PD-1 therapy compared to isotype control. While no overt changes in immune infiltrate were seen, gene set enrichment analysis (GSEA) showed significant positive enrichment in chemokine receptor interactions with anti-PD-1 treatment potentially playing a role in the differentiation of cardiac, immune cell populations.Furthermore, gene enrichment was also observed among metabolic pathways. Interestingly, upregulation of PDK4 was observed in the hearts of animals treated with anti-PD1 antibody. PDK4 activation restricts cardiomyocyte metabolic flexibility during stress. scRNA-seq data from patient PBMCs also indicates an increase in PDK4 levels in the monocytic population after anti-PD1 treatment, suggesting that this protein may be regulated due to checkpoint blockade.

Conclusions Cardiac inflammation due to checkpoint blockade is implicated in ICB-myocarditis However, RNA-seq data suggest that PD-1 therapy alters chemokine and metabolic pathways that may contribute to cardiac damage, suggesting potential early markers to identify cardiac irAEs

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