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EXPLORING MECHANISMS BY WHICH PHYSICAL EXERCISE FUELS ANTITUMOR CD8+ T CELL IMMUNITY AGAINST IMMUNOTHERAPY RESISTANT MELANOMA

Catherine M Phelps*, Jake Shapira, Alex C McPherson, Colin Laughlin, Marlies Meisel.
University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Background Melanoma is among the deadliest forms of cancer due to high rates (>60%) of resistance to common treatments including immune checkpoint inhibitor (ICI) therapy. Thus, it is imperative to identify factors that improve ICI therapy efficacy by enhancing antitumor interferon-gamma-producing CD8 + T cell (Tc1 cell) function, which is critical to ICI therapy success. Emerging evidence associates physical exercise with improved ICI therapy efficacy in cancer patients. Preclinical studies have shown that exercise improves ICI therapy efficacy in pancreatic and breast cancer models. Yet, mechanisms of how exercise enhances ICI efficacy, particularly in ICI-resistant melanoma, remain poorly understood.

Methods In this study, we utilize a mouse treadmill-running model to assess the impact of physical exercise on tumor immunity and ICI efficacy in a translationally relevant YUMM 1.7 melanoma model, which is resistant to ICI therapy and carries the common human melanoma mutation BRAF^{V600E}.

Results Our exciting preliminary data show that exercise is sufficient to restrain ICI-resistant YUMM1.7 melanoma tumor growth, enhance survival, and re-sensitize tumors to ICI therapy in both prophylactic and therapeutic settings. Exercise-induced tumor suppression was linked with an expansion of Tc1-cells in the tumor draining lymph node and tumor micro-environment, suggesting that exercise enhances antitumor Tc1 immunity during T cell priming and effector stages, respectively. The tumor suppressive effects of exercise in our model were found to be dependent on adaptive immunity and CD8 + T cells and independent of tumor model, as exercise similarly restrained B16 melanoma outgrowth. Our central hypothesis is that physical exercise enhances antitumor Tc1 immunity which consequently restrains tumor growth and re-sensitizes tumors to ICI therapy in ICI-resistant melanoma.

Conclusions In ongoing and future studies, we will (i) identify if exercise acts directly upon CD8+ T cells to promote antitumor function by defining exercise-induced changes to the CD8+ T cell transcriptome and epigenome on a single cell level, (ii) determine if exercise improves tumor-antigen specific CD8+ T cell immunity, and (iii) test if adoptive transfer of exercise-primed CD8+ T cells enhances ICI therapy efficacy in melanoma and other ICI-resistant cancers. Results of this study will define novel mechanisms by which physical exercise enhances antitumor CD8+ T cell immunity and identify new therapeutic targets that can be deployed as adjuvants to increase sensitivity to existing immunotherapies in ICI-resistant cancers.

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