The Role of Increased Physical Activity on Immune Response in Pancreatic Cancer

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Introduction

Pancreatic Ductal Adenocarcinoma (PDAC) is a lethal cancer due to the lack of early detection and treatment methods[1]. There is a dire need to develop better therapeutic approaches for PDAC. Immunotherapy has become a promising new treatment strategy for many cancers; however, it has not provided meaningful improvement to survival in PDAC patients due to the complexity of the pancreatic tumor microenvironment[2]. New research suggests that physical activity (PA) increases the number of circulating natural killer (NK) and T cells and improves survival outcomes in certain cancers[3,4]. Furthermore, interleukin-15 (IL-15) is a promising immune-oncology cytokine due to its ability to stimulate the proliferation and cytotoxic functions of NK and T cells[5]. Preliminary data from our laboratory showed that when comparing PDAC mice to control mice in either a PA or no-PA intervention, there was a higher expression of IL-15 in the adipose tissue of the PA group, regardless of cancer status. Therefore, we hypothesize that PA will alter the immune cell populations and circulating levels of IL-15 in a PDAC mouse model, which could allow for improved response to immunotherapy.

Methods

Splenocytes were isolated from mice that underwent two different PA interventions and were orthotopically injected with PDAC cells. Macrophages, T cells, NK cells and myeloid-derived suppressor cells (MDSCs) were stained and quantified via flow cytometry analysis. In the first intervention shown by **Fig 1.**, mice were given a high-fat diet (HFD) for nine weeks and then randomly assigned to four groups: no-PA + HFD; PA + HFD; no-PA + control diet (CD); PA + CD; for five weeks prior to orthotopic cancer cell injection. After, the mice continued on the same diet with no PA for four weeks. Splenocytes were used to quantify the population of NK cells, T cells, MDSCs and macrophages via flow-cytometry, and serum was collected to measure IL-15 levels via ELISA. In the second intervention shown by **Fig 2.**, mice were placed in either a no-PA or PA intervention for 13 weeks prior to orthotopic cancer cell injection. The mice had a one-week recovery and then continued on their PA or no-PA intervention combined with either saline or gemcitabine (GEM) treatment for 2.5 weeks until they were sacrificed. The same immune cell populations were analyzed via flow cytometry.

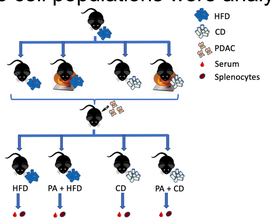

Figure 1: Experimental design of PDAC mice that underwent a diet and/or PA intervention. Mice were given a HFD for 9 weeks, followed by HFD/CD + PA/no-PA intervention and orthotopic cancer cell injections. Splenocytes and serum were collected.

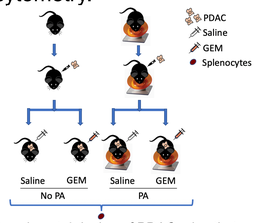

Figure 2: Experimental design of PDAC mice that underwent a PA or non-PA intervention for 13 weeks until orthotopic cancer cell injections of PDAC were given. After, the mice continued their intervention and were given saline or GEM injections for 2.5 weeks. Splenocytes were collected.

Results

A control diet intervention showed a slight increase in MDSCs and F480⁺ Macrophages in PDAC mice

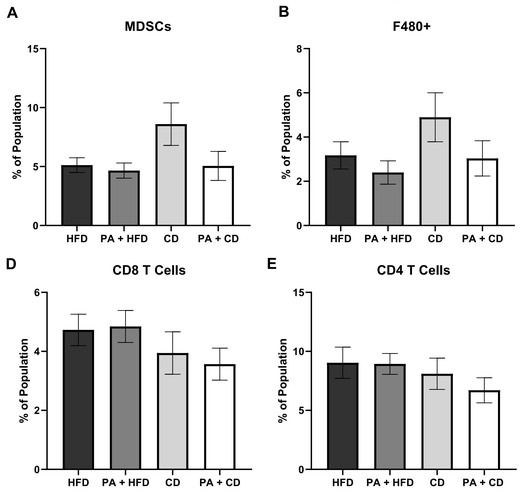

Figure 3: Flow cytometry was performed to analyze the population of immune cells in the splenocytes of PDAC mice in **Fig. 1** that underwent a PA/no-PA and/or HFD/CD intervention. (**A**) Population of MDSCs, (**B**) Population of F480⁺, (**C**) Population of NK Cells, (**D**) Population of CD8 T Cells, (**E**) Population of CD4 T Cells. A Kruskal-Wallis test was done to show statistical significance.

Gemcitabine in combination with a PA Intervention significantly increased the percentage of CD8 T Cells in PDAC mice

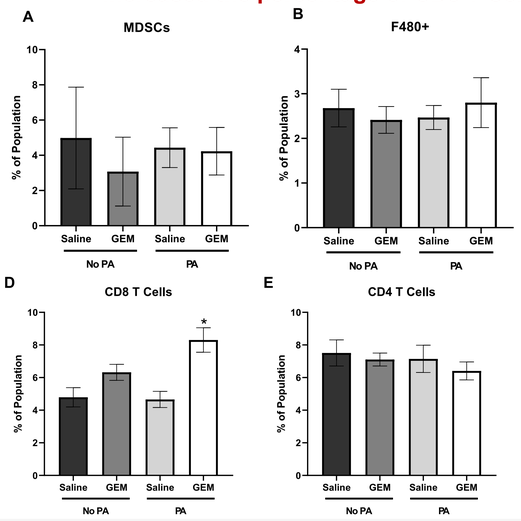

Figure 4: Flow cytometry was performed to analyze the population of immune cells in the splenocytes of PDAC mice in **Fig. 2** that underwent a Saline/GEM and/or PA/no-PA intervention. (**A**) Population of MDSCs, (**B**) Population of F480⁺, (**C**) Population of NK Cells, (**D**) Population of CD8 T Cells, (**E**) Population of CD4 T Cells. A Kruskal-Wallis test was done to show statistical significance. * denotes statistical significance p<0.05.

Results

PA in combination with HFD has no significant effect on the IL-15 serum levels of PDAC mice

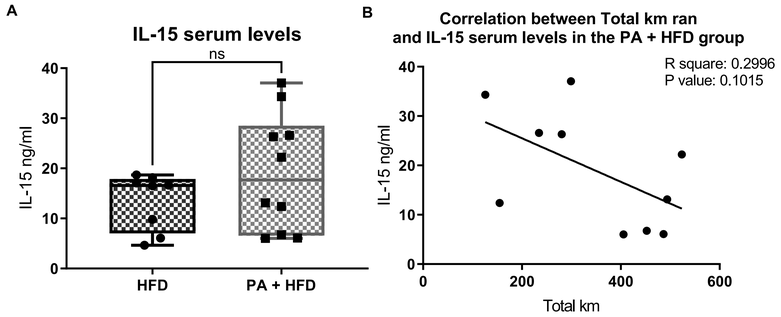

Figure 5: An IL-15 ELISA was performed from the serum of two groups of PDAC mice in **Fig. 1** that remained on a HFD and completed either a PA or no-PA intervention. (**A**) IL-15 serum levels, (**B**) Correlation between Total km ran and IL-15 serum levels.

Conclusions

This study shows that the PA and diet interventions examined do not significantly affect the percentage of macrophages, T cells, NK cells and MDSCs in the splenocytes or the circulating levels of IL-15 in the mice studied. However, PA and gemcitabine treatment combined increased the percentage of CD8+ T cells. Further studies are needed to determine if immunotherapy along with PA and gemcitabine improves PDAC outcomes.

Acknowledgements

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References

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