Aerobic Exercise Impacts the Tumor Microenvironment by Altering CAF Abundance and CAF-Activating Cytokines in Pancreatic Cancer

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Background
Pancreatic Ductal Adenocarcinoma (PDAC) is one of the deadliest types of cancer, due in part to resistance to anti-cancer therapies and a complex tumor microenvironment. Excessive deposition of extracellular matrix (ECM; desmoplasia) and the high density of cancer-associated fibroblasts (CAFs) contribute to this resistance and tumor growth. Desmoplasia causes a physical barrier to chemotherapy delivery and promotes cancer cell proliferation and metastasis. CAFs, beyond being responsible for ECM deposition, play a central role in tumorigenesis as regulatory cells able to promote tumor growth and anti-cancer therapy resistance via secretion of numerous growth factors.

Introduction

Aims:
1. To determine the effects of two different exercise intensities, low 8 meters/min and moderate 16 meters/min, on CAF abundance and desmoplasia in mice bearing PDAC Hy15549.
2. To determine the effect of the same exercise intensities on CAF-activating cytokines in mice bearing PDAC KPC 4662 cells.

Hypothesis: Exercise reduces CAF abundance and desmoplasia by reducing the levels of CAF-activating cytokines secreted by cancer cells.

Methods

In Vivo:
Mouse PDAC cell lines (Hy15549 or KPC 4662) were injected into the pancreas in C57BL/6J mice. When tumors reach around 30 mm³, mice were divided into sedentary, exercise at 8 meters/minute, and exercise at 16 meters/minute groups. Treadmill exercise was performed for 45 minutes daily, 5 days a week, for 3 weeks.

Ex Vivo:
Tumor desmoplasia was analyzed by Masson’s trichrome. CAF abundance will be assessed by immunofluorescence with antibodies against PDNP, αSMA, Desmin, NG2, and CD31. The levels of CAF-activating cytokines (TNF-α, IL-1b and TGF-β) will be measured by western blot.

Analysis of CAF-activating cytokines on KPC 4662 homogenates:
1. Perform western blot using antibodies against TNF-α, IL-1b or TGF-β.
2. Analyze and quantify bands relative to reference protein (β-actin).

Results

Figure 1: Effect of Exercise on CAF Abundance in PDAC Hy15549-Bearing Mice

Figure 2: Expression Levels of CAF-Activating Cytokines in PDAC KPC 4662-Bearing Mice

Figure 3: Effect of Exercise on Collagen Deposition in PDAC Hy15549-Bearing Mice

Conclusions

1. Exercise reduces the abundance of αSMA+ and NG2+ CAFs in Hy15549.
2. Exercise does not reduce the levels of CAF-activating cytokines in KPC 4662.
3. Exercise reduces the excessive deposition of collagen in Hy15549 with both either 8 m/min and 16 m/min intensities.

Exercise may be an effective tool for remodeling the PDAC microenvironment, possibly improving the efficacy of anti-cancer therapies.

References


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