Introduction

Solid tumor vasculature is dysfunctional containing structural abnormalities, heterogeneous perfusion patterns, and hyper-permeability. These abnormalities make it a challenge to deliver systemic therapies effectively. In addition, poor vasculature function promotes a hypoxic tumor environment conducive to therapeutic resistance. One method to normalize tumor vasculature is aerobic exercise. Our lab has observed significant reductions in hypoxia after exercise but no change in vessel perfusion in a murine model of melanoma. This may be due to an alteration in tumor metabolic flux or oxygen consumption after exercise. Thus, this project aims to study the effect of exercise on tumor metabolism. We hypothesized that exercise reduces expression of genes associated with metabolism in tumors, contributing to decreased hypoxia within the tumor microenvironment.

Methods

YUMMER melanoma cell line was injected into fourteen C571Bl/6 male mice subcutaneously. When tumors became palpable, mice were exercised 45 min/day, 5 days/week, for 14 days at 12 meters/minute using a forced treadmill model to achieve moderate aerobic exercise training. Prior to mouse euthanasia, pimonidazole HCl was injected intravenously in tumor bearing mice and tissue was frozen for analysis. Hypoxia and metabolism related proteins and genes were measured by western blot and qPCR, respectively. Differentially expressed metabolites were mined in a public dataset (Rundqvist et al. 2020. eLife) using the limma package on R.

Results

Exercise reduced tumor hypoxia, as indicated by pimonidazole staining. However, no changes in HIF1α mRNA or protein expression were detected in tumor homogenates. Decreasing trends were observed in mRNA levels of HIF1α target genes, VEGFa and Glut1.

Genes associated with Krebs cycle function showed increasing trend in tumors from exercised mice (ldh2, p=0.09; and Fth1, p=0.16).

No change in expression of ATP synthase related genes were observed (ATP5b, p=0.37; ATPaf2, p=0.27). However, expression of cytochrome c oxidase increased after exercise (Cox4i1, p=0.05).

Consistent with our findings, Krebs cycle metabolites including citrate, α-ketoglutarate, fumarate, and malate increased in mouse plasma samples after exercise.

Conclusions

Our original hypothesis was not supported as we saw an increase in several metabolism related genes. These results suggest that aerobic exercise does modulate metabolism, however, it is unclear why exercise may increase metabolism in tumor tissue and how this impacts tumor hypoxia. Additional studies like Seahorse assay to more directly determine metabolic flux and oxygen consumption are necessary to further elucidate the role of exercise in tumor metabolism.

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