Exercise training attenuates the variation of the phospholipidome of mitochondria from skeletal muscle induced by the urothelial carcinoma

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Cancer cachexia is a wasting paraneoplastic syndrome characterized by physical disability, reduced tolerance to cancer therapy and reduced survival of cancer patients. There is no cure for cancer cachexia and the pathophysiological process involved is largely unknown. Physical exercise is currently recommended for the clinical management of this syndrome.

In this study we used a lipidomic approach based on liquid chromatography coupled with high resolution mass spectrometry to study the effect of exercise in modulating the phospholipid composition of mitochondria isolated from the *gastrocnemius muscle*. We used a preclinical Wistar rat model of urothelial carcinoma-induced cachexia (BBN). The exercised BBN and control rats were submitted to 13 weeks of exercise on a treadmill. BBN sedentary rats and controls were also included in this study.

PCA multivariate analysis showed a cluster that included the BBN exercise group and the two control groups (sedentary control and exercise control), while the sedentary BBN group was clustered away (Figure 2). The main significant differences occurred in phosphatidylserine (PS) and cardiolipin (CL). PS with shorter fatty acyl chains were upregulated in the sedentary group BBN, while the other PS species with longer FA and a higher degree of unsaturation were downregulated. The BBN exercise group showed only small differences from the control groups.

The remodeling of the phospholipid profile of mitochondria from skeletal muscle of rats with urothelial carcinoma confirmed the importance of lipid metabolism in mitochondrial dysfunction and muscle wasting. Exercise training prevented the changes induced by cancer of the polar lipid profile and had a positive impact on the ability of mitochondria to produce ATP, restoring the healthy profile of phospholipids. These results support the current perspective that exercise is an adequate therapeutic approach for the management of muscle wasting linked to cancer.

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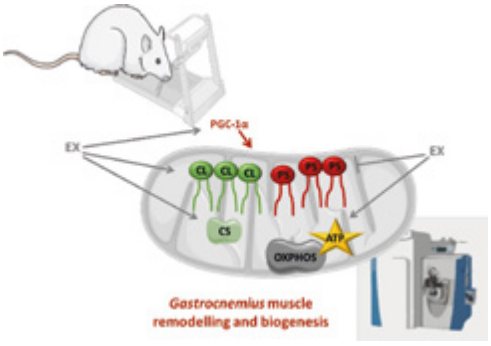

FIGURE 1
Graphical abstract

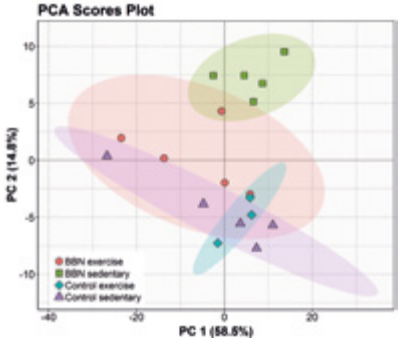

FIGURE 2
PCA of the phospholipid data set from preclinical Wistar rat model of urothelial cachexia acquired by LC-MS. Groups: Control sedentary, Control with exercise, urothelial cancer (BBN sedentary) and urothelial cancer submitted to exercise (BBN exercise).