Physical Activity Regulates Proteolytic Pathways to Protect Against Cancer-mediated Cardiac Cachexia

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Introduction: Cancer cachexia is a severe and progressive muscle-wasting syndrome characterized by a loss of lean muscle mass, systemic inflammation, and altered muscle metabolism. In addition to skeletal muscle, cardiac muscle often experiences atrophy and cardiac remodeling during cancer-induced cardiac cachexia. Aerobic exercise has been of recent interest as a therapeutic approach for cancer cachexia as it helps preserve muscle mass, however, the exact mechanism is still not fully understood. The purpose of this study is to determine how physical activity concurrent with tumor-bearing affects cardiac atrophy and metabolism in a preclinical lung cancer model. **Methods:** Male mice (n=8-10/group) were randomly assigned to groups: sedentary non-tumor (SED+NT), sedentary tumor (SED+T), wheel running non-tumor (WR+NT), and wheel running tumor (WR+T). Mice were inoculated with Lewis lung carcinoma tumor cells (5x10^5 LLC cells in flank) on day 1 and could (voluntarily) run on a wheel for 4 weeks. Echocardiograms were performed on days 0 and 28 to measure cardiac structure and function. **Results:** Male tumor-bearing mice exhibited the worst cardiac function compared to all other groups, and physical activity concurrent with tumor-bearing protected against tumor-mediated declines in cardiac function (fractional shortening - SED+T: 41% vs WR+T: 53%, $P<0.001$). Additionally, SED+T showed the highest cardiac protein expression of MuRF1, Atrogin-1, and GDF-15, while physically active (WR) mice had lowest cardiac expressions of MuRF1 and Atrogin1. Since MuRF1 and Atrogin1 are known to drive proteolysis resulting in muscle atrophy, this data highlights the critical role of concurrent physical activity in controlling proteolysis to protect against cardiac atrophy and dysfunction. **Conclusion:** Tumor-bearing resulted in severe cardiac dysfunction, atrophy, and proteolysis. Importantly, physical activity initiated during tumor-bearing was capable of downregulating proteolytic signaling to ultimately preserve cardiac structure and function. The study underscores the importance of physical activity for cancer patients experiencing detrimental muscle wasting. More research is needed to understand the exact mechanisms that drive the beneficial effects of exercise and physical activity for clinical populations – especially those suffering pathological muscle wasting. Such information is critical to the safe and effective implementation of rehabilitative exercise programs.