

Exploring the Relationship between Mitochondrial Dysfunction and Skeletal Muscle Weakness During Cancer

LJ Delfinis & CA Bellissimo, SN DiBenedetto, S Gandhi and CGR Perry.

School of Kinesiology and Health Science, Muscle Health Research Centre, York University, Toronto, ON.

Introduction: 1 of 2 males and 1 of 3 females will develop cancer at some point in their lives. 25-80% of cancer patients exhibit cachexia depending on the type and stage of cancer. Cancer cachexia is a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without fat mass loss) that cannot be fully reversed by conventional nutritional support. An emerging model proposes that cancer cachexia maybe be a result of damaged muscle metabolism. Mitochondria are organelles within muscle cells that regulate three vital cellular processes: ATP production, reactive oxygen species (ROS) generation and calcium retention capacity (CRC) in relation to triggering of the permeability transition pore prior to apoptosis. It was recently identified that cancer can induce mitochondrial dysfunction in skeletal muscle preceding the development of cachexia. Therefore, targeting skeletal mitochondria to preserve mitochondrial bioenergetics in early stages of tumour development may potentially attenuate cachexia.

Methods: To establish a mouse model of cachexia, 8-week-old CD2F1 mice (n=12) were injected subcutaneously with 5×10^5 colon 26 adenocarcinoma (C26) cancer cells or phosphate-buffered saline (PBS control, n=10) per flank. Tumours developed for 26-29 days. Tumour volume was measured daily. After tumour development, mice were sacrificed. Both the quadriceps and diaphragm muscles were separated into permeabilized muscle fibers and used for measurements of mitochondrial respiration.

Preliminary Results: After 26-29 days of tumour bearing, there were reductions in body weight (-19.6%) and muscle mass (-15%-28%) in the plantaris, gastrocnemius, tibialis anterior, extensor digitorum longus and quadriceps muscles compared to PBS. Mitochondrial respiration was increased in diaphragm and quadriceps in C26 vs PBS.

Conclusion: Preliminary data demonstrates that C26 cells induces muscle wasting but not mitochondrial respiratory dysfunction in diaphragm and quadriceps. Although increased mitochondrial respiration is perplexing, it is possible this is due to an adaptation in early onset mitochondrial dysfunction during tumour bearing. Ongoing work is investigating whether changes in mitochondrial respiration are due to shifts in fiber type and whether the mitochondrial-targeted enhancer SkQ1 upregulates mitochondrial respiration, ROS, and CRC as well as muscle mass and strength during cancer.