

## Mitochondrial Dysfunction in Diaphragm Muscle Precedes the Cachectic Phenotype in LLC Tumor-Bearing Mice.

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### ABSTRACT

The defining feature of cancer cachexia is extensive weight loss and skeletal muscle atrophy. It is clinically important because cachexia reduces patient survival, results in functional impairment, and is estimated to be directly responsible for 20-40% of cancer deaths. Unfortunately, no clinical therapy exists and therefore, it is important to understand the molecular mechanisms responsible for rapid muscle wasting. Compared to limb muscles, the diaphragm is relatively understudied in cancer cachexia, but is likely to be adversely affected because cachexia is a systemic disease. Wasting of the primary inspiratory muscle may result in difficulty breathing and inability to adjust minute ventilation in response to a respiratory challenge. Based on emerging evidence, it is clear that oxidative stress is present in cachexia-induced wasting of the diaphragm; we developed the hypothesis that mitochondrial dysfunction in the diaphragm precedes cachexia. **METHODS:** 1X10<sup>6</sup> Lewis Lung Carcinoma cells (LLC) or Phosphate-Buffered Saline (PBS, control) were implanted to the hind-flank of C57BL/6/J mice at 8 wks of age. Tumors were allowed to develop for 1, 2, 3, or 4 wks. At designated time points diaphragms were collected and mitochondrial function was assessed by respiration and ROS production. **RESULTS:** Cancer cachexia was evident only at the 4 wk time point demonstrated by decrease in body mass and muscle atrophy in several limb muscles. Mitochondrial respiration, assessed by respiratory control ratio (state3/state 4 respiration), was significantly lower at 1 wk ( $p < 0.05$ ) post-implantation and stayed depressed. ROS production was significantly elevated early in the time course (2 wk time point) compared to control ( $p < 0.05$ ), however wks 3 and 4 were not different from control. **CONCLUSIONS:** The molecular events that lead to muscle atrophy in cancer cachexia are unknown. We demonstrate that two hallmarks of mitochondrial dysfunction, altered respiration and ROS production, occur in the diaphragm well before the cancer cachexia phenotype is evident in the LLC model. These data suggest that the mitochondria are likely a suitable target to treat or prevent cancer cachexia-induced muscle wasting in the diaphragm.