TACSM Abstract

Males, but Not Females, Demonstrate Mitochondrial Dysfunction in the C26 Model of Cancer Cachexia

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ABSTRACT

Cancer cachexia is characterized by progressive muscle wasting that can lead to symptoms such as anemia, severe weight loss, and fatigue. These symptoms can lead to limitations in activities of daily living and can cause resistance to chemotherapy treatments in cancer patients. There are no current treatments available to treat cancer cachexia and a critical need remains to identify mechanisms of cancer cachexia. Recently, our group identified mitochondrial disfunction precedes muscle atrophy in males but not females in a model of lung cancer induced atrophy. However, it is unknown whether this finding is replicated when studying a different type of cancer. **PURPOSE**: This study set out to determine if mitochondrial respiration is impaired in the plantaris muscle in a well-established colon cancer model of cachexia. **METHODS**: The time-course study consisted of male and female mice in four groups per sex: An age-matched control (PBS), and three groups implanted with C26 tumors. Tumor growth for 10-15 days, 20 days, and 25 days. Tumors were implanted bilaterally into the hind flank for a total of $1X10^6$ cells PBS (one-half per each hindflank). The plantaris was weighed for wet mass then teased into small fiber bundles and permeabilized for the quantification of mitochondrial function. Mitochondrial dysfunction was classified by a decrease in the respiratory control ratio (RCR), which is the ratio of state 3 (maximal ADP stimulated respiration) to state 4 (oligomycin-induced leak respiration). Male and Female data were analyzed separately using a one-way ANOVA. **RESULTS**: The tumor burden increased as the number of days increased. Male RCR showed a mean difference in RCR at the early timepoint (10-15 day, $p=0.058$) and demonstrated significantly lower RCR at the 20 day timepoint compared to PBS control (20d= 1.170± 0.094, PBS= 2.41 ± 0.13, $p=0.031$). Interestingly, RCR was not significantly different between male PBS and 25 days (1.864± 0.21, $p=0.084$). RCR in the plantaris from females was not different among any of the groups ($p=0.401$). **CONCLUSION**: Along with our previously published data in a lung cancer model, these data indicate that the mechanisms of muscle atrophy are sex dependent. Specifically, mitochondrial dysfunction appears to play an important role in cancer-induced atrophy in male, but not female, mice.