Fractional Synthetic Rate and Markers of Protein Turnover are Altered in the Diaphragms of Cachectic Mice

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ABSTRACT

Cancer cachexia, a wasting syndrome characterized by rapid skeletal muscle wasting and fat loss, directly accounts for up to 20-40% of cancer-related deaths. All muscles, including respiratory muscles, are susceptible to atrophy because cancer cachexia is a systemic disease. Atrophy of the primary breathing muscle, the diaphragm, can lead to respiratory distress, which is commonly associated with a cachectic phenotype. Indeed, the diaphragm is more susceptible to atrophy in certain conditions, but little is known about the effects of cancer-cachexia on protein turnover in the diaphragm. Therefore, investigations into the alterations in protein turnover could provide insight to the molecular events and provide valuable information in the search for therapeutic targets. **PURPOSE**: The purpose of this study was to describe changes in diaphragmatic protein synthesis and molecular markers of synthesis and degradation during the progression of cancer cachexia. **METHODS:** C57BL6/J mice (8 wks old) were implanted with $1X10^6$ Lewis Lung Carcinoma cells (LLC) or Phosphate-Buffered Saline (PBS, control). Tumors developed over a 1-4 wk time course and diaphragms were harvested at each time point (1, 2, 3, or 4 wks). Fractional synthetic rates (FSR) were determined using deuterium incorporation into muscle. Selected markers of protein synthesis and degradation pathways were analyzed by immunoblot analysis. One-Way ANOVA was used for statistical analyses, with significance set at $p<0.05$. **RESULTS:** FSR trended downward over time, but did not reach significance. Similar to FSR, anabolic signaling markers (4EBP-1, ERK1/2, Deptor) did not demonstrate significant differences. p62, an autophagic degradation marker, was significantly less than PBS in 3 wk diaphragms ($p<0.05$). There were no alterations in phosphorylation of either of the atrogene transcription factors FOXO1 or FOXO3a across the time course. CONCLUSION: The negative trend for FSR suggests there may be decreased protein synthesis in the diaphragm with cancer cachexia. Based on differences in p62 content, increased protein degradation though autophagy may be occurring in the diaphragm during cancer cachexia.