Precision analysis of protein sequence and post-translational modification heterogeneity in pancreatic cancer induced cachexia

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Background and Hypothesis

Cachexia is a wasting syndrome commonly occurring in cancer patients that cannot be explained by decreased calorie intake alone. It results in decreased quality of life and increased mortality, and there are currently no effective treatments. To better understand cachexia, we aimed to profile protein heterogeneity seen in pancreatic ductal adenocarcinoma (PDAC) mouse models with cachexia. Since muscle is a readily available protein resource during catabolism, we hypothesize there are significant changes in protein sequence and post-translational modifications (PTMs) of muscle proteins during cachexia progression. As these proteins are scavenged, precise analysis of sequence variation can identify the exact mechanism of protein/muscle breakdown and better elucidate the molecular processes of PDAC-induced cachexia.

Experimental Design

We performed bioinformatic analysis of two proteomics datasets of cardiac and skeletal muscle samples from PDAC-induced cachexia mouse models. Two proteomics software algorithms, SEQUEST (within Proteome Discoverer (PD)) and PEAKS (a machine-learning algorithm), were used to identify all sample proteins and their PTMs. Because PEAKS can identify more PTMs than PD, we compared the most abundant proteins identified in PD and PEAKS, hypothesizing PEAKS would yield greater protein sequence coverage. Finally, we compiled unpublished PTMs and protein processing events for 25 of the most abundant proteins in both datasets.

Results

Notably, PEAKS reported greater sequence coverage for cardiac muscle than PD, while the skeletal muscle sample had similar coverage in both algorithms. This discrepancy may suggest cachectic processes degrade skeletal muscle at a greater rate than cardiac muscle, preventing PEAKS from increasing skeletal muscle sequence coverage relative to PD. In addition, several unpublished modifications, including those of actin and acetyl-CoA acetyltransferase, were recorded.

Potential Impact

These newly discovered protein modifications may indicate previously unknown molecular processes in the course of PDAC-induced cachexia. These modifications may serve as cornerstones of future research to identify novel therapeutic targets in cachexia treatment.