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TITLE
Modeling Human Pancreatic Cancer Cachexia Using Mouse Avatars

HYPOTHESIS:
Analysis of skeletal muscle biopsies of cachectic pancreatic ductal adenocarcinoma (PDAC) patients and skeletal muscle of PDAC patient-derived xenograft (PDX) mice, or mouse avatars, will reveal previously unidentified morphological and transcriptional features of skeletal muscle wasting in response to pancreatic cancer not previously identified by current pre-clinical models.

BACKGROUND/AIMS:
Two of the greatest impediments to progress in the field of cancer cachexia are 1) the lack of comprehensive data in skeletal muscle (SkM) of cachectic cancer patients and 2) reliance on pre-clinical mouse models that may not fully recapitulate the human condition. Thus, the current study aims to address these barriers by analyzing mechanisms of cancer-induced skeletal muscle wasting in a novel pancreatic ductal adenocarcinoma (PDAC) patient-derived xenograft (PDX) model of cancer cachexia and comparing these findings to histological and biochemical analysis of cachectic PDAC patient skeletal muscle biopsies.

METHODS:
Rectus abdominus biopsies were collected from cachectic pancreatic ductal adenocarcinoma (PDAC) patients (and controls). PDAC-PDX mice were created by implantation of 2x2mm\textsuperscript{2} portions of resected PDAC patient tumors into NSG mice. Tumor growth was monitored using ultrasound, and mouse avatars were sacrificed when tumors reach ~2cm in diameter (~8-10 weeks post implantation). Patient and PDX muscle was sectioned and stained with H&E or Masson’s Trichrome to assess morphology and fibrosis respectively, and microarray analysis was performed on RNA extracted from patient and PDX muscle to identified cachexia-associated changes in the SkM transcriptome.

RESULTS & CONCLUSIONS
Separate microarray analysis of TA muscles from two different PDX lines revealed similar transcriptional changes, with enriched functional categories related to apoptosis, lipid localization, and transcriptional repression among upregulated genes and extracellular matrix and sarcomere among downregulated genes (-1.5>f<1.5). Following H&E staining, we also compared the morphology of the TA and diaphragm to rectus abdominis muscles biopsied from PDAC patients and found evidence that the diaphragm may more closely recapitulate the pathology observed in PDAC patients. Subsequent microarray analysis of the diaphragm and comparison to microarray data collected from rectus abdominis muscles from PDAC patients supported our morphological findings, with significantly greater gene overlap identified than with the TA. In summary, using the PDX model, we are able to recapitulate key aspects of pancreatic cancer cachexia and find that the diaphragm, due perhaps to its biological functions and proximity to the tumor, may more closely recapitulate the cachectic phenotype observed in rectus abdominis muscles of cancer patients.