A Murine Model of Metastatic Kidney Cancer to Bone Demonstrates Muscle Wasting, Bone Loss, and IL-6/JAK/STAT3 Pathway Activation in Muscle

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INTRODUCTION: Cachexia, characterized by systemic muscle wasting and bone loss, accounts for 20–40% of cancer-related deaths, yet no therapies exist. Kidney cancer is both prone to bone metastases and associated with cachexia, with relatively long survival providing a window for therapeutic intervention. Preclinical models that reproduce metastatic bone disease and its systemic effects are lacking. We developed a novel surgical model of metastatic kidney cancer to bone to study cachexia biology.

METHODS: With IACUC approval, the metastatic human kidney cancer cell line Caki-1 was surgically implanted along the lateral tibia of male NSG mice after periosteal scoring. Tumor-bearing and sham-operated control mice were followed for 8 weeks. Cachexia outcomes included body weight, grip strength, EchoMRI, DEXA, and muscle weights at necropsy. Tibialis anterior muscle fiber area was quantified by immunofluorescence. Bone outcomes were assessed by micro-CT of femur and spine and torsional strength testing of the contralateral femur. Serum IL-6 was measured, STAT3 phosphorylation assessed by western blot, and qPCR performed for IL-6 target genes and other genes indicative of muscle health.

RESULTS: Caki-1 cells produced reproducible osteolytic tibial lesions on radiographs without distant metastases. Tumor-bearing mice developed progressive weight loss, reduced grip strength, and decreased lean mass by EchoMRI and DEXA (**Figure 1a–d**). At necropsy, skeletal muscles were significantly smaller with reduced tibialis anterior fiber cross-sectional area compared with controls (**Figure 1e–f**). Micro-CT revealed reduced vertebral bone volume and a trend toward decreased femoral volume in tumor-bearing mice (**Figure 2a–b**). Contralateral femoral torsional strength was not significantly different (not shown). Serum IL-6 was elevated, with corresponding STAT3 phosphorylation in muscle and upregulation of IL-6 target genes (**Figure 3a-c**).

DISCUSSION: This study establishes the first reproducible murine model of metastatic kidney cancer to bone that concurrently demonstrates muscle wasting and bone loss. The model recapitulates key features of clinical cachexia, including systemic muscle and bone loss. Importantly, IL-6/JAK/STAT3 activation provides a possible mechanistic link between tumor–bone interactions and systemic muscle wasting, consistent with prior preclinical and patient-derived observations. This system offers a translatable platform for dissecting tumor–bone–muscle crosstalk and inflammatory signaling in cachexia.

SIGNIFICANCE/CLINICAL RELEVANCE: These findings suggest that bone metastases can drive cachexia and highlight the IL-6 pathway as a therapeutic target. Given the availability of IL-6 inhibitors and JAK/STAT agents already in clinical use, this model provides a platform to evaluate repurposed or novel therapies aimed at reducing morbidity and mortality in cancer patients with metastatic bone disease.
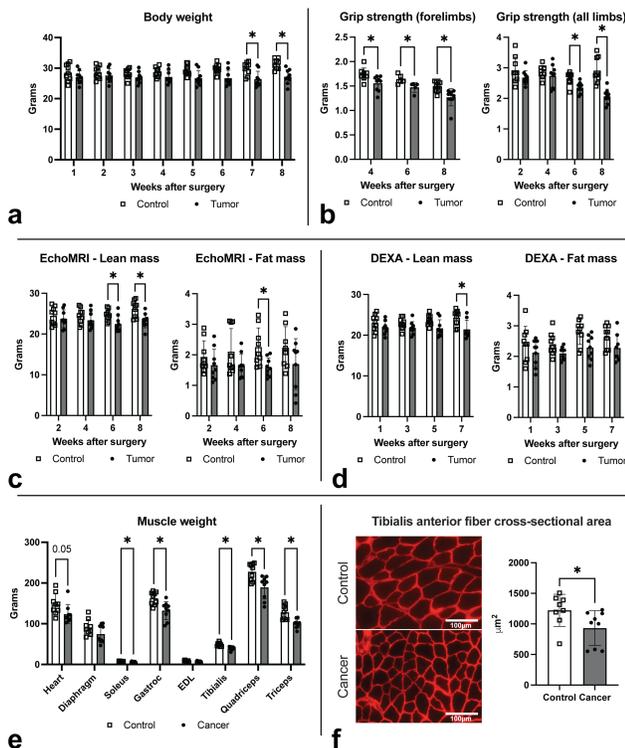
IMAGES AND TABLES:

Figure 1. Mouse model of kidney cancer bone metastasis demonstrates muscle loss. Body weight (a), grip strength (b), lean mass (c and d), muscle weight (e), and tibialis cross-sectional area (by dystrophin immunofluorescence) (f) were lower in tumor-bearing mice, compared to sham controls. * = p < 0.05.
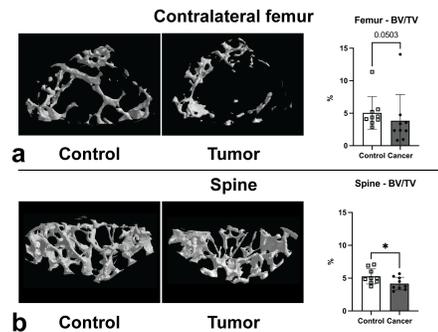

Figure 2. Mouse model of kidney cancer bone metastasis demonstrates bone loss. Representative µCT images show a trend towards reduced bone volume (BV) / total volume (TV) in contralateral mouse femora (a) and lumbar vertebrae (b). * = p < 0.05.
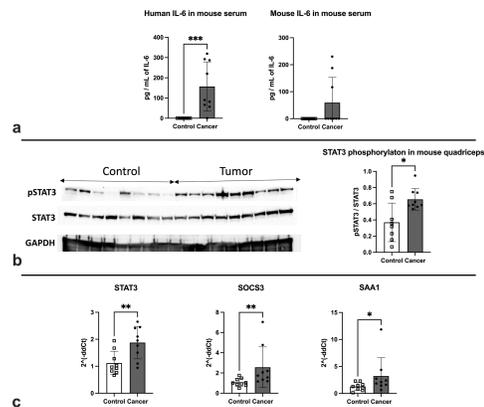

Figure 3. Serum IL-6 and downstream muscle STAT3 phosphorylation, IL-6 target genes are increased in tumor-bearing mice. Serum human and mouse IL-6 (a) muscle pSTAT3 (b) and the IL-6 target genes STAT3, SOCS3, SAA1 (c) were increased in mouse model of bone metastases with human Caki-1 cell line. Species specific antibodies were used. Each datapoint and blot represents an individual animal. * = p < 0.05.