Formation of liver metastases enhances the pro-cachectic signaling in colorectal cancer hosts

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Figure 1: LMs worsen CRC-induced body wasting

Background
- Colorectal cancer (CRC) is a deadly disease that in its most advanced stages metastasizes to the liver and is accompanied by cachexia.
- Cachexia is characterized by muscle and fat wasting, systemic inflammation, and reduced survival.
- Formation of liver metastases (LMs) accelerates cancer cachexia in tumor-bearing hosts.

Methods
- 8-week-old male NSG mice were injected subcutaneously with human HCT116 CRC cells, or in a xenograft model (mHCT116) to model the dissemination of LMs.
- Livers and tumors from the subcutaneous and metastatic models, alongside their respective controls, were collected and RNA sequencing performed.
- Animals were assessed for muscle force 24-hours prior to euthanasia, and skeletal muscles were collected for mass and morphological analyses.
- Co-culture of hepatocytes (AML12) and CRC cells (HCT116) was then modelled in vitro and conditioned media used to treat C2C12 myotubes.

Figure 2: LMs aggravate CRC-induced cachexia phenotype

Figure 3: Metastasis formation alters the molecular landscape of liver during cancer

Figure 4: Cachexia signaling is exacerbated in mHCT116 livers

Figure 5: Adhesion and Gap junction molecules are upregulated with LMs in tumor and host

Conclusions
- LMs of CRC enhance activation of cachexia associated signaling pathways.
- Worsened cachexia phenotype was coincident with upregulation in adhesion and gap junction molecules in liver and tumor.
- Hepatocyte (AML12) and CRC (HCT116) co-culture recapitulates these effects in vitro.
- Targeting LMs by disrupting cell-to-cell communication may present a viable strategy to reduce cachexia.

Acknowledgments
This study was supported by grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (P01AR067077, R01AR060051); the Snowberger Research Trust; The V Foundation for Cancer Research (VGT172011); the American Cancer Society (Research Scholar Grant SG1015-00-05GSG) and by institutional funding through a T32 Institutional Training Grant (T32GM007032) and a Postdoctoral Fellowship (F32AR070325).

Figure 6: AML12 and HCT116 crosstalk is sufficient to activate cachexia signaling