IGFBP1 mediates musculoskeletal defects in colorectal cancer

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Colorectal cancer (CRC) is frequently accompanied by cachexia, an uncured multi-systemic wasting syndrome that affects the majority of patients, especially when the disease recurs with liver metastases (LMs). Muscle and bone loss are amongst the most detrimental symptoms of cachexia and directly cause increased morbidity and mortality. We and others have shown that CRC also promotes metabolic and genomic perturbations of the liver, and further, that formation of LMs exacerbates muscle and bone wasting. These observations, along with evidence that liver-derived factors (i.e., hepatokines) may poorly influence musculoskeletal health, suggest an endocrine role of the liver in mediating cancer-induced cachexia. In the present study, we identified the hepatokine insulin-like growth factor binding protein 1 (IGFBP1) as a novel mediator of musculoskeletal wasting in CRC. Plasma from CRC patients and preclinical mouse models of CRC (C26, MC38, HCT116, $Apc^{Min/+}$) were assessed for circulating IGFBP1 levels. AML12 hepatocytes were cultured with CRC cells (C26, MC38, HCT116) to assess tumor induced hepatic IGFBP1 production, while C2C12 myotubes and osteoclast precursor cells were cultured to examine the *in vitro* effects of IGFBP1 on myotube atrophy and osteoclastogenesis. 8-week-old male wild-type (WT) C57BL/6J and IGFBP1-KO mice were intrasplenically injected with MC38 tumor cells (mMC38) to mimic hepatic dissemination of cancer cells, while sham-operated animals received saline. Animals were assessed for muscle force 24-hours prior to euthanasia, and skeletal muscles and bone were collected for molecular and morphological analyses. CRC patients and CRC tumor-bearing mice demonstrated markedly elevated circulating plasma IGFBP1, also supported by increased liver IGFBP1 mRNA expression in C26, MC38 and HCT116 hosts. Follow-up *in vitro* studies demonstrated that co-culturing CRC cells (lacking IGFBP1 expression) with AML12 hepatocytes promotes IGFBP1 production, thereby suggesting that IGFBP1 is purely host-derived. Further, treatment with recombinant IGFBP1 was sufficient to stimulate osteoclastogenesis, while also promoting atrophy of C2C12 myotubes. Conversely, use of anti-IGFBP1 neutralizing antibodies prevented osteoclastogenesis and preserved C2C12 myotube size when exposed to plasma from mice bearing CRCs. Notably, WT mMC38 bearers displayed reductions in muscle mass and strength, as well as in trabecular bone volume fraction (BV/TV) and trabecular number (Tb.N). Conversely, IGFBP1-KO tumor hosts exhibited preserved skeletal muscle and bone mass. Altogether, our data implicate IGFBP1, an exquisitely liver-derived factor, as a novel mediator of musculoskeletal deficits in CRC cachexia, and supports novel strategies to counteract host-derived factors in the treatment of cancer-associated multi-organ complications.