

Nonmetastatic Colon Cancer Model C26 Upregulates Glycolysis in Osteocytes *in Vitro* and Bone *in Vivo*

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Background: Developing effective treatments for musculoskeletal complications in cancer patients requires understanding metabolic effects of cancer on bone, and particularly osteocytes, the most abundant bone cell and key regulator of bone remodeling. However, little is known regarding how cancer impacts normal osteocyte energy metabolic pathways, such as glycolysis. Given that changes in metabolism are important regulators of cellular function, it is essential to determine how osteocyte metabolism is disrupted by cancer and how this may impact skeletal and whole-body health.

Methods: Mice inoculated with saline (N=5) or C26 cells (N=6) were sacrificed after 2 weeks. Bones were harvested for metabolic profiling by GC-MS, gene expression by RT-PCR and bone morphology by μ CT. Differentiated IDG-SW3 osteocyte-like cells were cocultured with C26 cells for 12-24hrs and metabolites and gene expression analyzed by GC-MS and RT-PCR.

Results: Trabecular bone mass was significantly decreased in the C26 mice. GC-MS analysis revealed decreased glucose in C26 mice tibiae, but no change in lactate. The bone resorption promoting gene *Rankl* was upregulated, whereas the inhibitor *Opg* was unchanged. Bone mineralization regulators *Mepe* and *Phex* were decreased. *In vitro* metabolic studies revealed increased glucose and lactate in IDG-SW3 cell lysate; culture media glucose levels were decreased whereas lactate was increased in the co-cultures with C26 cells. RT-PCR demonstrated increases in the glycolysis promoter *Hif1 α* in addition to glycolysis pathway genes including *Glut1*, *Hk2*, *Slc16a3* and *Pdk1*. *Rankl* was also increased in the IDG-SW3 cells co-cultured with the C26 cells whereas *Opg*, *Phex*, and *Mepe* were downregulated.

Conclusion: Glycolysis is upregulated in mouse bone and *in vitro* IDG-SW3 cells exposed to cancer. Our study provides novel understanding for how cancer affects bone metabolism. Integrating these results with whole body metabolism will aid in the development of novel therapeutic strategies to target musculoskeletal and systemic complications of cancer.