Alterations in hepatic carbohydrate metabolism impair the adaptive response to energy depletion in cancer.

**Objective**
Treatment and outcome for cancer patients relies upon patient resilience and physiologic reserve, yet little is understood about the biology underlying this phenomenon. Cancer provides a metabolic challenge to the host, both by direct competition for resources, as well as via systemic metabolic reprogramming, even in localized, early stage disease. We investigated how localized cancer affects the biochemical and behavioral responses to metabolic stress.

**Hypothesis**
Tumor-induced hepatic metabolic reprogramming impairs the adaptive physiologic response to energy depletion.

**Methods**
- Heterotopic syngeneic murine E6/E7 hRas (mEER) epithelial tumor in male C57BL/6 mice
- Three metabolic challenges were used in 2x2 factorial design:
  1. ± exercise, via voluntary wheel running
  2. ± fasting, via 16 hr food deprivation
  3. exercise ± fasting
- To test role of IL-6, rat anti-mouse IL-6 neutralizing antibody (na) was injected i.p. 200mg q.o.d. x 3, then 200mg q.o.d. x 3 during final 10 d of tumor growth
- Measures:
  - Behavioral: food intake, wheel running, fasting-induced foraging activity
  - Anthropometrics, tumor volumes gastrocnemius weights
  - Serum: glucose, β-hydroxybutyrate, lactate, IL-6, corticosterone
  - Liver: metabolic gene expression, glycogen, lactate
  - Muscle (gastroc): gene expression, lactate, glycogen

**Results**
- Tumor had no influence on body weight or food intake
- Exercise had no influence on tumor growth
- Tumors associated with
  - ↑ expression of glycolytic genes
  - ↓ expression of gluconeogenic genes
  - ↑ expression of Ppara, Pparg, Hif1a
- Under metabolic stress (exercise/fasting), tumors
  - ↓ blood glucose
  - ↓ Serum ketones
  - ↑ Muscle lactate; no Δ serum lactate
  - ↓ adaptive foraging behavior
- IL-6 blockade did not reverse any effects of tumor

**Model**

**Conclusions**
1. Tumor distinctly influences hepatic metabolic programming to reflect a state of energy surplus, even in the context of energy depletion.
2. Impaired adaptive responses to energy depletion could underlie cancer-related fatigue and susceptibility to undernutrition, and may provide important mechanistic insights into pre-cachexia.