Objective
Only 10-15% of patients with pancreatic ductal adenocarcinoma (PDAC) have an identifiable heritable risk, and no practical screening strategies to detect sporadic cases have been identified. Decreased daily activity, a hallmark of declining functional status, is among the first signs of PDAC, and therefore may be an early marker of PDAC. This proof-of-principle study was designed to test whether decreases in activity reliably precede the clinical detection of PDAC in an autochthonous model of pancreatic cancer characterized by variable latency to tumorogenesis.

Hypothesis
Decreases in volitional activity can be used to predict development of PDAC.

Methods
- High risk PDAC modeled using K-ras<sup>G12D</sup>/, p53<sup>R172H</sup>/; PdxCre (KPC) mice (n=8) and K-ras<sup>G12D</sup>/, p53<sup>R172H</sup>/ (KP) littermate controls (n=8)
- Weekly abdominal palpation followed by ultrasound prn to confirm and measure tumors
- Activity: continuous voluntary wheel running normalized to baseline average of running during wk 2 & 3
- Behavioral tests (at time of tumor Dx):
  - anxiety (zero maze)
  - depression-like (social interaction, forced swim test)
- Euthanized at earlier of 2 wks post-Dx or pre-moribund status w/ age-matched control
- Tissue measures:
  - inflammatory and metabolic gene expression in hypothalamus and liver using qPCR
  - serum IL-6
- Association between tumor detection and wheel running was assessed using logistic regression (continuous) and Fisher’s exact test (dichotomized as ≤75% baseline).

Results
- Median latency to tumor detection was 25 weeks (range 13-31 weeks). No metastatic disease was observed at time of termination.
- Wheel running demonstrated significant decrement ≥ 8 d prior to tumor dx (unit OR=1.10, P<.01)
- Decrease in wheel running ≤ 75% of baseline predicted tumor development within the following 14 days (RR 12.18, 95% CI 2.53 to 58.73, P=.003)
- No evidence of depression-like behavior or anhedonia was observed in tumor-bearing KPC mice. KPC mice spent less time in the open arms of the zero-maze, consistent with elevated anxiety-like behavior.
- Tumor growth was associated with significant increases in serum IL-6, hepatic cytokine expression, and hypothalamic IL-1β expression.
- Body weight and food intake did not differ between KPC and CTL mice at baseline, Dx, or termination.

Conclusions
1. Decreased activity reliably precedes tumor detection by palpation or imaging in the KPC mouse
2. Inflammatory cytokines may play a role in mediating the decrease in activity seen in early stage PDAC.
3. These data provide a compelling preclinical proof of principle for a new platform to improve the sensitivity of PDAC early detection.
Figure 2. Body mass (A) and daily food intake (B) were not significantly different in KPC mice compared to KP controls at baseline, time of tumor diagnosis, or termination.
Daily physical activity monitoring predicts early development of pancreatic adenocarcinoma in mice.

Aaron J. Grossberg1, Elisabeth G. Vichaya2, Jessica M. Molkentine3, Tara M. Fujimoto3, Philip S. Gross, Cullen Taniguchi3, & Robert Dantzer2
1Department of Radiation Medicine & Cancer Early Detection Advanced Research Center, Knight Cancer Institute, Oregon Health & Science University, Portland, OR
2Department of Symptom Research, The University of Texas MD Anderson Cancer Center, Houston, TX
3Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

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Hypothesis
Decreases in volitional activity can be used to predict development of PDAC

Methods
- High risk PDAC modeled using K-rasLSL.G12D/+, p53B172H/+, PdxCre (KPC) mice (n=8) and K-rasLSL.G12D/+, p53B172H/+ littermate controls (n=8)
- Weekly abdominal palpation followed by ultrasound prn to confirm and measure tumors
- Activity: continuous voluntary wheel running
  - normalized to baseline average of running during wk 2 & 3
- Behavioral tests (at time of tumor Dx): anxiety (zero maze)
  - depression-like (social interaction, forced swim test)
  - anhedonia (sucrose preference)
- Euthanized at earlier of 2 wks post-Dx or pre-moribund status w/ age-matched control
- Tissue measures:
  - inflammatory and metabolic gene expression in hypothalamus and liver using qPCR
  - serum IL-6 and glucose
- Association between tumor detection and wheel running was assessed using logistic regression (continuous) and Fisher’s exact test (dichotomized as ≤75% baseline).

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

Conclusions
1. Tumor distantly 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 undernourishment, and may provide important mechanistic insights into pre-cachexia.