Ketohexokinase is important for lung tumor growth

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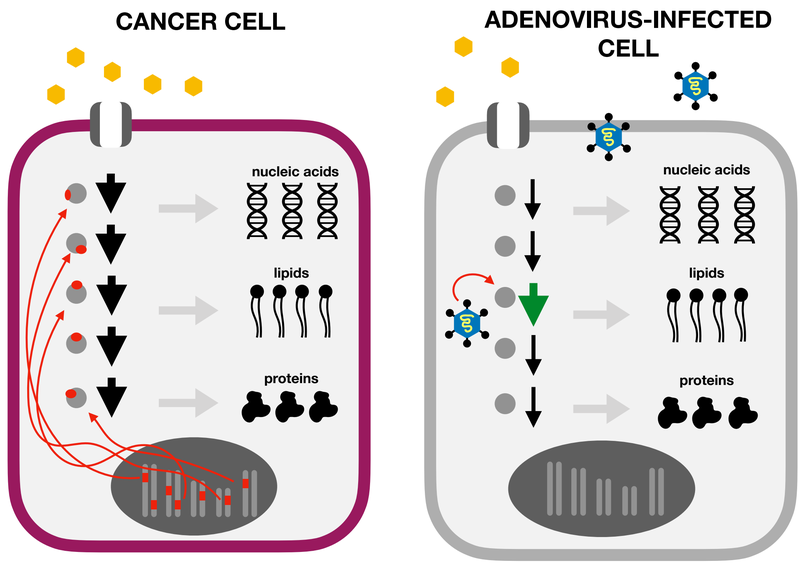
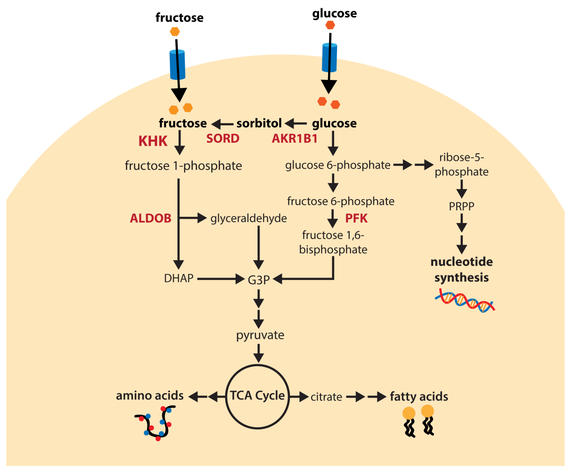
SUMMARY

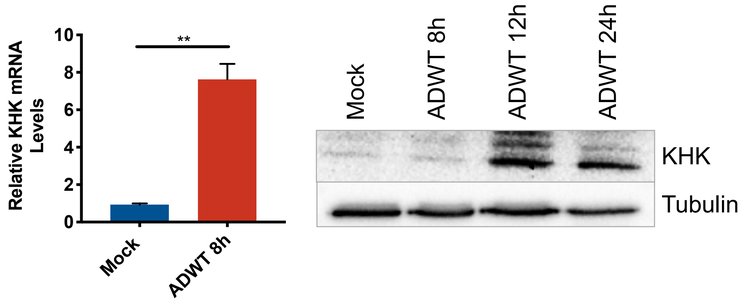
Cancer cells and viruses reprogram cell metabolism towards increased nutrient uptake and anabolism. Unlike cancer cells, viruses undergo intense selection for efficiency, only upregulating metabolic nodes critical for their rapid replication. Viruses are therefore powerful tools to identify essential metabolic pathways in cancer cells. One of the most highly upregulated metabolic genes during adenovirus infection is ketohexokinase (KHK), which phosphorylates fructose to fructose 1-phosphate and is elevated across many patient cancers, including lung cancer. Here we show that KHK is important for lung cancer growth *in vivo*. Lung tumor xenograft growth is impaired by KHK knockout and rescued by expression of splice variant KHK-A, but not KHK-C. We further provide evidence that the polyol pathway, which converts intracellular glucose to fructose, supports cancer growth: we show that polyol pathway activity is increased in lung tumor xenografts relative to healthy lung and that KHK promotes nucleotide biosynthesis and cancer cell proliferation in the absence of exogenous fructose *in vitro*. Notably, essential fructosuria, a genetic condition in which individuals lack KHK activity, is asymptomatic. We hypothesize that targeting KHK, which is important for tumor growth but dispensable in healthy tissue, may effectively blunt tumor growth with limited systemic toxicities.

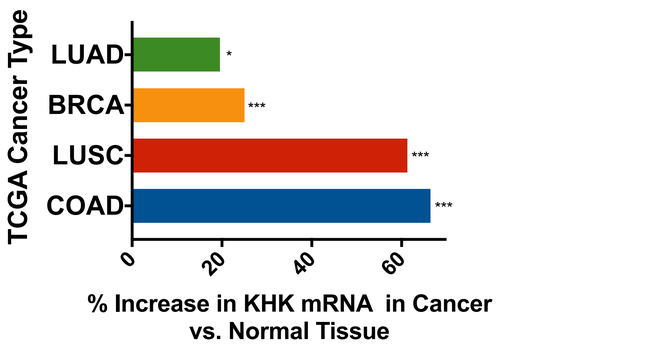
Viruses as a model to study cancer metabolism



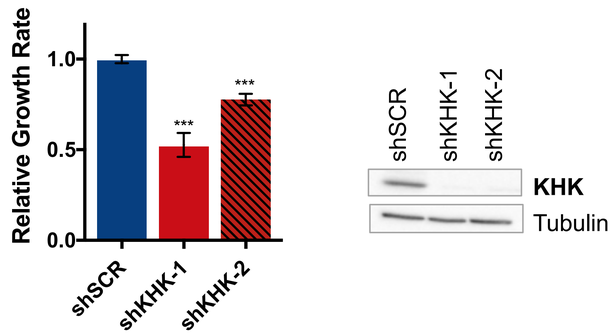
Ketohexokinase is involved in fructose metabolism and is upregulated during adenovirus infection and in different cancers

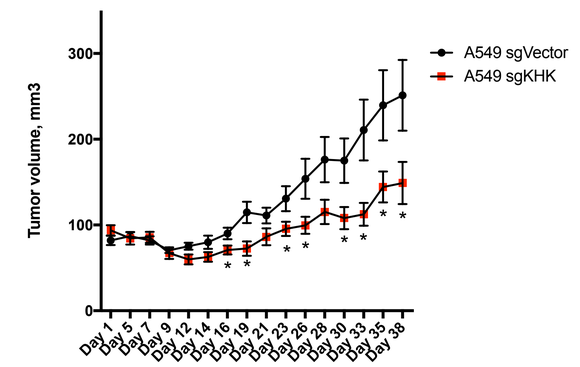




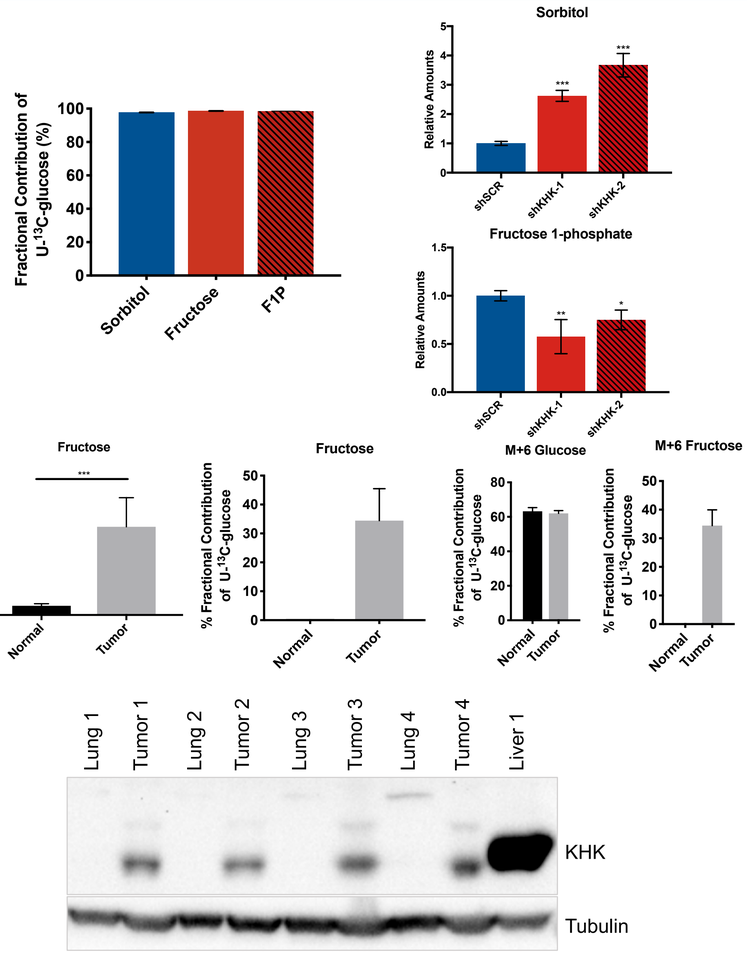


Reducing KHK levels decreases cancer cell proliferation *in vitro* and tumor growth *in vivo*

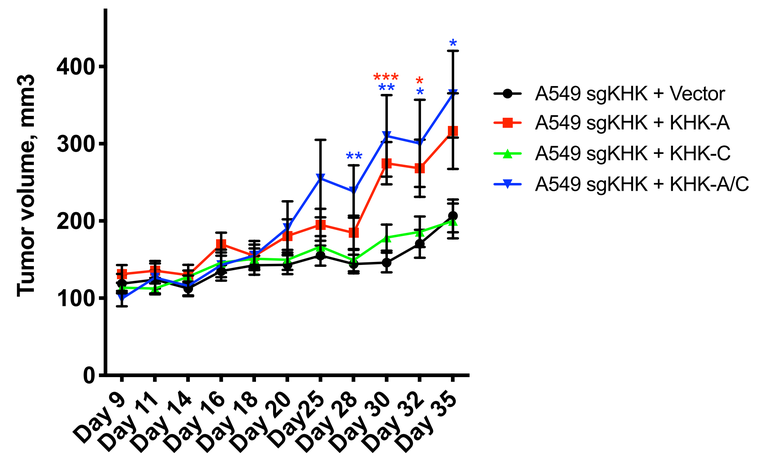


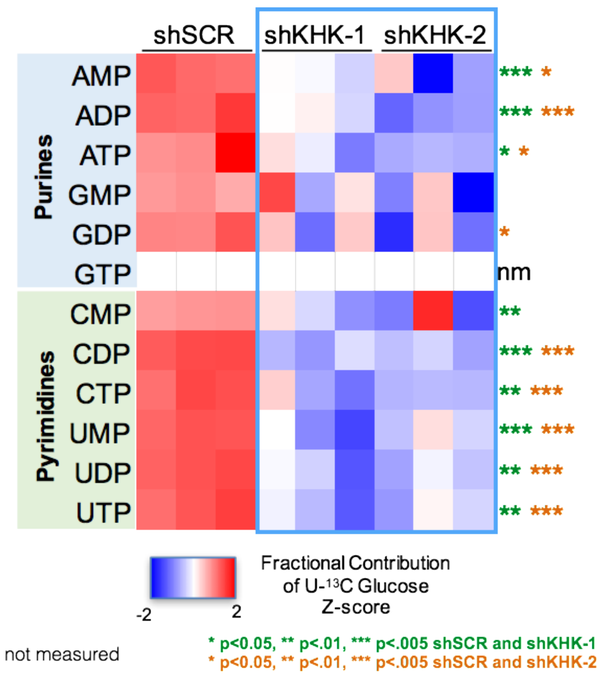


The polyol pathway is active in cultured lung cancer cells and lung xenografts *in vivo*



Ketohexokinase knockdown perturbs glucose incorporation into nucleotides





nm: not measured

* p<0.05, ** p<.01, *** p<.005 shSCR and shKHK-1
* p<0.05, ** p<.01, *** p<.005 shSCR and shKHK-2

Conclusions & Future Directions

- What is the mechanism by which KHK knockdown decreases proliferation of cancer cells?
- Are glucose and fructose utilized differently by cancer cells?
- Why do KHK-A and KHK-C have differential effects on tumor growth?
- **Implications:** Pharmacological KHK inhibition may inhibit lung tumor growth with minimal impact on healthy tissues

Acknowledgments

S.K.T. was supported by the UCLA Dissertation Year Fellowship, UCLA Tumor Immunology Training Grant, UCLA Virology and Gene Therapy Training Grant, and the UCLA Medical Scientist Training Program. HRC is awarded RSG-16-111-01-MPC from the American Cancer Society.