Targeting Pyruvate Kinase to Induce Metabolic Dependencies in Prostate Cancer

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Background

Prostate cancer growth is fuelled by a hypermetabolic state that depends on acquiring extracellular nutrients for proliferation, but no therapies target these altered metabolic requirements. Prostate cancer expresses exclusively the M2 isoform of pyruvate kinase (PK), the enzyme that catalyses the final step of glycolysis, and is unique among cancers in retaining PKM2 expression throughout disease progression. Prior data has shown that PKM2 must be in a low activity state for prostate cancer cells to proliferate. We therefore propose that pharmacologic activation of pyruvate kinase could be an effective treatment for prostate cancer.

Methods

Human prostate cancer cell lines were cultured in Minimal Essential Media with nutrient supplements and pyruvate kinase activators. Proliferation rate was determined by cell counts. Metabolite levels were measured by GC/MS or LC/MS. Tumor volume was determined by caliper measurements. Pathologic tumor response was determined by histologic evaluation of FFPE tumor tissue. Animal studies were approved by the IACUC at MIT. PKM2 expression in human prostate tumors was determined by IHC analysis of FFPE tissue obtained from the BIDMC Rapid Autopsy Program, approved by the BIDMC IRB.

Results

We show that PKM2 is the predominant PK isoform expressed in primary prostate cancer and metastases. In human prostate cancer cells lines we find that PK activator treatment reduces proliferation; however, the antiproliferative effects depend on the nutrient environment, with high levels of exogenous serine being able to completely rescue proliferation. When exogenous serine is low, PK activation rapidly depletes intracellular serine levels due to due to altered glycolytic flux resulting in activation of the GCN2/ATF4 pathway and induction of serine transporters. Serine is required for de novo nucleotide synthesis and deoxynucleotide levels are decreased upon PK activation when exogenous serine is limited. In vivo, we find that PK activators decrease proliferation of autochthonous Pten-null murine prostate tumors, slow growth of flank xenograft models in combination with low serine diet, and increase pathologic complete response rates when combined with radiotherapy.

Conclusions

PKM2 activation blocks endogenous serine production, which under low exogenous serine conditions, leads to reduced deoxynucleotide levels, DNA replication stress and senescence, inhibiting tumor growth. We hypothesize that replication stress and resulting DNA damage induced by PK activator therapy will increase the efficacy of radiation and/or antiandrogens, and that concomitantly inhibiting serine import to also limit nucleotide synthesis may further improve efficacy.

Funding Acknowledgements

DF/HCC SPORE in Prostate Cancer Training Award P50 CA090381-15, Harvard University KL2/Catalyst Medical Research Investigator Training Award TR002542, Joint Center for Radiation Therapy Foundation, Ludwig Center at MIT, MIT Center for Precision Cancer Medicine, Stand up to Cancer, Emerald Foundation, Howard Hughes Medical Institute faculty scholar award, and NIH grants P30CA1405141,

R35CA242379, P50CA090381, National Center for Advancing Translational Research and the Center for Cancer Research, NCI.

Conflicts of interest

MVH reports personal fees from Agios Pharmaceuticals, iTeos Therapeutics, Droia Ventures, Sage Therapeutics, Faeth Therapeutics, and Auron Therapeutics, and also has a patent for use of pyruvate kinase activators to treat cancer issued and licensed to Agios Pharmaceutics.