Targeting Pyruvate Kinase to Induce Metabolic Dependencies in Prostate Cancer

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Background

Prostate cancer growth is fueled by a hypermetabolic state that depends on acquiring extracellular nutrients and channelling them appropriately to fulfill the metabolic requirements of proliferating cells. PKM2 is the predominant PK isoform expressed in primary prostate cancer and metastases. We have previously shown that high activity of pyruvate kinase slows tumor progression in the Pten-null murine model of prostate cancer. We propose that pharmacologic activation of pyruvate kinase could be an effective treatment for prostate cancer and aim to identify the context in which PK activators will provide the most benefit for patients with 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. Gene expression analysis was performed by whole transcriptome RNA sequencing.

Results

Serine is rapidly depleted upon PK activator treatment and remains low as prostate cancer cells undergo proliferation arrest. After 24 hours of treatment cells begin to accumulate at G2/M indicating a block in mitosis/cytokinesis. Gene expression profiling was conducted at early and late time points after PK activator treatment of prostate cancer cell lines to identify the cause of proliferation arrest. This demonstrated early activation of the integrated stress response and induction of membrane amino acid transporters and enzymes of the serine biosynthesis pathway. Subsequently, gene expression programs involved in folate metabolism, unfolded protein response, and protein translation are activated, and there is a concurrent reduction in expression of cell cycle, DNA replication/repair, and nucleotide metabolism genes. To examine the metabolic context in which PK activator therapy would be most effective we systematically varied the concentration of nutrients in the media and found that addition of lactate potentiated the antiproliferative effect of PK activators, while both pyruvate and serine independently rescued proliferation. High lactate levels caused a reduction in NAD/NADH ratio, limiting glycolytic flux and further exacerbating the effect of PKM2 activation on serine synthesis.

Conclusions

PKM2 activation induces proliferation arrest by reducing the intracellular concentration of serine, which effects multiple anabolic processes required for proliferation, including folate-mediated methylation, protein synthesis, and membrane lipid synthesis. These effects are most pronounced in the context of a reducing environment such as hypoxic tumors where glycolytic flux is limited by NAD availability. This suggests that PK activators will be most effective in tumors with high lactate levels. Furthermore, PK activators could improve efficacy of radiotherapy by inducing metabolic stress in hypoxic cells which are more radioresistant than normoxic tissues.

Funding Acknowledgements

Supported by Prostate Cancer Foundation Young Investigator Award, Joint Center for Radiation Therapy Foundation, Dana-Farber/Harvard Cancer Center SPORE in Prostate Cancer (P50CA272390), Bridge Project MIT/DF/HCC, and Harvard Catalyst NCATS/NIH Award (KL2 TR002542).

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.