

Title

PKM2 Activation Sensitizes Radioresistant Tumors to Therapy by Disrupting Serine Synthesis Under Reductive Stress

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Background

Prostate cancer growth is fueled by a hypermetabolic state that depends on acquiring extracellular nutrients and channeling them appropriately to fulfill the metabolic requirements of proliferating cells. PKM2 is the predominant pyruvate kinase isoform expressed in primary prostate cancer and metastases. We have previously shown that high pyruvate kinase activity slows tumor progression in the Pten-null murine model of prostate cancer, suggesting that pharmacologic PK activation could be an effective treatment strategy. However, the efficacy of PK activators may be context-dependent. Interestingly, preliminary studies revealed that prostate cancer cell lines with diverse genetic backgrounds (varying AR status, p53 mutations, and PTEN status) showed remarkably similar sensitivity to PK activators when cultured in nutrient-restricted conditions. This finding suggests that metabolic context—specifically nutrient availability—rather than genetic profile determines sensitivity to PK activation. We hypothesized that PK activators would be particularly effective in nutrient-limited environments such as hypoxic tumors, and we aimed to define the specific metabolic conditions that create vulnerability to PK activation and enable radiosensitization.

Methods

Prostate cancer cell lines were cultured in minimal essential media and treated with pyruvate kinase activators under varying nutrient conditions. Proliferation was assessed by cell counts. Gene expression was analysed by RNA-seq and metabolites by LC/MS. In vitro radiosensitivity was determined by clonogenic survival assay and cell counts. For in vivo studies, PC3 and R22Rv1 xenografts were established in nude mice and treated with TEPP-46 (oral gavage) combined with focal radiation therapy. All animal work was approved by the MIT IACUC.

Results

We demonstrated that high lactate levels lower the NAD⁺/NADH ratio, creating reductive stress that restricts glycolytic flux at the GAPDH step. PKM2 activation under these conditions decouples upper and lower glycolysis, depleting glycolytic intermediates downstream of GAPDH and significantly reducing serine synthesis. When serine availability is limited, PKM2 activation induces sufficient serine deprivation to trigger the integrated stress response (ISR), resulting in cell cycle arrest and suppressed expression of nucleotide biosynthesis and DNA damage response genes. Importantly, PKM2 activation enhanced radiosensitivity both in vitro, with reduced clonogenic survival compared to radiation alone, and in vivo, with improved pathologic complete responses in xenografts treated with the combination ablative radiotherapy and PK activator.

Conclusions

Low pyruvate kinase activity provides cancer cells with a metabolic advantage in reductive stress environments where NAD⁺ availability constrains glycolytic flux. PKM2 activation creates a metabolic vulnerability by disrupting serine synthesis and triggering growth-inhibitory stress responses thereby sensitizing cells to radiation. These findings provide strong rationale for using PK activators to sensitize hypoxic, radioresistant tumors to radiation therapy.

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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 Pharmaceuticals.