Targeting hexokinase 2 in castration-resistant prostate cancer

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Aerobic glycolysis, known as the Warburg effect, is one of the hallmarks of cancer cells. We recently reported that the hexokinase 2 (HK2)-mediated Warburg effect is required for castration-resistant prostate cancer that is driven by Pten/p53 deficiency, suggesting that HK2 might be a therapeutic target for prostate cancer patients carrying PTEN and p53 mutations.

Accelerated glucose metabolism in cancer cells under aerobic conditions, a phenomenon known as the Warburg effect, leads to high uptake of the labeled glucose analog fluorodeoxyglucose (FDG), which can be clinically useful to detect tumors and monitor therapeutic responses of cancer patients by positron emission tomography (PET).１Thus, identification of the enzyme(s) that catalyze the elevated glucose metabolism in cancer cells could be exploited not only to distinguish cancer cells from normal cells, but also to preferentially target cancer cells while sparing healthy cells.

Hexokinases (HKs) catalyze the essentially irreversible first step of glucose metabolism in cells by phosphorylating glucose to glucose-6-phosphate (G-6-P). There are 4 HK isoforms encoded by separate genes, HK1, HK2, HK3, and HK4 (also known as glucokinase). HK1 is ubiquitously expressed in almost all mammalian tissues and HK2 is normally expressed in insulin-sensitive tissues such as adipose, skeletal, and cardiac muscles. HK3 is usually expressed at low levels and HK4 expression is restricted to the pancreas and liver.²

Although elevated HK2 expression has been observed in certain types of cancer cell and in tumor tissues from mouse models and/or human patients,³,⁴ the molecular mechanisms underlying HK2 upregulation remain incompletely understood. Accumulating evidence suggests that co-deletion of tumor suppressor genes, such as phosphatase and tensin homolog (PTEN) and tumor suppressor protein p53 (TP53, best known as p53), plays a crucial role in the development of castration-resistant prostate cancer (CRPC) in vivo.⁵ Through integrated analyses of mouse embryonic fibroblasts (MEFs) deficient in Pten and p53, prostate cancer cell lines, xenografts, and genetically engineered mouse models (GEMMs), as well as clinical prostate cancer samples, we have found that Pten/p53 deficiency selectively enhances expression of HK2, but not HK1, through post-transcriptional and translational regulation.⁶

Regarding the underlying mechanism, we have demonstrated that activation of AKT–mTORC1 signaling as a result of Pten deletion increases HK2 expression primarily at the translational level through phosphorylation of eIF4E-binding protein 1 (4E-BP1), whereas loss of p53 decreases the biogenesis of miR143, which in turn causes degradation of HK2 mRNA. As a result, the combined deficiency of PTEN and p53 in prostate cancer cells synergistically leads to robustly elevated HK2 expression (Fig. 1; ref. 6).

Notably, HK2 is almost exclusively expressed in human prostate cancer tissue compared with normal prostate tissue, and its expression is particularly elevated in human prostate cancer harboring PTEN/p53 mutations.⁶ In line with our findings that HK2 expression level positively correlates with the Gleason score, the sensitivity and positive predictive value of FDG-PET based on HK2-mediated phosphorylation of FDG for detecting
patients with advanced prostate cancers was as high as 87%. These results imply that HK2 expression distinguishes cancer cells from normal cells and could serve as a potential diagnostic and prognostic biomarker for advanced human prostate cancer, especially for patients harboring defects or mutations in PTEN and p53. Our genetic studies demonstrated that the HK2-mediated Warburg effect is required for the growth of Pten/p53-deficient prostate cancer cells in vitro and in xenograft models carrying mouse or human PTEN/p53-deficient prostate cancer cell lines in vivo. These findings are consistent with a previous study of glioblastoma showing that HK2 depletion by shRNA inhibits tumor growth in a xenograft model. More recently, a study using Hk2 conditional knockout mice found that HK2 is required for tumor initiation and maintenance in mouse models of Kras-driven lung cancer and ErbB2-driven breast cancer. Our study extends the biological significance of HK2 to prostate cancers carrying Pten/p53 mutations, which drive the genesis of currently incurable castration-resistant prostate cancer (CRPC).

Systemic deletion of Hk2 in genetic mouse models inhibits tumor progression but does not impair normal glucose homeostasis or elicit any notable phenotypes in vivo, indicating that HK2 could be a selective therapeutic target for cancer without any adverse physiological consequences. Given that our genetic findings support the crucial role of increased HK2 expression in driving the Warburg effect and prostate tumor progression in the presence of physiological levels of HK1, selectively targeting HK2 in these prostate cancer cells could be exploited as a promising personalized therapeutic strategy for patients with CRPC carrying Pten/p53 mutations (Fig. 1). However, it would be very challenging to design an isoform-specific pharmacological inhibitor because HK2 has overlapping enzymatic activities with the ubiquitously expressed HK1, which is required for glucose metabolism of normal cells. Considering that only the C-terminal half of HK1 retains catalytic activity, whereas both N- and C-terminal halves of HK2 are catalytically active with the N-terminal half showing higher enzyme activity, it is possible to use computational bioinformatics to identify small molecular compounds that might specifically block HK2 activity by targeting the N-terminal half of HK2 in cancer cells. In addition, the enzymatic activities of HK1 and HK2 are inhibited to the same extent by their own G-6-P, yet inorganic phosphate prevents the inhibition of HK1 by G-6-P while enhancing the inhibition of HK2. Thus, a G-6-P mimetic may preferentially inhibit HK2 activity in cancer cells.

Several critical questions arise from our findings. Does genetic deficiency of HK2 (conditional deletion of HK2 in prostate epithelial cells) effectively inhibit Pten/p53 deficiency-driven CRPC in genetically engineered “triple-deficient” mouse models? Can currently available HK2 enzymatic inhibitors such as 2-deoxyglucose (2-DG) and 3-bromopyruvate (3-BrpA) inhibit Pten/p53 deficiency-driven CRPC in vivo? Does AKT–mTORC1–4EBP1-mediated translation signaling contribute to HK2 overexpression in prostate cancer cells carrying alterations in genes other than Pten and p53? Addressing these questions will provide deeper insights into the regulation and crucial role of HK2 in prostate tumorigenesis and potentially open up new avenues to treat currently incurable CRPC.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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