Understanding the Metabolic Functions of Hexokinases with Applications in Cancer Treatment

by

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August 14, 2017

Abstract

Therapeutic selectivity is a very important consideration when designing cancer treatment. Therefore, targeting cancer-specific isoforms of key metabolic enzymes is a very promising strategy. Elevated glucose consumption and lactate secretion under aerobic conditions is a hallmark of many cancer cells. One of the major contributors to this highly glycolytic phenotype is hexokinase 2 isoform (HK2), which is significantly overexpressed in many tumors but not in normal adult tissue. Several small molecule inhibitors targeting HK have exhibited promising anticancer activity. However, these small molecule inhibitors cannot differentiate between HK isoforms, leading to severe side effects. Elucidating the differences between HK isoforms can guide us in designing isoform-specific inhibitors. Moreover, the complexity and robustness of cellular metabolism and the intricate mechanism underlying cancer development and progression make it very difficult to effectively treat cancer by targeting a single metabolic enzyme. The improved understanding of the metabolic functions of HK to cancer can guide us in identifying synergistic biochemical reactions and designing effective combination therapy.

We first studied the differential subcellular localizations of HK1 and HK2 via selective permeabilization and cell fractionation. We then characterized the metabolic functions of HK to cell growth and proliferation using stable isotope labeling and metabolic flux analysis. Key findings were verified in a hepatocellular carcinoma cell line using low glucose feeding or HK inhibitor. These experiments identified differential HK enzymatic activity in different cell compartments, and discovered key metabolic pathways co-regulated with glycolysis via cellular redox status. These findings may provide guidance in designing cancer-specific inhibitors or combination therapy targeting multiple synergistic metabolic pathways.

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