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How To Cure Cancer With A Pill? A Structure-Based Drug Design Study On Human Hexokinase 2 Targeting Different Tumor Types

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Abstract

Cancer is a major challenge worldwide with nearly 8 million people die from cancer every year, and it is one of the major causes of death in GCC Countries. Tumor and cancer cells in general utilize glucose at elevated levels to support their growth and proliferation, historically known as the Warburg effect, a phenomena used clinically in the Positron Emission Tomography (PET) scan to detect glycolytic tumors. Targeting glucose metabolism in cancer cells to limit tumor growth will enhance the survival rate and improve quality of life for cancer patients. Hexokinase, the first enzyme in the glycolytic pathway, catalyzes the phosphorylation of glucose, and is one of the three major steps in the regulation of the glycolytic pathway. However, humans have four isozymes of hexokinase in which Hexokinase 2 (HK2) is the most active and specifically expressed in cancer cells but not in normal tissues. In addition, gene expression profiling experiments of different types of cancer showed high expression levels of HK2, and various biological studies highlighted the importance of HK2 in tumor metastasis making it an ideal target for the development of new class of cancer therapeutics. Since HK2 is not found in normal cells, therapeutics that inhibit HK2 activity will target cancer cells only and will have minimum or no side effects. The new class of therapeutic will be safe and can be delivered orally to replace the current traditional chemotherapy that has to be administered on an in-patient basis, which dramatically increases the cost of cancer therapy.

We solved the crystal structure of human HK2 in complex with glucose and glucose-6-phosphate (PDB code: 2NZT), where it is a homodimer with catalytically active N- and C-terminal domains linked by a seven-turn helix. A hydrophobic α-helix at the beginning of the protein is known to interact with a voltage-dependent anion channel (VDAC) on the outer mitochondrial membrane (OMM) to facilitate coupling HK2 to ATP used in phosphorylation of glucose, thereby "kicking off" glucose metabolism. In addition, the localization of HK2 to OMM prevents apoptosis through repression of the formation of mitochondrial permeability transition pores. Through biochemical and biophysical characterization of HK2, we found that the N-terminal domain not only catalyze glucose phosphorylation but also regulate the stability and activity of the enzyme. In addition, deletion of the N-terminal helix altered the stability and catalytic activity of the full-length enzyme and N-terminal domain when expressed separately. Understanding the kinetic and regulation mechanism of human HK2 will accelerate the design and development of inhibitors to be used as cancer therapeutics. Our initial screen of a small drug library yielded an inhibitor that is a natural product that is known for its anticancer activity. Currently, we are implementing a structure-based drug design to further develop the target using 3D structural simulations of HK2. The new class of cancer therapeutics will increase the quality and lifespan of cancer patients and will cut the cost dramatically of the current expensive cancer chemotherapy.