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Characterization of the Catalytic and Structural Roles of the Human Hexokinase 2 in Cancer Progression

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Abstract : In this study, we aim to biochemically and structurally characterize the interactions of human HK2 with the mitochondria in addition to the role of its N-terminal domain in catalysis and stability of the full-length enzyme. Here, 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 α-helix. Different from the inactive N-terminal domains of isozymes 1 and 3, the N- domain of HK2 not only capable to catalyze a reaction but it is responsible for the thermodynamic stabilizes of the full-length enzyme. Deletion of first α-helix of the N-domain that binds to the mitochondria altered the stability and catalytic activity of the full-length HK2. In addition, we found the linker helix between the N- and C-terminal domains to play an important role in controlling the catalytic activity of the N-terminal domain. HK2 is a major step in the regulation of glucose metabolism in cancer making it an ideal target for the development of new anticancer therapeutics. Characterizing the structural and molecular mechanisms of human HK2 and its role in cancer metabolism will accelerate the design and development of new cancer therapeutics that are safe and cancer specific.

Keywords : cancer metabolism, enzymology, drug discovery, protein stability
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