

THE ROLE AND MECHANISMS OF HEXOKINASE-2-MEDIATED PROTECTION AGAINST CARDIAC CELL DEATH AND DISEASE

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ABSTRACT

Numerous cancer studies demonstrate that transformed cells exhibit both increased glucose metabolism and an increased propensity to survive in the face of stressful stimuli. These studies overwhelmingly correlate with overexpression of the rate-limiting glycolysis enzyme hexokinase-2 (HK2). However, the mechanisms linking increased glucose metabolism and survival are unknown. Additionally, there is limited evidence of increased glucose utilization being beneficial in normal cell cultures, as well as *in vivo*. Therefore, the current studies were designed to determine the mechanisms by which increased HK2 expression promotes cell survival, as well as investigate whether HK2 overexpression could attenuate a model of cardiac disease *in vivo*. Findings in **AIM1** demonstrate that HK2 binding to the voltage-dependent anion channel 3 (VDAC3) on the mitochondria is important for protection against reactive oxygen species (ROS)-induced cell death. In **AIM2**, we show that cardiac HK2 overexpression limits cardiomyocyte hypertrophy and cell death in response to chronic isoproterenol administration *in vivo*. Results from these studies demonstrate that HK2 limits ROS accumulation during cardiac hypertrophy, and that this attenuation of ROS is mediated via the pentose-phosphate pathway. Collectively, our data establish several mechanisms by which HK2 overexpression and increased glucose utilization protect against cardiac cell death and disease. Additionally, these findings raise the possibility that activation of HK2 may be a therapeutic target in cardiac pathologies.