Bioenergetics: Open Access
ISSN: 2167-7662
McCommis et al., Bioenergetics 2012, 1:2
DOI: 10.4172/2167-7662.1000e105
Editorial Open Access

The Balance of Glucose Metabolism and Cell Death: Uncovering Protective and Lethal Effects of Hexokinase-2

Kyle S. McCommis[1] and Christopher P. Baines[1,2,3*]

[1]*Department of Biomedical Sciences, University of Missouri, Columbia, MO, USA*
[2]*Department of Medical Pharmacology & Physiology, University of Missouri, Columbia, MO, USA*
[3]*Dalton Cardiovascular Research Center, University of Missouri, Columbia, MO, USA*

Ever since Warburg et al. [1] discoveries in the 1927s, it has been understood that energy metabolism and regulation of cell death are interdependent [2]. It is this correlation between enhanced glucose metabolism and resistance to cell death in transformed cells that has since been coined the "Warburg Effect". In the 1970s and 80s, Bustamante et al. [3,4] discovered that it was elevated expression and activity of Hexokinase 2 (HK2) that resulted in the high glycolytic activity of tumor cells. HK2-mediated protection against cell death has since then received a great deal of attention, but the mechanism(s) remain largely unknown.

These early studies also emphasized mitochondrial binding of hexokinase as important for elevated tumor glycolysis. Tumor mitochondria were found to have 3-4 times the amount of hexokinase activity compared to normal liver mitochondria [4]. Also, mitochondrial hexokinase activity was shown to be ~3 times that of cytosolic hexokinase activity [3,4]. In addition, mitochondrial hexokinase was shown to be much more resistant to glucose-6-phosphate (HK catalysis product) inhibition compared to unbound hexokinase [3]. These results explain how tumors with enhanced mitochondrial hexokinase levels exhibit increased and largely unregulated glycolysis. HK2 binds to the outer mitochondrial membrane (OMM) via voltage dependent anion channels (VDACs), particularly VDAC1 [5]. As VDACs are the primary route for exchange of ADP/ATP and most other metabolites through the OMM, it has been proposed that this OMM binding gives HK2 preferential access to mitochondrially-produced ATP [6].

The overall question in studies of HK2-mediated protection against cell death has been: "Is mitochondrial binding required, or Is increased glucose utilization somehow protective?" results have argued for both. Pastorino et al. [7] showed in HeLa cells that under baseline conditions, HK2 is mostly mitochondrial and Bax is mostly cytosolic. However, in cells treated with either clotrimazole, glucose-6-phosphate, or a peptide consisting of the HK2 mitochondrial binding sequence, HK2 is removed from the mitochondria into the cytosol, and Bax becomes associated with the mitochondria [7]. This Bax binding results in cytochrome c release into the cytosol and increased cell death [7]. However, in a recent elegant study Sun et al. [8] suggested a partial non-mitochondrial effect. Specifically, they produced HK constructs that were either full length (capable of both mitochondrial binding and glucosephosphorylation), truncated (no mitochondrial binding, but catalytically active), mutated (mitochondrial binding but not catalytically active), or both truncated and mutated (neither mitochondrial binding or catalytic activity). Interestingly, they found that full-length constructs almost fully protected 293 cells against H2O2-induced death, while either truncated or mutated HK2 offered only partial protection. The double truncated/mutated constructs offered no protection against death whatsoever. Thus, previous studies suggest that there may be multiple mechanisms to HK2-mediated protection against cell death, some of which do not directly involve the mitochondria.

New insight into the mechanisms of HK2-mediated protection has been provided by a recent study by Mergenthaler et al. published in The Proceedings of the National Academy of Sciences [9]. Here, overexpression of HK2 was shown to protect cultured neurons against combined Oxygen-Glucose Deprivation (OGD) as well as just Oxygen Deprivation (OD) alone. These protective actions of HK2 were no longer apparent when a catalytically inactive HK2 mutant, or a mutant HK2 that was incapable of mitochondrial binding, were overexpressed instead [9]. The investigators then went a few steps further in identifying Phosphoprotein Enriched in Astrocytes (PEA15) as a novel molecular interactor with HK2 in a yeast two-hybrid screen, which was further confirmed by co-immunoprecipitations, and whole-cell FLIM-FRET [9]. Over expression of PEA15 was shown to be protective against OGD, and overexpression of HK2 and PEA15 showed synergistic protection against OGD [9]. Importantly, in PEA15$^{-/-}$ neurons, overexpression of HK2 was no longer protective against OGD [9]. Likewise, knockdown of HK2 completely abolished the protection from overexpression of PEA15 [9].

Perhaps most intriguing was the finding by Mergenthaler et al. that HK2 under some circumstances could actually induce cell death, rather than prevent it. Historically, an increase in cell death was thought to be passive due to a "lack" of HK2, i.e., dislocation from mitochondria, inactivity, etc. Indeed, Mergenthaler et al. showed that the catalytically inactive and non-mitochondrial forms of HK2 increased neuronal death at baseline [9]. However, they demonstrated that when neurons were exposed to Glucose Deprivation (GD), normal HK2 overexpression actually exacerbated cell death; an effect not seen with the catalytically inactive mutant [9]. Thus, HK2 can actively kill cells under the right context. This also appears to be related to the HK2's capacity to bind PEA15, as GD was shown to disrupt the interaction between HK2 and PEA15, and HK2 was cytotoxic in the PEA15$^{-/-}$ fibroblasts [9]. Thus, PEA15 appears to be a key regulator of both HK2-mediated protection and cell death and vice-versa.

Together, these new findings of Mergenthaler et al. [9] provide a novel role for HK2 and PEA15 as sensors of metabolic state. Under hypoxia, increased glycolysis promotes survival. However, under a glycemia, increased glycolysis promotes apoptosis, perhaps to prevent nutrient depletion in the remaining tissue. The main limitation of these findings is the requirement of HK2-mitochondrial binding and that this HK2-PEA15 complex is mitochondrial. Their findings that a

***Corresponding author:** Christopher P. Baines, Dalton Cardiovascular Research Center, University of Missouri, 134 Research Park Dr, Columbia, MO 65211, USA, Tel: 573-884-8767; Fax: 573-884-4232; E-mail: bainesc@missouri.edu

Received May 05, 2012; **Accepted** May 05, 2012; **Published** May 08, 2012

Citation: McCommis KS, Baines CP (2012) The Balance of Glucose Metabolism and Cell Death: Uncovering Protective and Lethal Effects of Hexokinase-2. Bioenergetics 1:e105. doi:10.4172/2167-7662.1000e105

Copyright: © 2012 McCommis KS, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

HK2 mutant incapable of binding offered no protection against OGD is in disagreement with the study by Sun et al. [8] which showed partial protection without HK2 mitochondrial binding (albeit different cell lines and different death stimuli). More importantly, the HK2-PEA15 interaction was assumed to take place on the mitochondria, however, both proteins were shown to have significant cytosolic pools, and the immunoprecipitations (which appeared to be quite weak) was performed on whole cell lysates. More work is clearly needed to better define the subcellular localization and dynamics of this HK2-PEA15 complex.

Other more fundamental questions are also raised by this new study. Why and how does glucose deprivation alter HK2-PEA15 binding whereas hypoxia does not? How exactly does HK2 induce cell death when glucose is not available – Is it possible that HK2 can phosphorylate other substrates other than glucose under these circumstances? Perhaps most importantly can we exploit this newly found HK2-PEA15 interaction therapeutically, such that, for example, disruption of the HK2-PEA15 binding can turn on HK2's killing abilities in cancer cells that are already overexpressing HK2? Hopefully future research will help answer these questions.

References

1. Warburg O, Wind F, Negelein E (1927) The metabolism of tumors in the body. J Gen Physiol 8: 519-530.
2. Plas DR, Thompson CB (2002) Cell metabolism in the regulation of programmed cell death. Trends Endocrinol Metab 13: 75-78.
3. Bustamante E, Pedersen PL (1977) High aerobic glycolysis of rat hepatoma cells in culture: role of mitochondrial hexokinase. Proc Natl Acad Sci U S A 74: 3735-3739.
4. Bustamante E, Morris HP, Pedersen PL (1981) Energy metabolism of tumor cells. Requirement for a form of hexokinase with a propensity for mitochondrial binding. J Biol Chem 256: 8699-8704.
5. Anflous-Pharayra K, Cai ZJ, Craigen WJ (2007) VDAC1 serves as a mitochondrial binding site for hexokinase in oxidative muscles. Biochim Biophys Acta 1767: 136-142.
6. McCommis KS, Baines CP (2012) The role of VDAC in cell death: friend or foe? Biochim Biophys Acta 1818: 1444-1450.
7. Pastorino JG, Shulga N, Hoek JB (2002) Mitochondrial binding of hexokinase II inhibits Bax-induced cytochrome c release and apoptosis. J Biol Chem 277: 7610-7618.
8. Sun L, Shukair S, Naik TJ, Moazed F, Ardehali H (2008) Glucose phosphorylation and mitochondrial binding are required for the protective effects of hexokinases I and II. Mol Cell Biol 28: 1007-1017.
9. Mergenthaler P, Kahl A, Kamitz A, van Laak V, Stohlmann K, et al. (2012) Mitochondrial hexokinase II (HKII) and phosphoprotein enriched in astrocytes (PEA15) form a molecular switch governing cellular fate depending on the metabolic state. Proc Natl Acad Sci U S A 109: 1518-1523.