Hexokinase-2 bound to mitochondria: Cancer’s stygian link to the “Warburg effect” and a pivotal target for effective therapy

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Abstract

The most common metabolic hallmark of malignant tumors, i.e., the “Warburg effect” is their propensity to metabolize glucose to lactic acid at a high rate even in the presence of oxygen. The pivotal player in this frequent cancer phenotype is mitochondrial-bound hexokinase [Bustamante E, Pedersen PL. High aerobic glycolysis of rat hepatoma cells in culture: role of mitochondrial hexokinase. Proc Natl Acad Sci USA 1977;74(9):3735–9; Bustamante E, Morris HP, Pedersen PL. Energy metabolism of tumor cells. Requirement for a form of hexokinase with a propensity for mitochondrial binding. J Biol Chem 1981;256(16):8699–704]. Now, in clinics worldwide this prominent phenotype forms the basis of one of the most common detection systems for cancer, i.e., positron emission tomography (PET). Significantly, HK-2 is the major bound hexokinase isoform expressed in cancers that exhibit a “Warburg effect”. This includes most cancers that metastasize and kill their human host. By stationing itself on the outer mitochondrial membrane, HK-2 also helps immortalize cancer cells, escapes product inhibition and gains preferential access to newly synthesized ATP for phosphorylating glucose. The latter event traps this essential nutrient inside the tumor cells as glucose-6-P, some of which is funneled off to serve as carbon precursors to help promote the production of new cancer cells while much is converted to lactic acid that exits the cells. The resultant acidity likely wards off an immune response while preparing surrounding tissues for invasion. With the re-emergence and acceptance of both the “Warburg effect” as a prominent phenotype of most clinical cancers, and “metabolic targeting” as a rational therapeutic strategy, a number of laboratories are focusing on metabolite entry or exit steps. One remarkable success story [Ko YH, Smith BL, Wang Y, Pomper MG, Rini DA, Torbenson MS, et al. Advanced cancers: eradication in all cases using 3-bromopyruvate therapy to deplete ATP. Biochem Biophys Res Commun 2004;324(1):269–75] is the use of the small molecule 3-bromopyruvate (3-BP) that selectively enters and destroys the cells of large tumors in animals by targeting both HK-2 and the mitochondrial ATP synthase. This leads to very rapid ATP depletion and tumor destruction without harm to the animals. This review focuses on the multiple roles played by HK-2 in cancer and its potential as a metabolic target for complete cancer destruction.

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1. Isoforms of hexokinase

Hexokinase catalyzes the essentially irreversible first step of the glycolytic pathway where glucose is phosphorylated to glucose-6-phosphate (G-6-P) via phosphate transfer from ATP.

Glucose + Mg·ATP → Glucose-6-PO$_4$$^{2-}$ + Mg·ADP

The basis for this reaction is the entrapment of G-6-P inside the cell for commitment to either the glycolytic pathway, primarily for energy (ATP) generation via glycolysis and oxidative phosphorylation, or the shunting of this metabolite to the pentose–phosphate pathway to be utilized mainly for biosynthetic reactions. Mammalian tissues harbor four hexokinase isoforms designated as HK-1-4 [1–3]. Of these, HK-1-3, denoted as “hexokinases”, have an approximately 250-fold lower $K_m$ for glucose ($K_m = \sim 0.02$ mM) relative to HK-4, denoted “glucokinase” ($K_m = \sim 5$ mM) [1–3]. Based on primary sequence analysis, the hexokinases are postulated to have arisen via duplication of an ancestral gene similar to the HK-4 gene [4–7]. Thus, the enzyme HK-4 has a molecular mass of approximately 50 kDa, while each hexokinase has a molecular mass close to 100 kDa. HK-1 and HK-2 are localized predominantly on the outer
mitochondrial membrane, HK-3 in a perinuclear compartment [3], and HK-4 in the cytosol (liver and pancreas).

2. Discovery of the exceptional importance of HK-2 to cancer metabolism, i.e., to the “Warburg effect”

Glucose is an essential metabolite, both as a key source of cellular energy currency and a precursor carbon source for biosynthesis (anabolism) in mammalian tissues. Most normal tissues metabolize 6-carbon glucose to 3-carbon pyruvate (“glycolysis”) and then harness the energy within this molecule in the form of ATP via “oxidative phosphorylation” in mitochondria. That is, they oxidize the pyruvate to CO2 and H2O using the tricarboxylic acid cycle and the mitochondrial electron transport chain, and then use the resultant free energy to drive the ATP synthasome (ATP Synthase/Pi Carrier/Adenine Nucleotide Carrier complex) to make ATP from bound ADP and Pi in the presence of Mg++. In sharp contrast, numerous tumors by under utilizing their mitochondria rely much more (sometimes 50–70%) on the far less-efficient glycolytic conversion of 6-carbon glucose to 3-carbon lactic acid [8]. Significantly, this occurs even in the presence of ample tissue (tumor) oxygen, i.e., under conditions where one would expect pyruvate to enter the mitochondria with subsequent oxidation to CO2 and H2O. This unique phenotype, i.e., enhanced metabolism of glucose to lactic acid even in the presence of oxygen, was first described by Otto Warburg over 8 decades ago [9] and is commonly referred to as the “Warburg effect” [8–11] (Fig. 1).

The fundamental protein components that coax malignant tumors to scavenge and metabolize glucose at an abnormal rate were discovered over 5 decades later in rigorous biochemical studies [12,13], the first of which tested the “Warburg effect” of tumors in the presence of glucose or galactose. Significantly, a much lower rate of glycolytic conversion to lactic acid was observed with galactose. As the only difference between the two substrates' metabolism...
is that glucose enters glycolysis through hexokinase while galactose bypasses this enzyme, it was concluded that glycolysis is enhanced in malignant tumors by a form of hexokinase. The same study [12] also confirmed that the tumor's hexokinase is bound to the mitochondria (outer membrane) allowing it to both escape potent inhibition by its product G-6-P and obtain preferential access to newly generated ATP. In the second study [13] it was shown that when tumor mitochondria containing bound hexokinase are added to liver cytosol lacking mitochondria, this is the only enzyme addition necessary to bring this normal tissue's very low (almost negligible) glycolytic rate up to the high level catalyzed by the tumor cytoplasm.

Significantly, a later discovery in the same laboratory [14] would reveal that HK-2, the predominant isoform over-expressed in malignant tumors, is strategically located on the outer mitochondrial membrane protein “VDAC”, voltage-dependent anion channel (Fig. 1). Here, HK-2 gains both preferential access to mitochondrial generated ATP via the mitochondrial adenine nucleotide translocator (ANT), and protection from inhibition by its product G-6-P. Thus, tumors have cleverly overproduced HK-2, and neutralized its capacity to be controlled thereby forcing the reaction between ATP and the incoming glucose to produce G-6-P at a high rate. This in turn forces glycolysis and biosynthetic metabolic pathways within tumors to function at an enhanced capacity thus providing optimal support for uncontrolled tumor proliferation within the host’s tissues [10,14–16]. In addition, the acid secreted by the tumor likely helps pave the way for this process either by suppressing attacks by the immune system, preparing normal cells for invasion, or both.

3. Key events that led to the discovery that the HK-2 metabolic step can be used for monitoring clinical cancers via PET analysis

Subsequent to the discovery in 1977 [12] that a mitochondrial-bound form of hexokinase is the key player in the “Warburg effect” in cancer, a newly developed diagnostic tracer technology capitalized on this discovery to detect cancers non-invasively in humans. Thus, in 1982 and 1983 a “deoxy” analog of glucose (2-deoxy-glucose) that can be phosphorylated by HK-2 but not metabolized was added to liver cytosol lacking mitochondria, this is the only enzyme addition necessary to bring this normal tissue’s very low (almost negligible) glycolytic rate up to the high level catalyzed by the tumor cytoplasm.

5. Discoveries that revealed that the tumor HK-2 gene promoter is highly “promiscuous” in facilitating transcriptional up-regulation under both adverse and favorable metabolic states of the host

Several systemic and cellular stimuli promote the specific expression and transcriptional up-regulation of HK-2 (and to a lesser extent HK-1) in highly glycolytic malignant tumors. The first indication for enhanced transcription came via northern-blot based mRNA expression studies [21–24]. These revealed an approximately 100-fold increase in the mRNA levels for HK-2, strongly suggesting activation and up-regulation of HK-2 gene transcription. Based on these initial findings it became important to focus on the characterization of the regulatory elements within the HK-2 gene promoter which up to 1990 had been reported only for HK-4 (glucokinase) [25]. Significantly, the first cloning and sequence analysis of the HK-2 proximal promoter [23] revealed well-defined cis-elements for transcription initiation (TATA and CAAT elements) indicating that transcription is strongly regulated by cellular stimuli (as opposed to a “housekeeping” gene that lacks the initiation elements). Quite unexpectedly, cis-elements for activation by protein kinase-A (PKA) were the most proximal cis-elements near the transcription initiation site, amply subverting the “textbook expectation” of hexokinase being down-regulated by the hormone glucagon (i.e., under conditions of starvation or low blood-glucose levels in the host) or by signaling events initiated by glucagon (i.e., the CAMP initiated PKA pathway) [23]. As expected, protein kinase-C (PKC/RAS) pathways (activated by insulin or high glucose), and most significantly, response elements for hypoxia (HIF-1) and p53 were also located on the promoter [23,26,27]. Functional analysis via reporter gene analysis revealed modulation of the HK-2 gene promoter by glucose, hypoxia, CAMP analogs, and insulin, with the latter two tacitly implicating the involvement of PKA and PKC pathways in up-regulating this isoform in tumors [23,28]. Since the cis-element sequence motifs for glucose and insulin response have not been characterized to date, their precise locations or identities on the HK-2 promoter are yet to be identified.

Significantly, the above discoveries helped rationalize the selective expression of HK-2 by malignant tumors as part of a clever survival mechanism that allowed the tumor to continue metabolizing glucose regardless of the nutritional status of the tumor-bearing host. In fact, it could now be inferred why even at the terminal stages of cancer progression in a patient (i.e., tumor induced cachexia) the tumor will continue to scavenge glucose from the patient’s bloodstream and thrive while the patient’s physiology progressively shuts down.

The presence or absence of specific cis-elements between the HK-2 and HK-1 promoters helps explain the predominant expression of HK-2 in malignant tumors that exhibit the high glycolytic phenotype in the presence of oxygen, i.e., the Warburg effect. This argument is supported also when the proximal promoter region

of the two hexokinases are aligned for similarity [29]. Overall, the presence of “glycolysis-supportive” cis-elements on the HK-2 promoter are amply suited to provide a greater response in the tumor cell in response to external physiological stimuli, resulting in greater HK-2 synthesis, which in turn facilitates and maintains a high flux of glucose into the tumor.

6. Epigenetic and genetic factors involved in the marked over-expression of HK-2 in tumors—findings that revealed that in liver cancer cells exhibiting a pronounced Warburg effect the HK-2 gene is subject to both epigenetic regulation and regulation by amplification

Sequence analysis and comparison of the HK-2 promoters from normal tissue (hepatocytes) and a malignant tumor (AS-30D hepatoma) that exhibits a robust Warburg effect failed to identify any significant nucleotide differences. Less than 1% of the nucleotide positions were altered and were not in critical cis-element harboring regions [30]. In addition, based on available data (www.ncbi.nlm.nih.gov), it is known that each of the four hexokinase isozymes is encoded by different chromosomal loci. In humans, hexokinase genes HK-1-4 are localized on chromosome arms 10q22, 2p13, 5q35, and 7p15, respectively. Therefore, none of the hexokinases arise as a result of alternate exon splicing events from a single chromosomal locus or occur due to chromosomal rearrangements or deletions. This knowledge implicates epigenetic events (e.g., demethylation) and/or gene amplification as playing a significant role in the up-regulation of HK-2 gene expression during tumorigenesis.

Recently it was demonstrated that the HK-2 promoter does undergo epigenetic changes during hepatocarcinogenesis [30]. Here, HK-4 (glucokinase), with low affinity for glucose, is expressed exclusively in normal tissue (liver), while HK-2, with high affinity for glucose, is markedly expressed during malignant transformation to the highly glycolytic AS-30D hepatoma [8,10]. Significantly, methylation analysis of the chromosomal DNA in the HK-2 gene promoter region of normal hepatocytes and AS-30D hepatoma cells revealed different patterns. This evidence was further supported by bisulfite mediated methylation footprint analysis, which revealed 18 methylated CpG loci within a CpG island (~350 to +781 bp) in the hepatocyte expressed gene, while none were found in that from the hepatoma. Although these results indicate that one of the epigenetic events involved in HK-2 gene over-expression during tumorigenesis is demethylation, studies currently underway will have to be completed to fully identify all epigenetic events involved.

Another factor that can up-regulate expression of HK-2 during tumorigenesis is gene amplification. Here the story is very clear with the available data showing that the latter plays a very significant role in the enhanced expression of HK-2 in the highly glycolytic AS-30D hepatoma. This has been demonstrated both by Southern blot analysis and fluorescence in situ hybridization (FISH analysis) of hepatocytes and hepatoma chromosomal DNA. Significantly, the HK-2 gene is amplified by at least fivefold relative to that of normal hepatocytes [31]. This gene amplification was located within the same chromosomal arm, with the absence of any gene rearrangements. These findings add another facet to the multiple cellular and genetic events that facilitate the activation and over-expression of HK-2 in highly malignant tumors in support of the Warburg effect, i.e., high glycolysis to lactate even in the presence of oxygen. Evidence is lacking for similar events supporting the less-prominent HK-1 expression in tumors.

In contrast to tumors like the AS-30D hepatoma, it should be noted that most normal mammalian tissues, such as liver, express very little HK-2, with those from muscle, adipocytes, and lung expressing low but significant levels [1,3].

7. HK-2 as a possible metabolic and bio-energetic flux regulator of normal tissues that is dysfunctional in tumors

With its intimate metabolic coupling to mitochondrial ATP output (and the ADP input into mitochondria via “porins”, e.g., VDACs), HK-2 can be considered a metabolic regulator that closely balances fluxes between glycolysis and mitochondrial respiration as discussed in a recent review by Wilson [3]. In essence, in normal tissues where HK-2 is either silent or expressed at low levels, the phosphorylation rate of incoming glucose via HK-1 can be coordinated with the rate of mitochondrial oxidative phosphorylation, such that neither glycolysis (in this case, glucose to pyruvate metabolic flux) nor oxidative phosphorylation (pyruvate to ATP flux) gets “out-of-step” with the other. However, an excessive rate of glycolysis resulting from overexpression of HK-2 would ultimately result in generation of lactic acid (via lactic dehydrogenase) causing lactic acidosis in tissues. This appears to be the case in tumor tissue, indicating a deliberate uncoupling between net energy flux via glycolysis and oxidative phosphorylation so as to favor tumor proliferation via poisoning of the tumor microenvironment (and the surrounding normal tissues) with both lactic acid and low pH [32–34]. Although how the transformation of a normal cell to a tumor cell ultimately achieves this calculated uncoupling between glycolytic flux and mitochondrial respiration is not completely clear, it would seem that environmental and/or dietary factors that impact on the epigenetic regulation of HK-2 may be intimately involved.

8. Discovery that HK-2 in addition to its growth related roles in cancer also helps immortalize cancer cells

As noted above, HK-2 is localized predominantly on the outer mitochondrial membrane where it is bound to one or more VDAC proteins. Various metabolic and signal-transduction related stimuli have been implicated in regulating hexokinase-VDAC binding, including intracellular lactate, pH, ATP/ADP, glucose/glucose-6-phosphate metabolite couples, and protein kinase B (PKB/Akt) [35–37], among others. In addition to being critical for the unique metabolism of many cancers, hexokinase-mitochondrial interactions are now believed to be crucial also for promoting cancer survival via modulation of signaling events related to apoptosis [38–41]. Among cellular signaling molecules, the serine/threonine kinase Akt (protein kinase B; PKB) is a major mid-stream effector of growth factor-mediated cell survival. It also is a key mediator of the glycolytic metabolic pathway [38,42,43]. Studies by Hay and co-workers [38] showed that activated Akt functions as a potent anti-apoptotic factor in the presence of robust glycolysis, with the hexokinase-VDAC couple functioning as a downstream effector for Akt [38]. Members of the BCL2 family of proteins, which are either anti-apoptotic (e.g., Bcl, Bcl-XI) or pro-apoptotic (e.g., Bax, Bak, Bad), regulate the above process by their interactions with the protein oligomers/protein channels that control the mitochondrial membrane permeability transition (MPT) associated with the induction of apoptosis (Fig. 2). The anti-apoptotic phenotype is proposed to be modulated by two mechanisms; (1) enhancement of the HK-VDAC binding affinity to increase the mitochondrial-bound hexokinase fraction [38], and (2) mobilization of the anti-apoptotic Bcl2 member Bcl-XI to VDAC in the outer mitochondrial membrane (OMM) [44]. Significantly, the method by which Akt functions as an anti-apoptotic signaling molecule is believed to arise mainly due to its positive effect on HK-VDAC binding. In fact, disruption of the HK-VDAC interaction via non-Akt involved pathways, even in the absence of activation of pro-apoptotic factors such as Bax and Bak, induces apoptosis [45]. The precise mechanism remains unknown. In fact, the most recent literature using “gene knock-out” cells suggests that VDAC may not
Fig. 2. Metabolic targeting strategies against malignant tumors that rely on HK-2 facilitated glycolytic flux. The pyruvate analog 3-Br-pyruvate after entering tumor cells inhibits the function of both hexokinase-2 (1) and the ATP synthosome (ATP synthase/adenine nucleotide carrier/phosphate carrier complex) (2). Peptide analogs of the HK-2 N-terminal, or small-molecules clotrimazole, bifanazole or methyl jasmonate, can dislodge HK-2 from VDAC (1), depriving HK-2 of direct access to mitochondrial generated ATP and negating tolerance to G-6-P mediated product inhibition. Lactate efflux by the monocarboxylate transporters (MCTs) can be inhibited via small-molecule cinnamic acid derivatives, i.e., /H9251-cyano-4-hydroxy cinnamic acid (3) or silenced via siRNA; tumor specific lactate dehydrogenase (LDH) isoforms can be silenced via siRNA (4); the pyruvate analog dichloroacetate (DCA) can be administered to inhibit mitochondrial pyruvate dehydrogenase kinase (PDHK) (5), which prevents “inactivation” of mitochondrial pyruvate dehydrogenase (PDH). The “active” PDH facilitates a high rate of influx of pyruvate into mitochondria, with concomitant up-regulation of the TCA cycle, resulting in an altered tumor-mitochondrial redox status; tumor specific pyruvate kinase (PK) can be silenced via siRNA to alter the glycolytic flux by inhibiting the formation of pyruvate (6). Each of the above steps, which either target HK-2, the first step of the glycolytic pathway, or force the re-direction of pyruvate at the ultimate steps of the same, result in a highly disturbed metabolic status in the tumor mitochondria. This likely activates disruption of mitochondrial membrane integrity and release of cytochrome c to the cytoplasm, which in turn activates apoptotic cascades in the targeted tumor cells (MPTP, mitochondrial permeability transition pore).

always be involved in the induction of apoptosis, i.e., there may be other ways to die [46,47].

9. Targeting tumors for destruction by silencing the HK-2 transcript or via small-molecule-mediated inhibition of the enzyme

Based on the factors discussed above it is quite evident that “knock-down” or silencing of HK-2 expression should have a deleterious effect on tumor proliferation. This was evaluated first via anti-sense RNA approaches against HK-2, where anti-sense messages against HK-2 were expressed via retroviral-mediated transduction in malignant hepatoma cells (Mathupala and Pedersen, Proc Am Assoc Can Res 1999:22 (abstract # 145)). In this study, although a dramatic reduction in tumor proliferation was initially observed as the HK-2 message was silenced, upon continuous passage, the targeted tumors recovered, most likely by up-regulating or stabilizing the HK-2 message. Thus, these preliminary studies indicated the propensity by tumors to rapidly compensate for any deleterious effects at the transcriptional level; indicating that high affinity inhibitory molecules that can rapidly and irreversibly target the enzyme itself are necessary to disrupt the “Warburg effect” in such tumors.

This was subsequently accomplished a few years later by utilizing a “non-metabolizable” small-molecule analog of pyruvate, 3-bromopyruvate [48] to simultaneously target both mitochondria-bound HK-2 (among other hexokinases) and mitochondrial metabolism itself. Such studies demonstrated clearly that this small-molecule based HK-2/mitochondrial targeting strategy is highly effective in tumor implanted animal models in ameliorating the “Warburg” phenotype to bring about tumor cell death (Fig. 3). In fact, advanced cancers in all 19 animals subjected to treatment with 3-bromopyruvate were eradicated [49]. Pre-clinical studies utilizing 3-bromopyruvate against a multitude of tumors are currently being conducted in many laboratories, e.g., [50,51], indicating the universal interest in applying this metabolic targeting strategy to eradicate malignant tumors (which are frequently refractory to standard therapeutic regimens).

10. Releasing HK-2 from the VDAC anchor to disrupt tumor glycolysis

Based on current inferences on the HK-2/VDAC interaction in preventing tumor apoptosis, disruption of the same should facilitate tumor apoptosis. This in fact has been tested with several compounds that reportedly disrupt the VDAC-HK-2 interaction.
Fig. 3. Potent anticancer effect of 3-bromopyruvate. Notably, of all the anti-cancer agents noted in the legend to Fig. 2, 3-bromopyruvate has been the most effective in completely eradicating tumors in immuno-competent animals. Significantly, this tiny agent induces a rapid loss of cellular ATP in those tumors that exhibit a robust Warburg effect, and its mode of action extends beyond apoptotic effects per se and likely involves a combination of apoptotic and necrotic events. In the figure 3-bromopyruvate completely eradicates a large rat hepatocellular carcinoma (A) that projected on a human (B) would be the size of a large “grapefruit”. Complete eradication was obtained in 3 weeks with no recurrence (C), the animal living out a normal life thereafter. Tumor histopathology of the untreated animal (D). In the same study 18 other animals were freed of advanced cancer. All cancer free animals lived out a normal life without return of cancer (permission granted from Elsevier to reproduce Fig. 2 from Ref. [49]).

Among the compounds tested are the antifungal compounds clotrimazole and bifanazole [52], methyl jasmonate [53], and peptide sequences that correspond to the HK-2 N-terminal [45,46]. In each case, induction of apoptosis was observed in the targeted tumors indicating that such a “release” strategy may also be effective against highly glycolytic tumors. However, the latest reports, at least on use of clotrimazole [46] indicate the effect of these antifungals may be independent of the involvement of VDAC. Thus, further analysis is needed on the specificity of these compounds in targeting glycolysis of tumor cells.

11. The penultimate step in glycolysis—mitochondrial pyruvate metabolism and the Warburg effect

In contrast to the above approaches, others have examined the feasibility of targeting alternate steps of the glycolytic pathway as a mode of disrupting energy metabolism in malignant tumors [34,54–56] (Fig. 2). These have included (1) inhibition of lactic acid efflux from tumors by silencing or inhibiting lactate transporters via interfering RNA or cinnamic acid derivatives (ACCA) [34,55,56], (2) up-regulation of the influx of pyruvate into mitochondria by inhibiting pyruvate dehydrogenase kinase (PDK) via the 2-carbon
"pyruvate analog" dichroloacetate (DCA) [54,57], (3) inhibition of tumor expressed lactate dehydrogenase (LDH) isoforms via RNA interference to inhibit pyruvate to lactate conversion, with concomitant enhancement of mitochondrial pyruvate influx [58,59], and (4) switching between tumor expressed pyruvate kinase isoforms, again through RNA interference, to alter the kinetics of pyruvate synthesis [60].

Relaying on mitochondrial-bound HK-2 to coerce glucose down the metabolic steps toward mitochondrial respiration, most of these studies focus on the metabolic re-routing of pyruvate away from lactic acid formation and back to the mitochondria, in order to disturb the "aberrant respiratory homeostasis" of tumors. Of the above four strategies, the DCA mediated tumor targeting (by up-regulating mitochondrial pyruvate entry) strategy is currently in Phase I/II clinical studies.

12. Concluding remarks and prospects for the future

The work of a handful of dedicated, if not stubborn, tumor metabolism research groups over the past seven decades has systematically unraveled the biochemical choreography that exists between signal transduction cascades and metabolic pathways in tumors to promote malignancy (i.e., proliferation). A first benefit to cancer patients has been the utilization of the high glucose influx of malignant tumors via mitochondrial-bound hexokinase (HK-2 and to some extent HK-1) as a tool to develop radio-labeled glucose analogs for in vivo imaging of tumors via PET, which has now become a universal mode of tumor detection and staging. With the realization that hexokinase-mitochondrial interactions are crucial for tumor immortality and that small-molecule metabolite analogs can disrupt the tumors via multiple metabolic "target-points", a new class of potential anti-cancer therapies have appeared on the horizon. These are capable of usurping the tumors' aberrant metabolic machinery to re-direct the metabolites and cause self-destruction of the tumor. The sentinel enzyme that will likely facilitate the success or failure of these novel approaches will be mitochondrial-bound hexokinase (predominantly HK-2), straddled between the cytosolic and mitochondrial spaces in malignant cells while driving the first and committed step of glycolysis.

Conflict of interest

None.

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