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Review Article

Hexokinase 2 promotes tumor development and progression

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Abstract: Cancer remains a leading cause of morbidity and mortality worldwide, and the abnormal activation of glycolysis is a hallmark that enables tumor cells to adapt and sustain rapid proliferation. Beyond providing energy and biosynthetic precursors, glycolysis also supports tumor cell survival, invasion, and metastasis through multiple mechanisms. Hexokinase is a key rate-limiting enzyme in glycolysis, catalyzing the phosphorylation of glucose to glucose-6-phosphate. Among its isoforms, hexokinase 2 (HK2) exhibits particularly high enzymatic activity and substrate specificity, and it plays a central role in tumor metabolic reprogramming. Recent studies have shown that HK2 is markedly upregulated in many cancer types, where it promotes tumor initiation and progression by suppressing apoptosis and enhancing proliferation and metastasis. This review summarizes current evidence on the role of HK2 in tumor development and discusses emerging therapeutic strategies targeting HK2. By clarifying the link between HK2 and cancer, we aim to provide new insights and potential clinical applications for metabolism-based therapies.

Keywords: Hexokinase 2, tumor metabolism, Warburg effect, proliferation, apoptosis, drug resistance

Introduction

Hexokinase 2 (HK2) is the key enzyme that initiates glycolysis in cancer cells by catalyzing the phosphorylation of glucose to glucose-6-phosphate. Five hexokinase isoforms have been identified in mammalian cells [1]. HK-I is predominantly expressed in the brain and widely distributed in adult tissues [2]. HK-II is the main isoform in insulin-sensitive tissues such as adipose tissue, skeletal muscle, and cardiac muscle, and it is also abundantly present in fetal tissues and cancer cells [3]. HK-III is broadly expressed but not dominant in any specific tissue, whereas HK-IV (also known as glucokinase) is primarily localized to the liver and pancreas [4]. A fifth isoform has recently been discovered, although its characterization remains incomplete [5].

HK2 is widely expressed in metabolically active tissues, with particularly high levels in cancer cells. Its major functions include catalyzing glycolysis, inhibiting apoptosis, and reprogramming tumor metabolism. A hallmark of tumor metabolism is the Warburg effect, in which cancer cells preferentially rely on glycolysis rather than oxidative phosphorylation, even under aerobic conditions. This metabolic shift enables rapid ATP generation and provides biosynthetic intermediates essential for proliferation. Among glycolytic enzymes, HK2 acts as the central regulatory node. By catalyzing glucose phosphorylation and anchoring to the outer mitochondrial membrane, HK2 not only sustains glycolytic flux but also integrates metabolic reprogramming with survival signaling [6]. Earlier studies demonstrated that HK2 contributes to cancer initiation, progression, and metastasis across diverse tumor types [7, 8]. High HK2 expression enhances glucose uptake and utilization, thereby supporting tumor cell proliferation and survival under metabolic stress [9]. In addition, HK2 suppresses apopto-

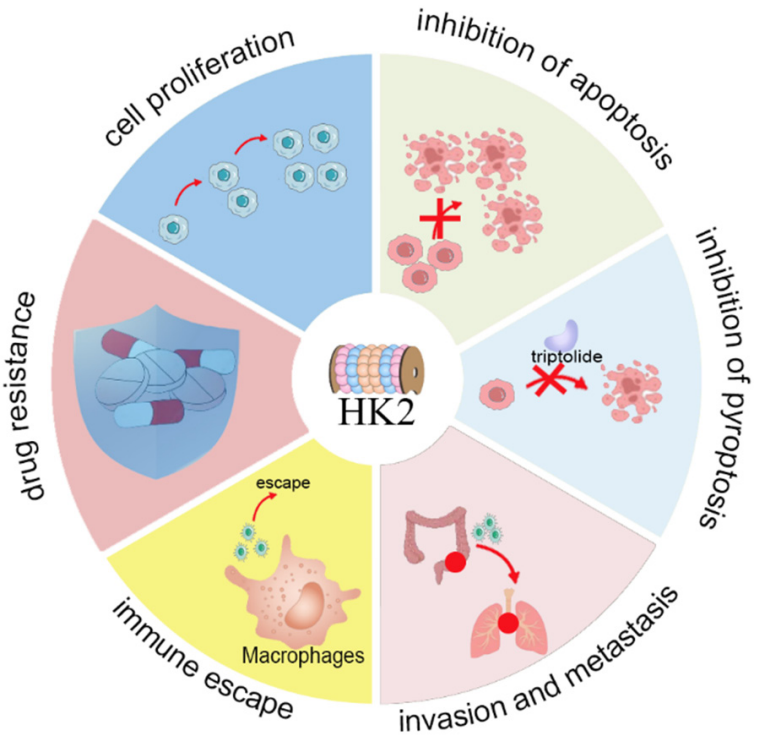

Figure 1. Summary of the key roles of Hexokinase 2.

sis by interacting with the mitochondrial outer membrane protein voltage-dependent anion channel (VDAC), which prevents apoptotic signaling [10]. More recent findings suggest that HK2 represents a promising therapeutic target. Inhibiting HK2 activity or reducing its expression disrupts tumor energy metabolism, induces apoptosis, and restrains tumor progression [11]. Nevertheless, the mechanisms of HK2 across different cancers remain incompletely understood, and clinical translation of HK2-targeted therapy faces considerable challenges.

This review explores the role of HK2 in tumor development and progression, examines its regulatory mechanisms in tumor metabolism, evaluates therapeutic strategies targeting HK2, and discusses future research directions (**Figure 1**).

HK2 promotes tumorigenesis

HK2 promotes tumor energy metabolism

HK2 and the Warburg effect: The energy metabolism of tumor cells differs fundamentally from that of normal tissues. Regardless of oxygen availability, tumor cells predominantly rely on glycolysis for energy production. Through this pathway, cancer cells generate large amounts of lactate and pyruvate, a phenomenon known as the Warburg effect. During glycolysis, glucose is converted into pyruvate while producing adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide (NADH). Importantly, NADH serves as a critical electron donor for the electron transport chain and is recycled to NAD+, thereby sustaining the NAD+/NADH cycle and ensuring the continuity of glycolysis [12]. Hexokinase 2 (HK2) is a central enzyme in this process and plays a decisive role in the Warburg effect. As early as the 1920s, Otto Warburg demonstrated that tumor cells preferentially convert glucose to lactate even under oxygen-rich conditions, in contrast to normal cells that metabolize glucose through mitochondrial oxidative phosphorylation [13]. This metabolic reprogramming allows tumor cells to rapidly generate ATP and biosynthetic precursors required for proliferation [14]. HK2 initiates glycolysis by phosphorylating glucose to glucose-6-phosphate (G6P) [15], and its expression is markedly upregulated in diverse cancers [16]. Elevated HK2 activity facilitates the establishment of the Warburg effect, enabling tumor cells to maintain high metabolic activity even under hypoxic conditions [17]. The consequent increase in lactate production acidifies the tumor microenvironment, degrading extracellular matrix components and promoting invasion into adjacent tissues [18].

HK2 and mitochondrial interaction: HK2 interacts with mitochondria by binding to voltage-dependent anion channels (VDACs), anchoring to the outer mitochondrial membrane to access ATP [19]. VDACs function as the primary channels for transporting ions and metabolites across the outer mitochondrial membrane [20]. Specifically, HK2 binds to VDAC1, facilitating the transfer of ATP generated in the mitochon-

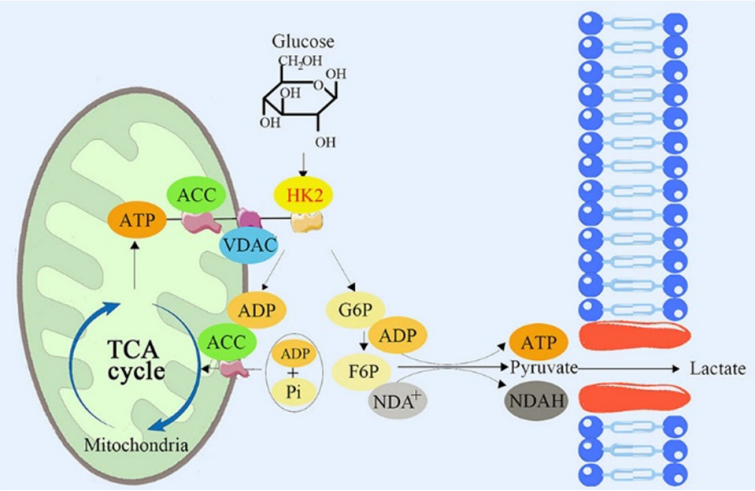

Figure 2. During glycolysis, HK2 facilitates the process in which ADP and inorganic phosphate (Pi) present in the cytoplasm are transported across the inner mitochondrial membrane into the mitochondrial matrix. This transport occurs when the AAC protein is in an open conformation, allowing these molecules to participate in the TCA cycle. When the AAC protein is in an open conformation within the matrix, ATP generated by the mitochondria is transferred into the intermembrane space. This ATP provides the necessary energy for HK2 to facilitate the conversion of glucose into glucose-6-phosphate (G6P). The lactic acid produced is transported out of the cells. HK2, hexokinase 2; AAC, mitochondrial ADP/ATP carrier; VDAC, voltage-dependent anion selective channel; G6P, glucose-6-phosphate; F6P, fructose-6-phosphate; TCA cycle, tricarboxylic acid cycle; NDA+, nicotinamide adenine dinucleotide; NDAH, nicotinamide adenine dinucleotide (prototype); Pyruvate, pyruvate; Lactate, lactic acid.

dria. During glycolysis, adenosine diphosphate (ADP) and inorganic phosphate (Pi) are shuttled into the mitochondrial matrix via the ADP/ATP carrier (AAC) when in an open conformation, fueling the tricarboxylic acid (TCA) cycle. Conversely, newly synthesized ATP is exported into the intermembrane space and subsequently delivered to HK2 through VDAC1, ensuring a continuous energy supply for its activity. HK2 then catalyzes the conversion of glucose to G6P, which is further transformed into fructose-6-phosphate (F6P). This sustained process maintains ATP consumption and supports essential cellular functions [21] (**Figure 2**).

HK2 and interactions with other metabolic enzymes: Recent studies reveal that HK2 functions within a cooperative enzymatic network rather than acting independently. Phosphofructokinase 1 (PFK1), another rate-limiting enzyme in glycolysis, works in synergy with HK2 to sustain glycolytic flux, and their co-expression has been correlated with poor prognosis in multiple cancers [22]. Pyruvate kinase M2 (PKM2) also collaborates with HK2 to maintain the anabolic phenotype of tumor cells, while additionally regulating extracellular vesicle secretion and signaling within the tumor microenvironment [23]. Lactate dehydrogenase A (LDHA), which catalyzes the conversion of pyruvate to lactate, operates downstream of HK2-mediated glycolysis. HK2 upregulation enhances LDHA activity, leading to lactate accumulation, acidification of the tumor microenvironment, and promotion of immune evasion [24]. Collectively, these findings underscore that HK2 amplifies the Warburg effect by orchestrating a metabolic network involving PFK1, PKM2, and LDHA, thereby reinforcing tumor aggressiveness.

HK2 promotes tumor cell proliferation

HK2 facilitates the rapid proliferation of tumor cells by supplying abundant energy and metabolic intermediates through its role in promoting glycolysis [25]. Increased expression of HK2 substantially enhances the rate at which glucose is taken up and metabolized [26], thereby providing critical precursors such as amino acids, fatty acids, and nucleotides that are indispensable for biosynthesis in proliferating tumor cells. These metabolites not only fulfill the requirements for tumor cell division and growth but also help maintain the intracellular reducing environment and resistance to oxidative stress, ultimately supporting tumor cell survival under the harsh conditions of the tumor microenvironment [27]. Hexokinase 2 plays a key role in the metabolism and proliferation of tumor cells, and the following is an overview of the mechanism of action of HK2 in different cancers.

Numerous studies have revealed that aberrant HK2 expression promotes proliferation in diverse tumor types through distinct molecular pathways. For instance, in hepatocellular carcinoma (HCC), HK2 expression is positively regu-

Table 1. A brief description of HK2 promoting the proliferation of different types of tumor cells and its mechanism/pathway

Tumor type	Mechanisms/Pathways	Clinical relevance	References
Hepatocellular carcinoma	ARHGAP4 positively regulates HK2	HK2 upregulation linked with poor prognosis; potential biomarker and therapeutic target	[28, 29]
Gastric cancer	WNT5A increases HK2 expression	WNT5A-HK2 axis may serve as target for gastric tumor progression	[30]
Diffuse large B-cell lymphoma	HK2 enhances ERK1/2 signaling	Supports lymphoma proliferation; potential for pathway-specific inhibition	[31]
Osteosarcoma	ROCK2-phosphorylated PI3K/AKT signaling upregulates HK2	Suggests PI3K/AKT-HK2 axis as target for bone sarcoma therapy	[32]
Gallbladder carcinoma	PVT1/miR-143/HK2 regulatory axis	Non-coding RNA-HK2 regulation may act as therapeutic entry point	[33]
Oral squamous cell carcinoma	circMDM2/miR-532-3p/HK2 axis	ncRNA-mediated HK2 regulation, possible biomarker	[34]
Nasopharyngeal carcinoma	MALAT1/miR-200b-3p/HK2	ncRNA-HK2 axis as therapeutic target	[35]
Glioma neuroma	HLA-F regulates HK2	HK2 inhibition may complement glioma immunotherapy	[36]
Prostate cancer	HK2 gene expression is upregulated	High HK2 linked to malignant phenotype, diagnostic biomarker potential	[37]
Bladder cancer	FAT10/EGFR/AKT signaling upregulates HK2	Clinical potential in EGFR-HK2 inhibition	[38]
Non-small cell lung cancer	c-Abl stabilizes HK2	Targetable in NSCLC chemoresistance	[39]
Ovarian cancer	Akt1/p-Akt1 and Wnt/β-catenin signaling upregulate HK2	Pathways linked to tumor proliferation; may guide combination therapy	[40-42]
Colorectal cancer	Xanthohumol downregulates HK2	Supports use of HK2-targeting natural compounds	[43]
Breast cancer	HK2 silencing inhibits proliferation	Potential chemosensitization strategy	[44]
Laryngeal squamous cell carcinoma	miR-125b-5p downregulates HK2	ncRNA modulation of HK2 as therapeutic avenue	[45]

lated by ARHGAP4, which drives tumorigenesis [28, 29]. In gastric cancer, WNT5A enhances HK2 expression in vivo, facilitating tumor growth [30]. In diffuse large B-cell lymphoma (DLBCL), HK2 amplifies ERK1/2 signaling to promote proliferation [31]. In osteosarcoma, rho-associated coiled-coil containing protein kinase 2 (ROCK2) upregulates HK2 expression via phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling, thereby driving tumor growth [32]. Similarly, HK2 is modulated by non-coding RNAs in several cancers: PVT1 sponges miR-143 to increase HK2 expression in gallbladder carcinoma [33], circMDM2 sponges miR-532-3p to promote HK2 in oral squamous cell carcinoma [34], and MALAT1 downregulation reduces HK2 expression via miR-200b-3p in nasopharyngeal carcinoma [35]. Other cancers also demonstrate HK2-dependent proliferation, including gliomas (regulated by HLA-F) [36], prostate cancer [37], bladder cancer (FAT10/AKT axis) [38], non-small cell lung cancer (c-Abl phosphorylation of HK2) [39], and ovarian cancer (Akt1/p-Akt1 and Wnt/β-catenin pathways) [40-42]. Inhibition studies further confirm this role: downregulation of HK2 impairs proliferation in colorectal [43], breast [44], and laryngeal squamous cell carcinoma [45]. Taken together, HK2 promotes tumor cell proliferation and growth through diverse mechanisms in multiple types of cancer (**Table 1**). Beyond fueling rapid proliferation, HK2-driven glycolysis also intersects with cell death pathways. To sustain continuous growth, tumor cells must simultaneously suppress apoptosis, and HK2 plays a pivotal role in this process by anchoring to mitochondria and interfering with pro-apoptotic signaling, thereby linking proliferative advantage with survival benefits.

Inhibition of tumor cell apoptosis by HK2

Beyond its involvement in metabolic processes, HK2 exhibits anti-apoptotic functions by binding to VDACs on the outer mitochondrial

membrane. Recent studies have further clarified the anti-apoptotic role of HK2. Mitochondria-bound HK2 interacts with voltage-dependent anion channels (VDAC) to antagonize Bax insertion into the outer mitochondrial membrane, thereby suppressing cytochrome c release and preventing apoptosis. For example, detachment of HK2 from mitochondria was shown to increase the Bax/Bcl-2 ratio and trigger cytochrome c-mediated apoptosis in lung cancer cells [46]. In oral cancer, HK2-VDAC complexes preserve mitochondrial membrane potential and protect against Bax-dependent apoptosis, whereas HK2 inhibition restores apoptotic sensitivity [47]. Moreover, combined inhibition of HK2 and pyruvate dehydrogenase kinase 1 has been reported to induce cytochrome c release and apoptosis in non-small cell lung cancer models [48]. Collectively, these findings highlight that HK2 not only prevents Bax accumulation and cytochrome c release but also contributes to tumor survival and chemoresistance, underscoring its potential as a therapeutic target. This mechanism provides tumor cells with a survival advantage, enabling them to evade apoptotic cues and withstand unfavorable conditions. HK2's role in preventing apoptosis acts as a vital defense mechanism for tumor cells. Conversely, the detachment of HK2 leads to mitochondrial damage, which ultimately inhibits tumor growth [49]. Patra et al. [50] demonstrated that the pyruvic acid analog 3-bromopyruvate (3BrPA) activates mitochondrial apoptotic signaling by inhibiting HK2, leading to its dissociation from VDAC and subsequent release of cytochrome c. The HK2 inhibitor 3-bromopyruvate induces apoptosis via the mitochondrial apoptotic pathway [51]. It has been shown that pentafluoridol affects apoptosis and glycolysis in CRC cells by downregulating hexokinase 2 [52]. Overexpression of HK2 significantly counteracts the pro-apoptotic effects and glycolytic inhibition induced by pentafluoridol. Additionally, HK2 promotes glycolysis in esophageal squamous cell carcinoma (ESCC) by targeting phosphofructose kinase L (PFKL) and activating the AMPK/FOXO3a/BIM signaling pathway, thereby inhibiting tumor progression [53]. Downregulation of circ-FOXM1 reduced hexokinase 2 levels and inhibited apoptosis [54] in melanoma cells. Research indicates that chrysin can suppress glycolysis and promote apoptosis in hepatocellular carcinoma tumors by specifically targeting hexokinase 2 [55]. Diosgenin disrupts the interaction between hexokinase 2 and VDAC-1, inhibits hexokinase 2 activity, significantly reduces tumor glycolysis, and induces apoptosis following diosgenin treatment [56]. Arsenic tetrasulfide has the ability to regulate the Warburg effect and promote apoptosis in B-cell acute lymphoblastic leukemia [57] by modulating HK2 expression. During the malignant progression of prostate cancer, the expression of the HK2 gene is significantly increased, contributing to the inhibition of early apoptosis [37].

These studies have shown that HK2 not only plays a crucial role in glycolysis but also affects cell survival and death by regulating signaling pathways associated with mitochondrial apoptosis. Whether through direct inhibition of HK2 or by targeting other metabolism-related enzymes, multiple studies have revealed the potential of HK2 as a metabolic target in tumors. Additionally, regulating the interaction of HK2 with other signaling pathways (e.g., PFKL, AMPK, etc.) provides new directions for cancer therapy. Importantly, the anti-apoptotic function of HK2 is not only critical for maintaining tumor cell survival but also forms the mechanistic basis of drug resistance. By preventing apoptosis and sustaining glycolytic metabolism, HK2 enables tumor cells to withstand the cytotoxic stress imposed by chemotherapy, thereby directly contributing to treatment failure.

HK2 prevents triptolide-induced pyroptosis

Pyroptosis refers to a form of programmed inflammatory cell death characterized by cellular swelling and lysis [58]. Unlike apoptosis, pyroptosis causes cells to rupture, releasing intracellular inflammatory factors that further activate the immune system. Consequently, cellular pyroptosis is commonly associated with bacterial infections, tumors, immune responses, and autoimmune diseases. Triptolide, a bioactive compound with antitumor potential, has been reported to modulate the interplay between HK2 and pyroptosis. By inhibiting HK2 expression in mitochondria and disrupting its role in glycolysis, triptolide further promotes Gasdermin E (GSDME)-mediated pyroptosis, especially in head and neck cancer cells. This study suggests that triptolide not only inhibits cellular metabolism by down-regulating HK2

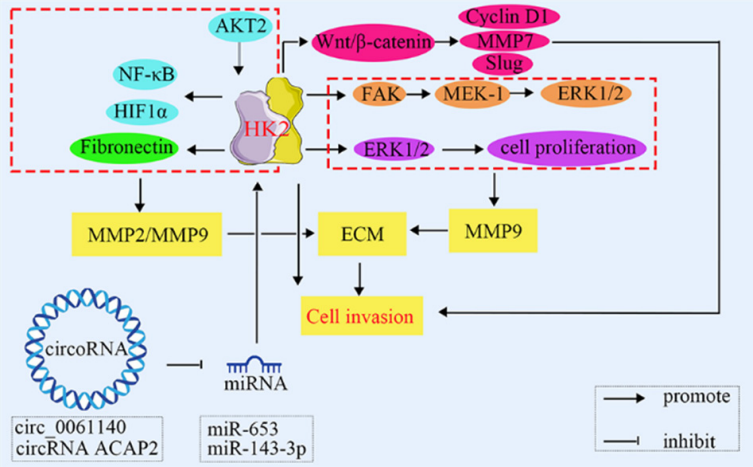

Figure 3. Signaling pathways and circoRNAs/miRNAs associated with HK2 promote tumor invasion and metastasis. Wnt/β-catenin, canonical Wnt/β-catenin pathway; Cycl in D1, G1/S-specific cyclin-D1; MMP2, matrix metalloproteinase 2; MMP7, matrix metalloproteinase 7; MMP9, matrix metalloproteinase 9; Slug protein, zinc finger transcription factor; FAK, focal adhesion kinase; MEK-1, mitogen-activated protein kinase kinase 1; ERK1/2, extracellular regulated protein kinase; AKT2, protein kinase B; NF-κB, transcription factor protein family; HIF1α, hypoxia-inducible factor 1 subunit αGen; ECM, extracellular matrix; , cicroRNA; , miRNA.

but also triggers tumor cell pyroptosis by contributing to the activation of GSDME. This process enhances tumor recognition by the immune system and promotes anti-tumor immune responses [59].

HK2 promotes tumor progression

HK2 promotes tumor invasion and metastasis

Tumor invasion refers to the process by which tumor cells penetrate the basement membrane and extracellular matrix of the primary tumor to invade surrounding normal tissues [60], and metastasis is the process by which tumor cells spread from the primary site to distant organs through the blood or lymphatic system and grow in the new environment to form secondary tumors [61]. Hexokinase II is closely related to tumor invasion and metastasis. In a mouse model of prostate tumors characterized by phosphatase and tensin homolog (PTEN) deficiency, the systemic knockout of HK2 was found to inhibit both tumor growth and metastatic spread [62]. Nanomotors have been shown to downregulate HK2 expression by delivering small interfering RNA (siRNA), thereby inhibiting aerobic glycolysis and enhancing the antimetastatic effects of chemotherapy [63]. Furthermore, HK2 promotes the migration and invasion of ovarian cancer cells by activating the FAK/ERK1/2/MMP9 signaling pathway [64]. Additionally, in colon cancer cells, the AKT2-HK2-NF-κB/HIF1α/MMP2/MMP9 signaling axis has been demonstrated to promote invasion, tumorigenesis, and metastasis in vitro while also driving lung metastasis in vivo in nude mice [65]. In cervical cancer cells, HK2 promotes cell motility and facilitates distant metastasis by increasing the expression of fibronectin, MMP2, and MMP9 [66]. Additionally, HK2 enhances the migration and invasion of cervical cancer cells by increasing the levels of ERK1/2 and its phosphorylated form, p-ERK1/2 [67]. Research has demonstrated that HK2 enhances the expression of Cyclin D1, MMP7, and Slug proteins via the Wnt/β-catenin signaling pathway, thereby facilitating the migration and invasion of cervical cancer cells [68]. HK2 promotes the migration and invasion of diffuse large B-cell lymphoma cells by enhancing the extracellular signal-regulated kinase (ERK1/2) signaling pathways [31]. circ0061140 promotes hypoxia-induced migration and invasion in lung adenocarcinoma cells by suppressing miR-653 expression and upregulating HK2 levels [69]. CircRNA ACAP2 promotes the migration and invasion of human neuroblastoma cells by regulating the signaling pathway involving miR-143-3p and HK2 [70]. Collectively, these studies indicate that HK2 not only facilitates the proliferation of tumor cells but also enhances their migratory, invasive, and metastatic capabilities through the regulation of diverse signaling pathways across multiple tumor types (**Figure 3**).

High lactic acid content and subsequent acidification due to cell glycolytic metabolism may promote carcinogenesis, leading to immune escape, invasiveness, metastasis, and the development of resistance to chemotherapy and radiotherapy. Lactate generated from the glycolysis of glucose is excreted by tumor cells,

leading to the acidification of the surrounding tumor microenvironment. This acidic microenvironment promotes tumor metastasis and can additionally drive tumor cell proliferation, trigger transcription factor activation, upregulate target gene expression, and facilitate further tumor progression [71]. Research has demonstrated that HK2 indirectly enhances tumor aggressiveness by modifying the acidic microenvironment of tumor tissue through the regulation of concentrations of metabolic substances, such as lactate and other metabolites, within the tumor microenvironment [72]. HK2 not only directly influences the metabolism of tumor cells [73] but also significantly modifies the tumor microenvironment through the secretion of its metabolites [74]. Elevated levels of lactic acid suppress immune cell function while facilitating immune evasion [75] and also promote angiogenesis by stimulating endothelial cells and pericytes [76]. Research indicates that glycolysis driven by pericyte-expressed HK2 leads to abnormal tumor vasculature through triggering ROCK2-MLC2-dependent contractile activity [77]. In summary, HK2 can alter the acidic condition of the tumor microenvironment by regulating the production and accumulation of lactic acid, thereby indirectly promoting tumor invasiveness and immune escape.

HK2 promotes tumor immune escape

Increasing evidence indicates that HK2 is not only a regulator of tumor metabolism but also a critical mediator of immune escape within the tumor microenvironment. In glioblastoma, aerobic glycolysis promotes the dissociation of HK2 from mitochondria, enabling it to phosphorylate IκBα and activate NF-κB signaling, thereby facilitating immune evasion [78]. Moreover, HK2-driven glycolysis contributes to lactate accumulation and acidification of the tumor microenvironment, which impairs T-cell surveillance and promotes immunosuppression [79]. In colorectal cancer, HK2-mediated metabolic reprogramming has been directly associated with immune escape and resistance to immune checkpoint inhibitors, suggesting that targeting glycolysis may enhance tumor sensitivity to immunotherapy [80]. In addition, several studies have further emphasized the role of HK2 as a metabolic checkpoint in cancer immunotherapy. Targeting HK2 and other glycolytic enzymes could reprogram the tumor microenvironment, overcome hypoxia-induced immunosuppression, and improve the efficacy of immune checkpoint blockade [81]. Similarly, other reports propose that HK2 functions as a metabolic checkpoint regulating both tumor glycolysis and immune metabolism, and that its pharmacological inhibition may synergize with immunotherapies to strengthen antitumor immune responses [82]. Taken together, these findings suggest that HK2 not only promotes tumor growth through metabolic reprogramming but also modulates immune escape, underscoring its potential as a promising therapeutic target in combination with immunotherapy.

HK2 promotes drug resistance in tumor cells

An increasing body of evidence suggests a strong association between glycolytic metabolism in cancer cells and the emergence of drug resistance [83]. The Warburg effect implies that the primary mechanism of glucose metabolism in cancer cells is aerobic glycolysis. When mitochondrial oxidative phosphorylation (OXPHOS) is inhibited, cells compensate for energy demands by enhancing glycolysis, which elevates lactate production. Accumulation of lactate not only alters the intracellular pH environment but also affects protein function through lactylation modifications, thereby promoting drug resistance [84, 85]. The study found that lactation induces a modification at the K388 site of the NBS1 protein. This modification enhances the interaction between NBS1 and MRE11, facilitating the formation of the MRN complex, which promotes the repair of DNA double-strand breaks. Consequently, this process reduces the effectiveness of chemotherapy drugs [86]. As a key enzyme in glycolysis, upregulated expression of HK2 can disrupt glycolytic regulation, thereby contributing to resistance to cancer therapy [87]. In the mechanism through which HK2 promotes resistance, caspase-8 cleaves the BH3-interacting domain (BID) to produce truncated BID (tBID); this process inhibits the pro-survival BCL-2 proteins, leading to the activation of pro-apoptotic proteins BAX and BAK [88, 89]. BAX and BAK undergo oligomerization, which leads to increased permeability of the outer mitochondrial membrane. This alteration promotes the release of cytochrome c (cyt c), initiating a cascade of cysteine-aspartate proteases that ulti-

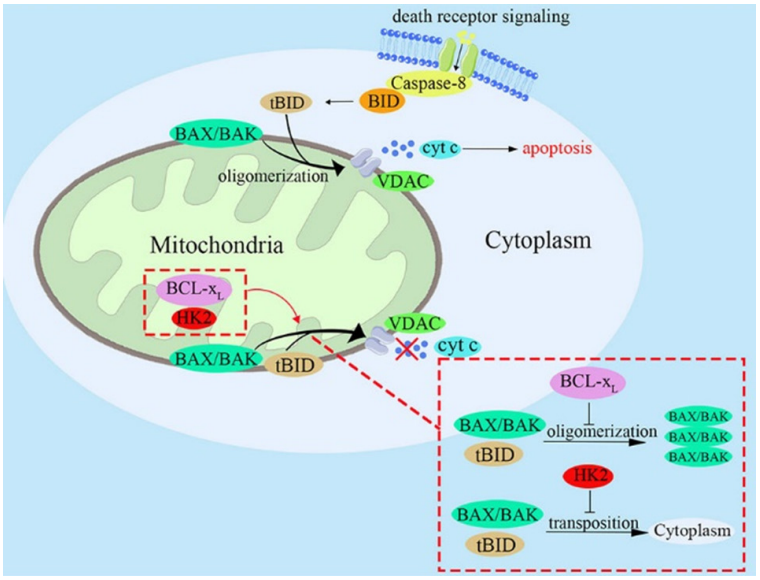

Figure 4. Mechanisms by which HK2 promotes resistance. Truncated BID of caspase-8 generates tBID. When located in the outer mitochondrial membrane, tBID interacts with BAX and BAK, facilitating their oligomerization and subsequent release of cytochrome c (cyt c); HK2 and BCL-xL facilitate the reverse translocation of tBID and BAX/BAK from the outer mitochondrial membrane back into the cytoplasm. ×, means inhibition.

mately results in cell death [20, 90]. It has been demonstrated that hexokinase (HK1/2) can translocate to reverse tBID, thereby hindering the activation of BAX/BAK, inhibiting oligomerization and cytochrome c release, and promoting cell survival [91] (**Figure 4**). Furthermore, by interacting with DNA repair proteins, nuclear HK2 potentiates the DNA damage response and facilitates DNA repair, consequently augmenting tumor cell chemo-resistance [92]. In non-small cell lung cancer (NSCLC) cells, HK2 has been shown to enhance glycolysis and contribute to chemoresistance in these cells [93]. Studies have indicated that suppression of the mTOR-S6K signaling pathway leads to increased HK2 expression, consequently inducing tamoxifen resistance in Michigan Cancer Foundation-7 (MCF-7) breast cancer cells [94]. Additionally, HK2 modulates the expression of ABC and SLC transporter genes, contributing to the development of paclitaxel resistance in ovarian clear cell carcinoma [95]. Phosphorylation of HK2 by PIM2 enhances paclitaxel resistance in breast cancer cells [96]. The dimerization of HK2, along with its interaction with VDAC, enhances resistance to gemcitabine in pancreatic cancer cells [97]. In summary, HK2 regulates tumor metabolism and drug resistance through multiple pathways, underscoring its critical role in reducing the efficacy of cancer therapies.

HK2 is a target for cancer therapy

Development status of HK2 inhibitors

At present, the development of inhibitors targeting HK2 remains in its early stages. In laboratory settings, small molecules such as 2-deoxyglucose (2-DG), 3-bromopyruvate (3-BrPA), lonidamine (LND), and metformin have been extensively studied as HK2 inhibitors. These inhibitors have shown some antitumor activity in cell and animal models, but their clinical translation has been challenging. For instance, 2-DG was discontinued for clinical antitumor applications owing to its limited tolerability and adverse effects. 3-BrPA has the following limitations: rapid inactivation or development of resistance in tumors rich in glutathione, nonselective alkylation characteristics, potential off-target interactions with unidentified proteins, and difficulties in crossing the blood-brain barrier for glioma therapy present significant challenges [98, 99]. LND is a targeted compound effective against various tumors and has received approval for use in certain countries. However, its efficacy as an independent chemotherapeutic agent is limited in inhibiting cancer cell proliferation in both in vitro and in vivo studies [100]. Nevertheless, LND exhibited significant toxicities when used in conjunction with other chemotherapeutic agents [100]. Consequently, LND is often employed as a chemosensitizer.

3-Bromopyruvate (3-BrPA), metformin (Met), and 2-deoxyglucose (2-DG) are inhibitors of HK2 [101]. 3-Bromopyruvate (3-BrPA) exerts anticancer effects by targeting HK2 [102], and metformin has antitumor activity [103], while 2-DG can inhibit activity [104] of HK2. D-mannoheptulose is a natural hexokinase inhibitor that, when combined with the oncolytic Newcastle disease virus (NDV), shows thera-

Table 2. HK2 inhibitors and their anti-cancer mechanisms: a brief description

Category	HK2 inhibitors	Mechanism/Pathways	Clinical Relevance	References
Small-molecule inhibitors	3-Bromopyruvate (3-BrPA)	Alkylates HK2, disrupts glycolysis, induces apoptosis	Preclinical efficacy, limited by glutathione-rich tumor resistance and toxicity	[100, 101]
	2-Deoxyglucose (2-DG)	Competes with glucose, inhibits HK2 activity, disrupts glycolysis	Evaluated in clinical trials but limited by toxicity and poor tolerability	[104]
	Metformin	Activates AMPK pathway, indirectly inhibits HK2	Widely used antidiabetic drug with repurposing potential in cancer	[103]
	D-Mannoheptulose	Blocks glucose phosphorylation at HK2 level	Limited to experimental studies, not yet in clinical development	[105]
	Benitrobenrazide	Directly binds HK2, induces apoptosis	Identified as a potent HK2 inhibitor in preclinical screening	[106]
	Benserazide	Selectively inhibits HK2 enzymatic activity	Potential repositioning of existing drug for cancer therapy	[107]
	Compound 3j	Direct interaction with HK2, inhibits proliferation	Represents new class of synthetic HK2-targeting molecules	[109]
	Glucose-6-phosphate	Natural feedback inhibitor, displaces HK2 from mitochondria	Serves as physiological regulator, limited therapeutic potential	[78]
	Methyl Jasmonate	Disrupts HK2-VDAC binding, inhibits glycolysis	Preclinical studies suggest potential adjuvant role	[110]
Natural compounds	Ganoderma-derived steroid (compound 2)	Structure-based binding to HK2, inhibits activity	Novel natural HK2 inhibitor under investigation	[101]
	Bergenin	Downregulates HK2, suppresses glycolysis, induces apoptosis	Shown to overcome radiation resistance in vitro	[111]
	Epigallocatechin gallate (EGCG), Quercetin	Docking studies confirm strong HK2 binding affinity	Potential dietary-derived adjuvants, need in vivo validation	[112]
	Curcumin	Multi-target activity, reduces HK2 activity indirectly	Safe natural agent but limited by low bioavailability	[113]
Clinical agents under evaluation	Lonidamine (LND)	Inhibits HK2-related glycolysis, enhances chemosensitivity	Tested in clinical settings, but toxicity limits monotherapy use	[100]
	Arsenic	Directly inhibits HK2 enzymatic activity, induces apoptosis	Historically used in leukemia, potential repurposing in solid tumors	[108]

peutic potential in breast cancer [105]. Benitrobenrazide demonstrates potent HK2 inhibition at submicromolar concentrations [106]. Benserazide selectively targets HK2 activity, leading to the induction of apoptosis in colorectal cancer cells [107]. Arsenic inhibits HK2 enzyme activity and induces apoptosis in cancer cells [108]. Glucose-6-phosphate acts as a natural inhibitor of HK2, promoting its translocation from the mitochondria to the cytoplasm [78]. Compound 3j represents a new class of HK2 inhibitors that effectively reduce cancer cell proliferation by directly interacting with HK2 [109]. Methyl jasmonate suppresses tumor cell proliferation by hindering glycolysis, which results from the disruption of the interaction between HK2 and VDAC on mitochondrial membranes [110] (**Table 2**).

Natural compounds

Certain natural compounds can inhibit the activity of HK2 and thus exert anti-tumor effects. Extracts from *Ganoderma lucidum* display antitumor properties [114, 115]. A new steroid, (22E,24R)-6β-methoxyergosta-7,9(11),22-triene-3β,5α-diol (2) from Ganoderma sinense, was predicted to have high binding affinity to HK2 using structure-based virtual screening. In vitro assays confirmed compound 2 as an HK2 inhibitor [101]. Furthermore, research has demonstrated that the natural compound bergenin exhibits inhibitory effects on HK2. Studies have indicated that bergenin suppresses the glycolysis process in cancer cells and induces apoptosis by downregulating HK2 expression, consequently inhibiting tumor

growth and overcoming radiation resistance [111]. Asifa Khan identified epigallocatechin gallate (EGCG) and quercetin as potential HK2 inhibitors using molecular docking. These compounds showed high affinity, efficiency, and specificity for the HK2 binding pocket, making them promising drug candidates [112]. Curcumin is a promising anticancer compound with multi-target activity against cancer cells and low toxicity toward normal cells. However, its low bioavailability and poor absorption, due to its hydrophobic nature, limit its effectiveness, as most of it is metabolized into inactive hydrophilic derivatives in the liver [113]. Natural compounds have demonstrated promising potential as inhibitors of hexokinase 2 (HK2) in anti-tumor studies. However, their monotherapy exhibits limited efficacy and specificity, along with a higher incidence of adverse effects. Future research should prioritize the development of HK2 inhibitors that possess greater potency and selectivity.

Combination of HK2 inhibitors with other therapies

Combining HK2 inhibitors with conventional chemotherapy drugs may improve the effectiveness of cancer treatment. Research has shown that targeting HK2 can enhance the susceptibility of cancer cells to chemotherapeutic drugs such as cisplatin. This effect may arise because HK2 inhibitors impair the energy metabolism of tumor cells, leading to decreased resistance to these drugs [116]. In addition, the combination of HK2 inhibitors with immune checkpoint inhibitors, including PD-1/PD-L1 antibodies, holds promise for enhancing therapeutic outcomes and strengthening antitumor immune responses [117]. Rapamycin, an immunosuppressive agent, in combination with 3-BrPA, significantly induced apoptosis in human neuroblastoma cells and synergistically suppressed proliferation in lung cancer cells [118, 119]. The combination of HK2 inhibitors with doxorubicin markedly suppressed tumor growth by promoting MLC2-mediated vascular remodeling. This approach reduced tumor hypoxia without negatively impacting tumor vessel density or pericyte coverage [77].

Immunotherapy is recognized as a crucial strategy in cancer treatment. Recent studies have underscored the importance of considering T-cell metabolic reprogramming and NK cell function in the design of combination immunotherapies. Tumor-driven aerobic glycolysis impairs effector T-cell proliferation and contributes to immune exhaustion, while simultaneously reshaping T-cell subsets that regulate antitumor immunity [120]. Intriguingly, intrinsic STING signaling in $CD8^+$ T cells has been shown to limit glycolysis by directly inhibiting HK2, thereby promoting memory formation and enhancing antitumor activity [121]. In parallel, metabolic reprogramming of NK cells within the tumor microenvironment profoundly affects their cytotoxicity and IFN-γ production, suggesting that metabolic interventions may boost NK-cell-based immunotherapy [122]. Furthermore, excessive lactate accumulation and hypoxia jointly impair both T-cell and NK-cell function, underscoring the need to integrate metabolic checkpoint targeting with immunotherapy strategies [123]. Collectively, these insights suggest that combination therapies targeting HK2-mediated glycolysis, alongside immune checkpoint inhibitors or NK-cell-based therapies, hold promise for restoring antitumor immune responses and improving immunotherapy efficacy.

Future directions for targeting HK2

In recent years, the development of inhibitors targeting hexokinase 2 (HK2) has emerged as a critical research direction in cancer therapy. A review published in 2022 examined the progress of small molecule inhibitors targeting HK2, with an emphasis on the structural features of HK2, binding mechanisms between inhibitors and targets, and strategies for designing efficient and selective inhibitors [124]. Another review from 2019 highlighted the potential of selectively inhibiting hexokinase-2 (HK2) as a therapeutic approach for cancer, particularly for tumors that are resistant to hexokinase-1 inhibition or overexpress HK2. It was proposed that combined inhibition of glycolysis, oxidative phosphorylation, and fatty acid oxidation could serve as a "tumor-agnostic therapy" [10]. Compared to earlier reviews, this more recent review delves into the pivotal role of HK2 in tumor metabolism, specifically how HK2 facilitates tumor progression by reprogramming glycolysis. It also underscores the function of HK2 in inhibiting apoptosis in cancer cells, notably through its interaction with VDAC1, which prevents the release of cytochrome c and blocks the apoptotic pathway. Additionally, the review

touches upon the potential involvement of HK2 in drug resistance within tumor cells.

Future studies should prioritize the development of more selective HK2 inhibitors to minimize toxicity to normal tissues, thereby enhancing safety and efficacy in clinical applications. In addition to glycolysis, HK2 may also play a role in regulating various metabolic pathways and signaling cascades. Therefore, a more thorough investigation into the function of HK2 in cancer may aid in discovering new therapeutic targets and strategies.

Clinical application of HK2

High expression of HK2 is closely associated with the glycolytic activity of tumor cells, positioning it as a potential biomarker in positron emission tomography (PET) imaging. PET imaging utilizes 18F-fluorodeoxyglucose (FDG) to evaluate glucose uptake in tumor tissues, and HK2 plays a critical role in catalyzing the phosphorylation of FDG, thereby enabling its "metabolic trapping" within cells. Consequently, HK2 has traditionally been regarded as one of the key factors influencing FDG uptake. However, the relationship between HK2 and FDG uptake is not a straightforward linear correlation. For instance, Tian et al. investigated HK2 expression in untreated oral squamous cell carcinoma (OSCC) patients and compared it with glucose metabolic activity observed in FDG PET imaging. Their findings indicated that despite high HK2 expression in OSCC tissues, relying solely on HK2 levels for predicting glucose metabolic activity in FDG PET imaging may be inadequate. Additionally, studies have shown that FDG uptake in breast cancer tissue correlates with Glut-1 expression but not with HK2, and that FDG uptake can vary based on tumor stage and histology [125]. Furthermore, FDG uptake may be influenced by multiple factors, including glucose transporter (GLUT-1) expression, hypoxia in the tumor microenvironment, and lactate metabolism [126]. Therefore, combining HK2, Glut-1, and other metabolic markers could provide a more accurate clinical evaluation of tumor metabolic characteristics and PET imaging results.

Conclusion and outlook

Hexokinase 2 is a pivotal enzyme in the glycolytic pathway and is aberrantly expressed across multiple cancer types. As a central mediator of the Warburg effect, HK2 not only promotes tumor proliferation and survival by providing energy and biosynthetic intermediates but also regulates apoptosis resistance, invasion, immune escape, and drug resistance. Collectively, these studies highlight HK2 as a multifunctional regulator of tumor metabolism, underscoring its significance as a potential therapeutic target.

Nevertheless, despite abundant preclinical evidence, the clinical translation of HK2-targeted strategies remains limited. One key challenge lies in the lack of specificity of HK2 inhibitors, as normal tissues with high metabolic demands may also be affected, raising concerns about systemic toxicity. Furthermore, the heterogeneity of HK2 expression and function across different tumor types suggests that a universal therapeutic strategy is unlikely to be effective. In our view, future investigations should not only focus on developing highly selective and safer HK2 inhibitors but also explore rational combination strategies. For example, integrating HK2 inhibition with immunotherapy or targeting multiple metabolic checkpoints simultaneously may enhance antitumor efficacy while minimizing resistance.

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Disclosure of conflict of interest

None.

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