Emerging Roles and Therapeutic Interventions of Aerobic Glycolysis in Glioma

Abstract: Glioma is the most common type of intracranial malignant tumor, with a great recurrence rate due to its infiltrative growth, treatment resistance, intra- and intertumoral genetic heterogeneity. Recently, accumulating studies have illustrated that activated aerobic glycolysis participated in various cellular and clinical activities of glioma, thus influencing the efficacy of radiotherapy and chemotherapy. However, the glycolytic process is too complicated and ambiguous to serve as a novel therapy for glioma. In this review, we generalized the implication of key enzymes, glucose transporters (GLUTs), signalings and transcription factors in the glycolytic process of glioma. In addition, we summarized therapeutic interventions via the above aspects and discussed promising clinical applications for glioma.

Keywords: aerobic glycolysis, glioma, biological roles, therapeutic interventions, clinical application

Introduction
Glioma, deriving from neuroepithelial cells, is the most prevalent primary tumor in the central nervous system (CNS), with a proportion of 80% of intracranial malignancies. According to World Health Organization (WHO) classification and cellular morphology, gliomas of WHO I-IV could be categorized into several classes including astrocytoma, oligodendroglioma, ependymoma, etc. Notably, gliomas are characterized by their rapid proliferation, infiltrative growth, treatment resistance, intra- and intertumoral genetic heterogeneity. Despite the fact that most glioma patients could receive maximal safe surgical resection with adjuvant chemotherapy and radiotherapy, the recurrence rate of them is still high and the prognosis is poor, which is still less than 15 months.

Glycolysis refers to a biological process that glucose or glycogen is decomposed into lactic acid accompanied by moderate production of ATP without ample oxygen. Despite the presence of abundant oxygen, cancer cells tend to produce energy via glycolysis even in a higher pace, which was put forward by Otto Warburg, namely the Warburg effect. Based on previous studies, key enzymes (HKs, PFK-1, and PKs), glucose transporters (GLUTs) and transcript factors (HIF-1α, c-myc, and p53) have been recognized as main regulators in the glycolytic activities. In addition, PI3K/Akt, mTOR, and AMPK signalings were also strongly relevant to glycolysis in multiple solid tumors. More importantly, the glycolytic process was tightly correlated with various cellular activities, evoking promising therapeutic targets for various tumors. For instance, IncRNA maternally
expressed gene 3 (MEG3) suppressed proliferation and invasion via regulation of glycolysis in colorectal cancer.\textsuperscript{14} Similarly, the curcumin analogue WZ35 inhibited glycolysis and facilitated the generation of reactive oxygen species (ROS), promoting JNK-dependent apoptosis of gastric cancer cells.\textsuperscript{15} Xi et al\textsuperscript{16} also reported that human equilibrative nucleoside transporter 1 (hENT1) was involved in modulating chemotherapy sensitivity of pancreatic cancer cells by inhibiting glycolysis. Recently, gathering investigations have intensively focused on the roles and therapeutic interventions of the glycolytic process in glioma. In this review, we have summarized the roles of key glycolytic enzymes, GLUTs, main signaling pathways, and transcription factors detected in glycolysis of glioma, which may offer possibilities for novel therapies.

**Implication of Key Enzymes and GLUTs in Aerobic Glycolysis**

**Hexokinases (HKs)**

HKs catalyze the first step of glycolytic procedure by phosphorylating glucose in the mitochondrial outer membrane of brain and tumor cells, ultimately generating glucose-6-phosphate (G-6-P).\textsuperscript{17,18} Further gene detection has revealed that HKs exist as five HK isoforms including HKI-IV and HK domain-containing protein 1 (HKDC1), with separate locations of different chromosomes.\textsuperscript{19} Interestingly, HKII, identified as a “housekeeping enzyme”, is highly expressed in all mammalian tissues, while the other HKs were characterized with distinct tissue-specificity and differential expression.\textsuperscript{20} Additionally, HKII has been verified to facilitate glycolysis via multiple central metabolic pathways.\textsuperscript{21} It was also acknowledged that malignant transformation of neural stem cells was paralleled by overexpression of HKII.\textsuperscript{22} Recently, accumulating trials demonstrated that aberrant expression of HKII triggered multiple mechanisms to regulate the progression of multiple solid tumors, especially in glioma.\textsuperscript{23,25}

Noteworthily, HKII knockdown transformed the glycolytic process to oxidative phosphorylation (OXPHOS), accompanied by the production of ROS in glioma.\textsuperscript{26} Conversely, a higher glycolytic index along with activated procedures of lipid and protein synthesis was induced by HKII overexpression.\textsuperscript{27} Nie et al\textsuperscript{28} also reported that the elevated HKII contributed to an increase in glucose uptake and lactate production in glioma cells with IDH1R132H mutation. Further in vitro experiments illustrated that HKII was significantly upregulated in gliomas and related to proliferation, invasion, apoptosis, and angiogenesis.\textsuperscript{29} The clonogenic power and cell-cycle progression of glioma cells were also mediated by misregulation of HKII.\textsuperscript{27,30} Regarding autophagic death, HKII was confirmed its relevance with glioma cells treated by RSL3, a novel compound of small molecules targeting glutathione peroxidase 4 (GPX4).\textsuperscript{31}

Subsequent functional investigation has been carried out for roles of HKII in glioma, which may emerge as a promising therapeutic target for glioma treatment. For example, X box-binding protein 1 (XBP1) knockdown promoted decreases of cellular viability, tumor formation capacity, and the production of ATP/lactate by inhibition of HKII expression.\textsuperscript{32} Concurrently, some signalings were correlated with biological activities of HKII. The silence of PERK signaling, usually activated upon the lack of oxygen and glucose, decreased tumor formation capacity via mitochondria translocation of HKII.\textsuperscript{33} Nodal signaling was also involved in boosting xenograft development through upregulation of HKII.\textsuperscript{34} Moreover, miRNAs could serve as critical regulators of glycolysis in glioma due to their roles in regulating gene expression. Overexpression of miR-1297 markedly inhibited HKII targeting karyopherin α2 (KPNA2), thus promoting cellular proliferation and glycolysis in glioma.\textsuperscript{35} Similar activities could also be detected in glioma with elevated expression of miR-378e via targeting ribophorin-II (RPN2).\textsuperscript{36} In addition, it was confirmed that HKII was regulated by miR-218/Bmi1 pathway to exert its tumorigenic effects on glioma.\textsuperscript{25} Zhao et al\textsuperscript{17} also reported that miR-143 laid suppressive effects on glycolysis, tumor formation capacity, and promoted differentiation by directly targeting HKII. Notably, 2-deoxy-D-glucose (2-DG), known as a suppressor for glycolysis, was identified to have synergistic effects in the inhibition of HKII by miR-143. Collectively, it has been verified that HKII exerted a pivotal role in the glycolytic pathway and could be a reliable target for glioma.

**Phosphofructokinase-1 (PFK-1)**

It has been widely recognized that PFK-1 catalyzes the second rate-limiting procedure of glycolysis, transforming fructose-6-phosphate (F-6-P) to fructose-1, 6-biphosphate (F-1, 6-BP) mediated by Mg\textsuperscript{2+} and ATP.\textsuperscript{38} Interestingly, PFK-1 could be allosterically activated by ADP, AMP and F-2, 6-BP, and inhibited by citric acid and ATP.\textsuperscript{39} PFK-1 is mainly composed of three different isoforms, including
PKM (muscle), PFKP (platelet), and PFKL (liver). Noteworthily, other isoforms including PKM1, PKM2, PKMR, and PFKFB1-4 have been explored in the glycolytic process.\textsuperscript{43} Gathering evidence has revealed that PKF-1 mediates the metabolic process by regulating the oxidation of glucose.\textsuperscript{42} More importantly, the glycolytic flux of tumor cells could be modulated by PFK-1, usually activated in a significant number of tumor types, thus affecting cellular growth, invasiveness, and survival.\textsuperscript{43,44}

Clinically, it was reported that the elevated expression of PFKFB4 was found in glioma patients and also associated with a shorter survival.\textsuperscript{45} Similar increased activity of PFK-1 was also detected in the glioma cell lines.\textsuperscript{46} In the glycolytic process of glioma, PFKFB3 mRNA and protein expression could be motivated by TGF-β1, thus upregulating glycolytic flux.\textsuperscript{47} Further in vitro experiments showed that the inhibition of PFK-1 consistently decreased glioma cell viability and migration.\textsuperscript{48} More significantly, glioma cells with PFK-1 knockdown induced more caspase-dependent cell death.\textsuperscript{49} Regarding angiogenesis, the biological effects of lacking PFK-1 was reflected by the decreased number and length vascular tubules.\textsuperscript{49}

Accumulating studies have illustrated that PFK-1 could serve as a surprising target for glioma therapy. For example, citrate, a natural organic acid, targeted PFK-1 to exert anti-tumor effects via inhibiting glycolysis.\textsuperscript{49} Due to the relevance of glycolysis with mitochondria, voltage-dependent anion channel 2 (VDAC2) coupled PFKP to influence the glycolytic process.\textsuperscript{50} Moreover, the Smad, p38/MAPK, and PI3K/Akt signalings also participated in the activities of PFKFB3 in glioma.\textsuperscript{47} Similarly, multiple lines of evidence suggested that gene transcription regulation was involved in the biological activities of PFK-1. LncRNA urothelial cancer associated 1 (UCA1) downregulated the expression of miR-182, which was directly bound to PFKFB2, modulating C-X-C motif ligand 14 (CXCL14) secretion, glycolysis, and invasion of glioma cells.\textsuperscript{51} Li et al\textsuperscript{35} also found that KPNA2, a key regulator of glycolysis in glioma, would be targeted by miR-1297 decreasing the functions of PFK-1. In summary, all the above results have suggested that targeting the PFK-1 might be a promising therapeutic target for glioma.

**Pyruvate Kinases (PKs)**

PKs, the third and last key rate-limiting enzymes of glycolysis, irreversibly catalyze the production of pyruvic acid and ATP from phosphoenolpyruvate (PEP) and ADP.\textsuperscript{52} Four different subtypes of PKs, including PKL, PKR, PKM1, and PKM2, have been detected in the glycolytic process.\textsuperscript{53} In addition, these isoforms with definite or indefinite biological activity are distributed in diverse tissues and organs.\textsuperscript{54} It has been verified that PKs play vital roles in the glycolytic process via controlling the metabolic flux and ATP production.\textsuperscript{55} Apart from their biological effects in glycolysis, PKs regulate major cell signalings by phosphorylating key proteins to adjust gene expression in the nucleus.\textsuperscript{56} Recently, PKM1 and PKM2, two main subtypes of PKs in the brain tissue, have become hotspots in glioma treatment for its correlation with radiation sensitivity.\textsuperscript{57}

PKM2 was involved in adapting glioma cells to a different microenvironment through regulating nutrients and growth signaling pathways allosterically.\textsuperscript{58} More clinical databases have revealed that the translocation of PKM2, induced by epidermal growth factor receptor (EGFR), transactivated β-catenin signaling in promoting brain tumor development.\textsuperscript{59} It was also qualified that the expression of PKM2 was related to malignancy grades and prognosis of patients with glioma.\textsuperscript{60} Mechanically, the low expression of PKM2 was consistent with glycolysis dysfunction, accompanied by the decreased concentration of intracellular ATP and pyruvate.\textsuperscript{51} In vitro, PKM2 also participated in regulating cellular proliferation, migration, and invasion.\textsuperscript{61} Moreover, the cell-cycle progression could be activated by PKM2 along with elevated contents of cyclin D1 and c-myc.\textsuperscript{60} More importantly, the upregulation of PKM2 contributed to an increased apoptosis rate in glioma cells via stabilizing Bcl2.\textsuperscript{52,62} Besides, the activation of autophagic responses was found to be relevant with PKM2.\textsuperscript{64}

Surprisingly, gathering functional regulators for PKM1 and PKM2 have emerged, providing a new insight into the investigation of therapeutic interventions for glioma treatment. HSP90α1’s ATPase could activate PKM2 and subsequently facilitate combination with Bcl2 in ROS adaptation of glioma cells.\textsuperscript{63} G9a knockdown induced accumulation of Akt and HIF-1α expression, which drive PKM2-Yes-associated protein 1 (YAP1) cross talk in glioma cells.\textsuperscript{64} Yang et al\textsuperscript{60,65} also revealed that PKM2, activated by EGFR, exerted its pro-tumor effects via being directly bound with histone H3 or the distinct regulation of NF-κB signaling pathways. Moreover, β-catenin signaling was also correlated with biological activities of PKM2 in glioma.\textsuperscript{59} Besides, lncRNAs or miRNAs were found to be relevant with biological activities of PKs. MiRNA let-7a modulated c-myc/hnRNPA1 axis to promote glucose
metabolism and cell growth by PKM. Surprisingly, miR-1297 silencing facilitated the activities of PKM in glioma via downregulation of KPNA2. It was also detected by Liu et al that lin00689 competitively interacted with miR-338-3p to boost PKM2 expression, therefore influencing the malignant phenotypes of glioma cells. Overall, PKs have been verified to participate in the glycolytic process, forecasting the potential application for glioma treatment.

**Glucose Transporters (GLUTs)**

GLUTs, a sort of membrane protein controlling glycolytic flux, mainly take part in transmembrane transport of glucose. GLUTs share a similar structure with 12 transmembrane domains, with amino and carboxy terminal domains on the cytoplasmic side. According to sequence similarity and substrate specificity, GLUTs family of 14 members could be classified into three categories. Additionally, different affinities for glucose of GLUTs in different organs revealed their specificity tissue distribution. For instance, GLUT1 and GLUT3 were distributed in the brain which demands more glucose than other organs. GLUT3 and GLUT10 were predominantly detected in the muscle tissues. Moreover, GLUT4 is mainly observed in muscle and fat cells due to its role in glucose transportation. Surprisingly, it has been reported that upregulation of GLUTs was correlated with poor survival, therapy resistance in tumor patients, accompanied by promotion effects on cellular growth and invasion in vitro.

In glioma, overexpression of GLUT1 and GLUT3, related to higher pathological grades, have been detected in glioma patients. It was also reported that GLUT3 was mainly in the plasma membrane, whereas GLUT1 could be detected in both plasma membrane and cytoplasm. Further studies have disclosed that GLUT1 regulated glycolysis through extracellular deoxyglucose uptake and glucose transport, while GLUT3, predominantly in neurons, might play a pivotal role in neuronal glucose influx. Interestingly, GLUT1 and GLUT3 were paralleled with the expression of key enzymes of glycolysis including HKII, PKM2, pyruvate dehydrogenase (PDH), and lactate dehydrogenase A (LDH-A). While in vitro, GLUT1 exerted its pro-tumor effects in proliferation, invasion, and tumorigenesis. Dai et al also indicated that the proliferation and cell-cycle of glioma cells were also mediated by GLUT3. When it regards angiogenesis, targeting GLUT1 or GLUT3 could unlock the potential for clinical application. A study by Kuang et al also verified that GLUT3 overexpression promoted metabolic reprogramming associated with antiangiogenic therapy resistance. Surprisingly, the inhibition of GLUT1 could suppress tumor initiating cells, thus facilitating the capacity of temozolomide (TMZ) against glioma.

Further clinical investigations have uncovered that KPNA2 overexpression significantly upregulated the expression of GLUT-1 residing on the plasma membrane and 2-DG uptake. A study by Chen et al also revealed that CAMP-response element binding protein 1 (CREB1) affected the expression of GLUT1 and was involved in the metabolic process of glioma. In addition, some signalings participated in the activities of GLUTs in glioma. The activation of GLUT1 expression and Warburg effect could be mediated by PI3K/Akt signaling pathway. The Nodal signaling has also been verified to regulate the energy metabolism in glioma cells. Similar biological effects were also observed in IDH1R132H mutant or Ras knockdown glioma cells via the HIF-1α/GLUT1 axis. Besides, miRNA-451, targeting recombinant human calcium binding protein 39 (CAB39) to regulate GLUT1 inhibited the glucose metabolism, the proliferation, and invasion of glioma cells. Similarly, miR-495 increased GLUT1 to promote glucose uptake and lactate production in glioma. Regarding the functional activities of GLUT3, the same regulating role of HIF-1α was explored, which may be reliable predictors of the biological behavior of glioma. MiR-106a knockdown also inhibited glioma cell glucose uptake and proliferation by targeting GLUT3. Taken together, GLUT1 could be a therapeutic target and predictor for glioma treatment, while the biological roles of GLUT3 and other glucose transporters are still ambiguous, which needs further exploration (Figure 1 and Table 1).

**Roles of Main Signaling Pathways in Aerobic Glycolysis**

**PI3K/Akt Signaling**

The dysregulation of PI3K/Akt signaling has been found in most of the human cancers, which plays a vital role in cellular proliferation, invasion, migration, apoptosis, and angiogenesis. The PI3Ks are a family of kinase enzymes that could phosphorylate phosphatidylinositol 4, 5-bisphosphate (PIP2) to generate phosphatidylinositol 3, 4, 5-trisphosphate (PIP3), thus promoting phosphorylation of Akt and activating several downstream targets. The PI3Ks could be divided into three subtypes in accordance with...
structural features and substrate specificities. Class IA PI3K and class IB PI3K are heterodimers, both comprising of a regulatory subunit and a catalytic subunit. While class II PI3Ks consisted of three isoforms (PI3KC2α, PI3KC2β, and PI3KC2γ), which could be stimulated by cytokine receptors, receptor tyrosine kinases (RTKs), and integrins. Besides, class III PI3Ks mainly contain a catalytic VPS34 subunit. Akt, also named protein kinase B, is a serine/threonine protein kinase that could be activated by PI3Ks inducing downstream effector proteins including mTOR, Bcl-2 family, glycogen synthase kinase 3, E2F, forkhead transcription factor (FKHR), and S6 protein kinase. Currently, metabolic pathways, especially aerobic glycolysis, could be modulated by PI3K/Akt signaling, which may provide evidence for clinical interventions in glioma.

Gathering evidence has confirmed the relevance of glycolysis with PI3K/Akt signaling in glioma. It has been found that the activities of glycolysis were modulated by PI3K/Akt signaling in regulating glucose uptake, lactic acid production, and nicotinamide adenine dinucleotide (NAD) level. In addition, the ATP level was also involved in the biological functions of PI3K/Akt signaling. As one of the three key enzymes, PFKFB3 could be elevated significantly through activation of PI3K/Akt signaling, thus resulting in an increase in F-2, 6-BP concentration, glucose uptake, glycolytic flux, and lactate production. Similarly, the inhibition of HKII mitochondria translocation, mediated by partial block of Akt, inhibited glioma cell growth under low glucose stress. Qian et al also found that the autophosphorylated phosphoglycerate kinase 1 (PGK1) was dephosphorylated and inhibited in the suppression of glycolysis via PI3K/Akt signaling. Besides, the pyruvate dehydrogenase kinase 1 (PDK1) on Thr346 would be phosphorylated by active Akt accumulates in the mitochondria. Interestingly, several cellular activities have been found to be relevant with glycolysis modulated by PI3K/Akt signaling. The suppression of PI3K/Akt signaling significantly inhibited glycolysis to participate in regulating the proliferation, invasion, and migration of glioma cells. The involvement of epithelial-mesenchymal transition (EMT) was also in PI3K/Akt signaling and glycolysis. Moreover, the cell-cycle progression and autophagic responses could be detected in PI3K/Akt signaling and glycolysis. More importantly, the repression of PI3K/Akt signaling promoted the accumulation of ROS and subsequent induction of apoptosis in syk-positive or syk-negative gliomas. Furthermore, the ERK pathway,
an apoptosis-related signaling, could also be activated by PI3K/Akt signaling.\textsuperscript{102} Further investigation was performed for clinical application of PI3K/Akt signaling in modulation of glycolysis of glioma. Petunidin-3-O-glucoside (Pt3glc), an anthocyanin in the red grape and derived beverages, caused significant changes in glioma cell morphology, leading to more pronounced apoptotic cell death via PI3K/Akt signaling.\textsuperscript{102} A study by Guo et al\textsuperscript{84} revealed that miR-451 repressed PI3K/Akt signaling targeting CAB39 via downregulation of GLUT1 in glioma. In addition, some biological molecules were also found in the functional effects of PI3K/Akt signaling in glioma. Phosphatase and tensin homolog (PTEN) suppressed glycolysis targeting PGK1 or glycogen synthase kinase-3β (GSK3β) via PI3K/Akt signaling.\textsuperscript{103,108} It was also reported that WW domain-binding protein 2 (WPB2) exerted oncogenic effects by modulating PI3K/Akt signaling and targeting glycolytic enzyme enolase 1 (ENO1) in glioma.\textsuperscript{109} Rodriguez-Garcia et al\textsuperscript{47} still found that the expression of PFKFB3, upregulated by TGF-β1, was involved in cell proliferation via its role in carbohydrate metabolism. Besides, PX-866 (an effective specific inhibitor of PI3K) and Y2129 (a class of inhibitors of the calcineurin-NFAT pathway) regulated glycolysis and other cellular activities via PI3K/Akt signaling.\textsuperscript{106,110} Intriguingly, there were still a certain number of regulators targeting Akt to affect the glycolytic process. Tricyclodecan-9-yl-xanthogenate (D609) influenced cell proliferation and invasion targeting CXCR4 via interfering with AKT and EGFR.\textsuperscript{111} The pMU and pMC treatments laid an inhibitory effect on Akt, ROS induction, and an increase of cytosolic cytochrome c accumulation.\textsuperscript{26} In addition, Tp53 induced glycolysis and apoptosis regulator (TIGAR) promoted Akt activation and bound to Akt, thus promoting glycolysis of glioma cells.\textsuperscript{105} Upon G9a inhibition, PKM2-YAP1 activated autophagic activities via the Akt-HIF-1α axis in glioma.\textsuperscript{112} Moreover, signalings or miRNAs were also related to modulation of Akt in glycolysis of glioma. PERK silencing repressed HKII mitochondria translocation through p-AKT knockdown, thus inhibiting glioma cell growth.\textsuperscript{33} MiR-7 suppressed colony formation of glioma cells in vitro and decreased the p-Akt expression level via insulin-like growth factor 1 receptor (IGF-1R).\textsuperscript{113} Therefore, PI3K/Akt signaling has shown its significance in modulating

\begin{table}
\centering
\caption{Roles of RNAs Modulating Glycolytic Key Regulators in Glioma}
\begin{tabular}{|l|l|l|l|l|}
\hline
\textbf{Key Regulators} & \textbf{RNAs} & \textbf{Correlation} & \textbf{Targets} & \textbf{Related Biological Activities} & \textbf{Reference} \\
\hline
HKII & miR-1297 & Negative & KPNA2 & Proliferation and overall survival & [35] \\
& circNFIx & Positive & miR-378e/RPN2 & Cell cycle, migration, invasion, apoptosis, xenograft tumor growth and clinical outcome & [36] \\
& miR-218 & Negative & Bmi1 & Proliferation, migration, invasion and xenograft tumor growth & [25] \\
& miR-143 & Negative & / & Proliferation and xenograft tumor growth & [37] \\
\hline
PKFB2 & IncRNA UCA1 & Positive & miR-182 & Invasion and clinical prognosis & [51] \\
\hline
PFK-1 & miR-1297 & Negative & KPNA2 & Proliferation and overall survival & [35] \\
\hline
PKM2 & miRNA let-7a & Negative & c-myc/hnRNPA1 & Proliferation and xenograft tumor growth & [66] \\
& miR-1297 & Negative & KPNA2 & Proliferation and overall survival & [35] \\
& linc00689 & Positive & miR-338-3p & Proliferation, migration, invasion, tumor size, tumor grade, clinical prognosis & [61] \\
\hline
GLUT1 & miRNA-451 & Negative & CAB39 & Proliferation and invasion & [84] \\
& miR-495 & Positive & / & Proliferation and growth & [92] \\
& miR-106a & Negative & SLC2A3 & Proliferation and clinical prognosis & [85] \\
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\end{tabular}
\end{table}

\textit{Abbreviations}: HKII, hexokinase II; KPNA2, karyopherin α2; RPN2, ribophorin-II; PKFB2, 6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatase 2; UCA1, urothelial carcinoma associated 1; PKF-1, phosphofructokinase-1; PKM2, pyruvate kinase isozyme type M2; GLUT, glucose transporter; CAB39, recombinant human calcium binding protein 39; SLC2A3, solute carrier family 2 (facilitated glucose transporter) member 3.
the glycolysis of glioma, which may be a promising therapy for glioma treatment.

3.2 mTOR Signaling
The mechanistic target of rapamycin (mTOR) signaling, usually activated in tumors, plays a significant role in tumor metabolism modulating gene transcription and protein synthesis to influence cellular activities.114,115 The mTOR, expert in integrating environmental stimulations into cellular responses, is an evolutionary conserved serine/threonine kinase.116 Additionally, mTOR could be classified into two complexes, including mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2).117 The conserved components of mTORC1 include mTOR, regulatory-associated protein of mTOR (Raptor), proline-rich AKT substrate 40 kDa (PRAS40), DEP-domain-containing mTOR-interacting protein (Depotr), and mammalian lethal with Sec13 protein 8 (mLST8) whereas mTORC2 consists of mTOR, rapamycin-insensitive companion of mTOR (Rictor), stress-activated protein kinase-interacting protein (SIN1) and mLST8.118,119 The biological activities mediated by the two complexes are different due to their unique binding proteins; mTORC1 mainly influences protein, lipid, nucleotide, and glucose metabolism, autophagy, energy metabolism, lysosome biogenesis, cell survival, and cytoskeletal organization, whereas mTORC2 is involved in cell cytoskeletal remodeling, cell migration, glucose metabolism, ion transport, and cell survival.120

The activation of mTOR signaling in clinical samples were highly related to shorter survival time in glioma patients.121 Mechanically, activated glycolysis along with high glucose consumption, extracellular lactate flow, and upregulation of glycolysis-associated genes, have been detected in mTOR signaling.122 In addition, the expression of glycolytic enzymes, including HKII and PKFP, were modulated by mTOR signaling as consequences of metabolic adaptation.123 As one of the two main forms of mTOR, it has been verified that mTORC1 was paralleled with the process of glycolysis.124 Besides, mTORC2 targeted the c-myc/GFAT1 axis to regulate the interaction between glycolysis and glutaminolysis in glioma.125 mTORC2 signaling also positively promoted H3K56Ac to regulate cellular activities via phosphorylating AGC kinases.126 Clinically, chemoresistance of 1,3Bis (2-chloroethyl)-1-nitrosourea (BCNU) and cisplatin to glioma might be regulated by mTOR signaling.122 Further in vitro experiments have shown that mTOR knockdown suppressed the motility, migration, and invasive behavior of glioma cells.124 The proliferation and clone formation of glioma cells were also involved in mTOR signaling.127 More importantly, the mTOR signaling played a pivotal role in the cell-cycle arrest and induction of apoptosis.106

Surprisingly, preliminary clinical studies illustrated that rapamycin in combination with doxycycline might exert promising anti-tumor effects on glioma via mTOR signaling.123 It was also reported that metformin decreased ATP production by glycolytic process via inhibition of mTOR signaling. Interestingly, metformin in combination with temozolomide or irradiation would induce a synergistic anti-tumor response.128 Furthermore, biological molecules were found to be relevant with mTOR signaling in glycolysis of glioma. Carboxypeptidase E (CPE) activated mTORC1 signaling in glioma cells and subsequently phosphorylated ribosomal protein S6 (RPS6), thus promoting glycolysis.124 Monocarboxylic acid transporter 1 (MCT1) and YZ129 were also found to exert regulating effects on mTOR signaling axis, thus inhibiting glycolysis.106,127 Zhang et al122 disclosed that knockdown of Clock 1 (Clk1) elevated HIF-1α expression of glioma cells, which was mediated by mTOR signaling. In summary, the multiple roles of mTOR signaling have been studied in regulating glycolysis of glioma, which could be utilized for glioma treatment.

AMPK Signaling
The AMP-activated protein kinase (AMPK), a cellular metabolic sensor, participates in maintaining energy homeostasis under external stresses in multiple human cancers.129 The AMPK, expressed extensively in all eukaryotic cells, comprises of a catalytic subunit (α) and two regulatory subunits (β and γ).130,132 According to different inputs, outputs, functions, and sub-cellular localizations, a total of 12 potential AMPK complexes were assembled by various isoforms of each subunit.131 Moreover, the α subunit, phosphorylated at Thr-172, translocates a phosphate group from ATP to the Ser/Thr sites, known as a biomarker for AMPK signaling.132 The γ subunit serves as an allosteric activator, while the β subunit provides a structural bridge between α and γ subunits.134,136 Therefore, upon binding to γ-subunit, AMPK would be elevated via the allosteric activation of AMP, which could also be precisely modulated by upstream kinases.137,138 More importantly, phosphorylating of AMPK signaling depends on adenosine triphosphate (ATP)/AMP ratio to a great extent.139,140

Interestingly, AMPK signaling expressed a dual role to protect normal brain cells from energy stress while
repressing the tumor cells.\textsuperscript{141} It has been reported that activities of glycolysis including glucose uptake, ATP levels, and lactate production were regulated by AMPK signaling in glioma cells.\textsuperscript{84} Zhang et al\textsuperscript{122} also found that the extracellular acidification rate (ECAR), an indirect indicator of lactate production and enhanced glycolytic metabolism, was significantly increased in the activation of AMPK signaling. In addition, key enzymes of the glycolytic process, such as HKII, PFK, PDK1, LDH-A, and GLUT1, depended on the vitality of AMPK signaling.\textsuperscript{122,142} Further in vitro experiments revealed that AMPK signaling was tightly related to cellular proliferation, migration, and invasion of glioma.\textsuperscript{84} Senen et al\textsuperscript{128} also delivered a bulletin that cellular activities including cell-cycle arrest, autophagy, apoptosis, and cell death were mediated by AMPK signaling. As for tumor survival and angiogenesis, AMPK α2, one of the AMPK alpha isoforms, exerted pro-tumor effects via modulating vascular endothelial growth factor (VEGF) production on glioma patients.\textsuperscript{143} Besides, the chemoresistance of glioma cells was verified to be correlated with AMPK signaling.\textsuperscript{122} Notably, the cytotoxicity induced by EGFR inhibition could also be eliminated by AMPK signaling in glioma.\textsuperscript{144}

More regulators concerning AMPK signaling have been further studied. It was verified that amentoflavone increased miR-124-3p by inhibiting DNA cytosine-5-methyltransferase 1 (DNMT1) through Sp1.\textsuperscript{145} Besides, methylene blue activated AMPK signaling and subsequently inhibited downstream targets, thus reversing the Warburg effect.\textsuperscript{146} Senen et al\textsuperscript{128} also revealed that metformin decreased oxygen consumption and ATP production, and upregulated lactate and glycolytic ATP production through AMPK signaling. The cell cycle arrest at G0/G1 phase could also be blocked by metformin, thus promoting mitochondria-dependent apoptosis through activation of AMPK signaling.\textsuperscript{147} Moreover, 7 beta-hydroxycholesterol (7b-HC) provoked metabolic response to change lipid draft composition via AMPK activation in glioma. Interestingly, 7b-HC also influenced the affinity of PKs to their substrates.\textsuperscript{142} Surprisingly, several chemical molecules were connected with regulation of glycolysis in glioma. Clk1, encoding an enzyme concerning ubiquinone biosynthesis, elevated HIF-1α expression via AMPK signaling in glioma.\textsuperscript{122} Additionally, a mitochondrial adenylate kinase 4 (AK4) regulated ATP levels and AMPK signaling, which was connected with overall survival of glioma patients.\textsuperscript{148} Research by Guo et al\textsuperscript{149} pointed out that the AMPK agonist AICAR suppressed glioma cell proliferation via inhibiting the synthesis of cholesterol and fatty acid. Similarly, miR-451 regulated metabolism of glucose via AMPK signaling to decrease GLUT1 expression in glioma.\textsuperscript{84} JCV, a human neurotropic virus, targeted T-antigen to regulate the expression level of ROS and ATP production via AMPK signaling.\textsuperscript{150} Above all, the AMPK signaling could also be a promising target for glioma treatment for its distinctive roles in regulation of glycolysis (Figure 2).

### Interplay of Transcription Factors in Aerobic Glycolysis

**HIF-1α**

Hypoxia, the most common biological feature of most solid tumors, plays a prominent role in tumor metabolisms, especially in glycolysis.\textsuperscript{151} Hypoxia-inducible factor 1 (HIF-1), known as one of the major regulators for hypoxia, is a heterodimeric transcription factor composed of an inducible HIF-1α subunit and a constitutive HIF-1β subunit.\textsuperscript{152} Importantly, activity of HIF-1 is mainly determined by HIF-1α subunit, which is an oxygen-sensitive subunit of 120 kDa diffusely expressed in all tissues.\textsuperscript{153} Recently, more and more studies have been carried out focusing on the roles of HIF-1α in glycolysis, while glioma is no exception.\textsuperscript{154,156}

HIF-1α was found to direct glucose away from mitochondria, resulting in regulatory T cells (Tregs) utilizing fatty acids for mitochondrial metabolism under hypoxia.\textsuperscript{157} It has also been recognized that HIF-1α transformed glycolysis to pentose phosphate pathway.\textsuperscript{158} Mechanically, HIF-1α induced glucose uptake and lactate accumulation, lowered intracellular ATP concentrations, and elevated mitochondrial membrane potential, which was paralleled with the expression level GLUTs, HK II, PKM2, PDK1, and LDH-A.\textsuperscript{29} Interestingly, HIF-1α overexpression facilitated the VEGF pathway of vasculogenesis.\textsuperscript{29} Subsequent in vitro experiments have illustrated that a decreased cell proliferative activity and an elevated apoptosis rate were found in the activity of HIF-1α in glioma.\textsuperscript{34,62} Moreover, growth inhibition was also associated with tumor vessels reduction, enhanced levels of ROS, and autophagic responses.\textsuperscript{64,158,159} HIF-1α signaling was also involved in regulating the metabolism, tumor-specific immunity, and tumor growth in glioma.\textsuperscript{160} Regarding the effects of chemotherapy and radiotherapy, HIF-1α signaling participated in regulating
The effectiveness of irradiation and temozolomide of glioma via the glycolytic process.\textsuperscript{158,161}

Surprisingly, more and more regulators have been detected in the functional activities of HIF-1$\alpha$ in glioma. The hypoxic condition could contribute to the upregulation of HIF-1$\alpha$ via elevating the expression of TIGAR, while prolyl hydroxylation of HIF-1$\alpha$ would happen under normoxic conditions.\textsuperscript{29,158}

Conversely, glioma cells with IDH mutant produced more 2-hydroxyglutarate to facilitate HIF-1$\alpha$ degradation.\textsuperscript{162} Signalings were also key components in the activities of HIF-1$\alpha$. The Wnt/$\beta$-catenin and AHR signaling could be modulated by HIF-1$\alpha$ regulating the tumor growth.\textsuperscript{29,160} Nodal signaling also regulated energy metabolism in glioma by elevating HIF-1$\alpha$.\textsuperscript{34} Ahmad et al\textsuperscript{64} still found that G9a inhibition activated autophagic responses targeting the Akt-HIF-1$\alpha$ axis in glioma. Further, the von Hippel-Lindau tumor suppressor protein (pVHL) suppressed tumor development by binding to HIF-1$\alpha$, subsequently suppressing HIF-1, VEGF, and Bcl-2 partially.\textsuperscript{159} Besides, miR-448 could inhibit HIF-1$\alpha$ signaling and then negatively control the glycolysis process in glioma.\textsuperscript{161} Hence, HIF-1$\alpha$ might be a promising biomarker and target for the glycolytic process of glioma.

\textbf{c-Myc}

Myc family proteins, comprising of c-myc, l-myc, and n-myc, are nuclear transcription factors that regulate the metabolic process, cellular proliferation, and cell-cycle progression.\textsuperscript{163} Due to their high conservation in genome, ribonucleic acid, and protein sequences, they share a similar general presentation.\textsuperscript{164} Interestingly, c-myc is expressed in many kinds of adult tissues while n-myc is found mostly in early developmental stages of neuronal tissues. L-myc is prominently located in embryonic brain, lung, and kidney, which needs further investigation.\textsuperscript{165} Noteworthily, c-myc exhibits many important functions modulating signaling transduction of cancerous cells, involving cell growth, differentiation, genome stability, survival, and angiogenesis.\textsuperscript{166,168}

In metabolic imaging, glycolytic activity had a positive correlation with c-myc expression in xenograft models of glioma.\textsuperscript{169} c-myc was also reported to be involved in deoxyglucose uptake, lactate production, level of OXPHOS, and activities of the key glycolytic enzymes including HKII, PFK1, PKM2, and GLUT1.\textsuperscript{79} In addition, the increased expression of amino-acid transporter 2 (ASCT2), ENO1, LDH-A, LDH-B, PDK1, and MCT1 were detected in c-myc-overexpressed glioma cells.\textsuperscript{170} The c-myc signaling is
also involved in modulating the interaction between glycolysis and glutaminolysis of glioma. Further in vitro investigation has demonstrated that cellular proliferation, migration, and cell cycle arrest at different checkpoints participated in the activities of c-myc. More importantly, the expression of c-myc was relevant to brain tumorigenesis in vivo.

In the glycolytic process, PKM2 promoted glucose metabolism of glioma targeting miRNA let-7a, promoting c-myc/hnRNP A1 axis. Moreover, PKM2 could induce histone H3 modifications, upregulating cyclin D1 and c-myc via EGF. Clinically, diclofenac and ibuprofen reduced the expression of c-myc and LDH-A via signal transducers and activators of transcription 3 (STAT-3) phosphorylation. Several signalings were also involved in the modulation of the expression level of c-myc. c-myc relatively elevated expression of fructose-6-phosphate aminotransferase 1 (GFAT1) targeting mTORC2 signaling. It was also observed that Wnt/β-catenin signaling could be activated by c-myc. Besides, KPNA2 elevated the expression of c-myc by translocating E2F1, thus influencing the glycolytic process. Kim et al also found that the K+ channel tetramerization domain-containing 2 (KCTD2) affected glycolysis via c-myc degradation by ubiquitination. Overall, given the crucial roles of c-myc in the progression of glioma, therapeutic interventions elevating expression of c-myc might be a reliable therapy for glioma.

**p53**

The p53 gene family, named as an important tumor suppressor, is composed of p53, p63, and p73, which avoid damage from widely mutated genomes under outer stress. As one of main transcription factors, p53 exerts suppressive effects on tumor cells via modulating gene transcription, facilitating cell-cycle arrest, apoptosis, and even death. More importantly, it is observed that p53 represses the glycolytic process and boosts mitochondrial respiration, which also participates in the regulation of several metabolic processes. However, p53 mutation is an event with high frequency in tumorigenesis, leading to key roles of its downstream target TIGAR in glycolysis of malignancy. TIGAR, highly expressed in cancers, is involved in regulating glycolysis and tumor growth redox balance mediated by pentose phosphate pathway (PPP). Therefore, p53 and TIGAR would be regulators of glycolysis, which needs to be summarized and further explored.

TIGAR overexpression has been acknowledged in gliomas, which may reduce glycolysis and induce the PPP pathway, protecting glioma cells away from oxidative damage. Moreover, generation of F-2, 6-P, lactate, and ROS levels were reduced with a concomitant elevation in glutathione (GSH) levels in TIGAR-expressed cells. Further in vitro experiments revealed that the cell growth and capacity of forming colonies was inhibited in TIGAR-knockdown glioma cell lines. As the main regulator of cell cycle, p53 could induce cell cycle arrest, which in turn facilitated Bax-dependent apoptosis. Clinically, TIGAR sensitized glioma cells to hypoxia, irradiation, and TMZ.

Accumulating evidence demonstrated that the expression of TIGAR was significantly decreased in glioma patients with IDH1 mutations, accompanied by elevated expression of H3K9me3 in the initial transcription of TIGAR. TIGAR, upregulated by HIF-1α, could also modulate metabolic processes resulting from spontaneous homeostasis and outer stimulations. Interestingly, it has been detected that the expression level of TIGAR was apparently upregulated under exposure to irradiation. IFNγ was found to increase the expression level of retinoic acid inducible gene (RIG-I), further elevating p53 and TIGAR. Other interventions of manumycin or TGF-β elevated hCG-β expression of glioma cells, which abrogated expression of TIGAR. In addition, repressing transketolase isoenzyme transketolase-like 1 (TKTL1) could diminish activities of TIGAR. The functional activities of DCA were also connected with DCA-induced Foxo3 and p53 expression, contributing to high expression of Bad, Noxa, and Puma. Notably, Bartesaghi et al also reported that p53 mutations were observed alterations in ETC subunit composition and activity in glioma-initiating neural stem cells. Therefore, the suppressive roles of p53 and its downstream target TIGAR have been confirmed preliminarily, which still needs more investigation (Figure 3 and Table 2).

**Discussion**

Over the past 50 years, disturbances in the crosstalk between glycolysis and the progression of glioma have received much attention and investigation. Accumulating evidence has illustrated that it would be promising to apply the glycolytic process for diagnosis and treatment of glioma. With increased number of lncRNAs, miRNAs, biological molecules and chemical drugs found in modulating glycolysis of glioma, it is of great
significance to summarize the interactions between glycolysis and glioma for clinical application.

However, there are still several deficiencies and limitations in the clinical application of glycolysis for glioma treatment. Firstly, lncRNAs and miRNAs play pivotal roles in regulating glycolysis for glioma treatment, of which the clinical application still poses an obstacle in glioma. Surprisingly, lncRNAs or miRNAs themselves could serve as therapeutic molecules for treatment individualization. Apart from this, nucleic acid analogs also facilitated the application of these RNAs. Ray et al. have found that peptide nucleic acid (PNA) specifically recognized DNA or RNA and invaded into duplex homopurine sequences of DNA, thus modulating gene expression level. Interestingly, the lncRNA-miRNA-mRNA network may also offer promising interventions for gene therapy for glioma.

Secondly, owing to the fact that glycolysis was observed in both tumor and normal cells, targeting key enzymes and GLUTs of the glycolytic process may exert uncertain side-effects on normal tissues. For example, diclofenac and ibuprofen, as suppressive drugs in glioma treatment, may induce a series of symptoms in the upper gastrointestinal tract. Oteiza et al. and Fukuda et al. also reported that citrate could contribute to hypocalcemia and neurotoxicity of CNS and the peripheral nervous system (PNS). Hence, aiming at the systemic toxicity, the emergence of selective targeted delivery may provide a promising choice to settle the awkward situation. Moreover, it is a challenge to confirm treatment prescription according to clinical responses and toxic effects.

Thirdly, though targeting glycolysis has been testified scientific and reasonable for glioma treatment, it is still far from reality.
from achieving clinical success before entering clinical arena. Notably, metformin was verified to possess both an inhibitory effect of glioma cells and a protective effect of neurons.128,198 Conversely, rapamycin and doxycycline were reported to exert suppressive effects via inhibition of glycolysis through mTOR signaling.123 McMahon et al199 found the neurotoxicity of rapamycin may cause abnormal activation of mTOR signaling and subsequent epilepsy in human or animal models. Therefore, it is imperative to carry out more clinical trials to detect the biological function of chemical drugs, providing evidence for further application of these drugs.

Fourthly, gathering experiments have explored the potential of combining targeted glycolysis with other treatment strategies. A study by Meng et al200,201 unfolded that decreased glycolysis could gain increased anti-cancer effects of immuno-therapy via induction of immune sensitive surface ligands. Functionally, the activated glycolytic process is positively correlated with immune evasion,202,203 activities of tumor microenvironment (TME),204 and cytokine storm,205 contributing to an anti-PD-1/PD-L1 immunotherapy response.201,204 Besides, glycolysis also boosts activated immune cell proliferation, including T cells and monocytes, leading to immune tolerance and resistance.206,207 Surprisingly, the combination of glycolysis suppression with radiotherapy or chemotherapy led to the elevated sensitivity and anti-tumor effects.208,210 In addition, Fiorillo et al.211 also probed the possible application of targeting glycolysis for endocrine therapy and photothermal therapy.212 Thus, targeting glycolysis might sensitize glioma cells to other treatment strategies, which could predict another application of the glycolytic process for glioma.

In conclusion, distinctly activated glycolysis is an inherent feature of metabolic reprogramming in glioma, which could be regulated by key enzymes (HKs, PFK-1, and PKs), GLUTs, signalings (PI3K/Akt, mTOR, and AMPK), and transcription factors (HIF-1α, c-myc, and p53). More importantly, targeted therapy, gene therapy, and immunotherapy might act as novel therapeutic approaches for application of glycolysis in glioma treatment, which still needs more clinical experiments.

**Abbreviations**

HK, hexokinase; PFK-1, phosphofructokinase-1; PK, pyruvate kinase; GLUT, glucose transporter; mTOR, mammalian target of rapamycin; AMPK, adenosine 5′-monophosphate (AMP)-activated protein kinase; HIF-1α, hypoxia inducible factor-1α; CNS, central nervous system; WHO, World Health Organization; ATP, adenosine triphosphate; MEG3, maternally expressed gene 3; ROS, reactive oxygen species; hENT1, human equilibrative nucleoside transporter 1; INK, c-Jun N-terminal kinase; hENT1, human equilibrated nucleoside transporter 1; G-6-P, glucose-6-phosphate; HKDC1, HK domain-containing protein 1; OXPHOS, oxidative phosphorylation; IDH, isocitrate dehydrogenase; GPX4, glutathione peroxidase 4; XBP1, X box-binding protein 1; PERK, phosphorylated extracellular regulated protein kinase; KPN2, karyopherin α2; RN2, ribophorin-II; 2-DG, 2-deoxy-D-glucose; F-6-P, fructose-6-phosphate; F-1, 6-BP, fructose-1, 6-biphosphate; ADP, adenosine diphosphate; AMP, adenosine monophosphate; PFKM, phosphofructokinase-muscle; PFKP, phosphofructokinase-platelet; PFKL, phosphofructokinase-liver; TGF-β1, transforming growth factor-β1; VDAC2, voltage-dependent anion channel 2; UCA1, urothelial cancer associated 1; CXCL14, C-X-C motif ligand 14; PEP, phosphoenolpyruvate; EGFR, epidermal growth factor receptor; HSP, heat shock protein; YAP1, Yes-associated protein 1; PDH, pyruvase dehydrogenase; LDH, lactate dehydrogenase; TMZ, temozolomide; CREB1, cAMP-response element binding protein 1; CAB39, recombinant human calcium binding protein 39; PI2P, phosphatidylinositol 4, 5-bisphosphate; PIP3, phosphatidylinositol 3, 4, 5-triphosphate; PIP2, phosphatidylinositol 4, 5-bisphosphate; RTK, receptor tyrosine kinase; FKHR, forkhead transcription factor; NAD, nicotinamide adenine dinucleotide; PGK1, phosphoglycerate kinase 1; PDK1, pyruvate dehydrogenase kinase 1; EMT, epithelial-mesenchymal transition; ERK, extracellular regulated protein kinase; Pt3gic, Petunidin-3-O-glucoside; PTEN, phosphatase and tensin homolog; GSK3β, glycogen synthase kinase-3β; WBP2, WW domain-binding protein 2; ENO1, enolase 1; NFAT, nuclear factor of activated T cells; D609, trelyclocdecan-9-yl-xanthogenerate; CXCRA4, C-X-C motif receptor 4; TIGAR, Tp53 induced glycolysis and apoptosis regulator; PDGF, platelet-derived growth factor; PDGF, platelet-derived growth factor receptor; IGF-1R, insulin-like growth factor 1 receptor; mTOR, mechanistic target of rapamycin; mTORC1, mTOR complex 1; mTORC2, mTOR complex 2; Raptor, regulatory-associated protein of mTOR; PRAS40, proline-rich AKT substrate 40 kDa; Dpotepr, Dpotepr-domain-containing mTOR-interacting protein; mLST8, mammalian lethal with Sec13 protein 8; Rictor, rapsasin-in-sensitive companion of mTOR; SIN1, stress-activated protein kinase-interacting protein; BCNU, 1,3Bis (2-chloroethyl)-1-nitrosourea; CPE, carboxypeptidase E; RPS6, ribosomal protein S6; MCT1, monocarboxylic acid transporter 1;
Clk1, clock 1; AMPK, AMP-activated protein kinase; CBM, carbohydrate-binding module; ECAR, extracellular acidification rate; VEGF, vascular endothelial growth factor; DNMT1, DNA (cytosine-5)-methyltransferase 1; 7b-HC, 7 beta-hydroxycholesterol; AK4, adenyate kinase 4; Tregs, regulatory T cells; PDX, patient-derived xenograft; ASCT2, amino-acid transporter 2; STAT-3, signal transducers and activators of transcription 3; GFTAT1, fructose-6-phosphate aminotransferase 1; KCDT2, K+ channel tetramerization domain-containing 2; PPP, pentose phosphate pathway; GSH, glutathione; RIG-I, retinoic acid inducible gene; TKTL1, transketolase-like 1; DCA, Dichloroacetate; ETC, electron transport chain; PNS, peripheral nervous system; PNA, peptide nucleic acid; TME, tumor microenvironment.

Disclosure

The authors declare that they have no competing interests.

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