

# Research progress on the interaction between long non-coding RNAs and RNA-binding proteins to influence the reprogramming of tumor glucose metabolism (Review)

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**Abstract.** As epigenetic regulators, long non-coding RNAs (lncRNAs) are involved in various important regulatory processes and typically interact with RNA-binding proteins (RBPs) to exert their core functional effects. An increasing number of studies have demonstrated that lncRNAs can regulate the occurrence and development of cancer through a variety of complex mechanisms and can also participate in tumor glucose metabolism by directly or indirectly regulating the Warburg effect. As one of the metabolic characteristics of tumor cells, the Warburg effect provides a large amount of energy and numerous intermediate products to meet the consumption demands of tumor metabolism, providing advantages for the occurrence and development of tumors. The present review article summarizes the regulatory effects of lncRNAs on the reprogramming of glucose metabolism after interacting with RBPs in tumors. The findings discussed herein may aid in the better understanding of the pathogenesis of malignancies, and may provide novel therapeutic targets, as well as new diagnostic and prognostic markers for human cancers.

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## 1. Introduction

In recent years, due to advancements being made in research on tumors, the reprogramming of glucose metabolism in tumor cells has gradually become a focus of research. In normal cells, glucose-converted pyruvate enters the tricarboxylic acid cycle (TCA) for oxidative phosphorylation while in an aerobic environment and undergoes glycolysis to produce lactate only during hypoxia. However, tumor cells still prefer the glycolytic pathway for energy even in an aerobic environment (1). This change in the energy pathway provides certain advantages for the occurrence and development of tumors. First, aerobic glycolysis produces more adenosine triphosphate (ATP) than oxidative phosphorylation for consumption by tumor cells when the substrate is sufficient and the recycling efficiency is sufficiently high (1,2). Second, aerobic glycolysis can improve cellular tolerance to hypoxia and avoid oxidative phosphorylation-induced apoptosis (3). In addition, glycolytic intermediates can also provide the raw materials for anabolism, and the increased production of lactic acid can also decompose and destroy the cellular matrix around tumor cells, which promotes tumor cell migration (4). The scientist, Otto Warburg, discovered the phenomenon of aerobic glycolysis in tumor cells as early as the 1920s and defined it as the Warburg effect (5).

For tumor cells to carry out the Warburg effect, two necessary conditions must be met. On the one hand, due to the increased consumption of glucose by tumor cells, greater amounts of glucose need to be taken up from the extracellular environment. On the other hand, there are numerous enzymatic reactions in the glycolytic pathway, and these glycolytic enzymes play a crucial regulatory role. Therefore, the regulation of these two aspects has become critical for the regulation of the Warburg effect.

Glucose transporters (GLUTs) have been reported to enable glucose to cross hydrophobic cell membranes into cells, thereby mediating the use of glucose (6). Previous research has found that the upregulation of GLUTs promotes the Warburg effect in multiple cancer types (7). Other studies have indicated that the transcriptional upregulation of glycolytic enzymes is closely related to the occurrence of tumors, and that changes in their activity and stability have a direct impact on the Warburg effect (8-10). In addition, the abnormal expression of certain upstream molecules of GLUTs and glycolytic enzymes will

affect them to a certain extent, thereby indirectly regulating the Warburg effect (11).

Long non-coding RNAs (lncRNAs) can participate in tumor metabolism by regulating the metabolic remodeling of various substances, including the metabolic reprogramming of glucose (12,13). lncRNAs refer to a class of RNAs whose transcripts are >200 nucleotides in length and have limited protein-coding capacity; they are one of the most widely studied classes of non-coding RNAs (14). It is necessary for lncRNAs to interact with other cellular macromolecules, such as DNA, proteins and RNA, to drive the cancer phenotype, and their functional effect is to interact with proteins. Through lncRNA-protein interactions, lncRNAs can regulate the functions of proteins directly or regulate protein interactions between other proteins (15). Such RNA-binding and interacting proteins are termed RNA-binding proteins (RBPs), which bind to RNA through one or more globular RNA-binding domains and alter the fate or function of the bound RNA (16). At present, the intricate interaction mechanisms of RNA-RBPs have been reported by a large number of studies (17). The present review article summarizes and discusses the interaction between lncRNAs and RBPs in tumor cells, and their direct or indirect effects on the Warburg effect. Furthermore, the present review article elaborates on the different mechanisms in the cited articles. The topics covered in the present review article are summarized in Figs. 1 and 2, and Table I.

## 2. lncRNAs interact with RBPs to regulate the reprogramming of glucose metabolism in tumor cells through direct action

*GLUTs.* Tumor cells have a higher demand for glucose as their metabolic rate is substantially greater than that of normal cells, which require a constant supply of energy and nutrients. It has been demonstrated that the first step in energy metabolism is the uptake of glucose into cells through GLUTs. The gene name of the GLUT family is solute carrier 2 (SLC2A). The family consists of 14 members, of which GLUT1-4 are the four most well-known subtypes, and the expression of GLUT family members is increased in various types of cancer (7). There are numerous cases of lncRNAs affecting glucose metabolism by regulating GLUT, such as lncRNA HOTAIR promoting glycolysis by upregulating GLUT and activating mammalian target of rapamycin (mTOR) signaling, whereas the knock-down of HOTAIR suppresses this effect (18). However, it was found that when lncRNAs interact with RBPs to modulate the Warburg effect through the modulation of GLUTs, the predominantly regulated isoform is GLUT1 (19,20).

It has been found that lncRNA CASC11 interacts with eukaryotic translation initiation factor 4A3 (EIF4A3) in hepatocellular carcinoma (HCC) and modulates the Warburg effect and tumor progression by affecting the expression of GLUT1 (19). EIF4A3 has been reported to be an important exon junction complex involved in the development of mRNA secondary structure in the 5'untranslated region (UTR) region and promotes the initiation of protein translation (21,22). Mechanistically, the interaction of CASC11 with EIF4A3 leads to an increased expression of the downstream transcription factor E2F1 due to its enhanced mRNA stability, which in turn enhances GLUT1 expression and aerobic glycolysis. Following

the silencing of CASC11, GLUT1 expression was found to be downregulated, and tumor progression was also significantly inhibited (19). E2F1 mentioned is an important promoter for cells to enter S phase, can promote the reprogramming of glycolysis and the energy metabolism of tumor cells (23), and plays a critical role in the occurrence and development of various malignant tumors (24,25), as well as being able to function directly as an RBP. In lung adenocarcinoma, lncRNA Gas6-AS1 is downregulated as a tumor suppressor (20). It has been found that Gas6-AS1 directly interacts with E2F1 and downregulates GLUT1 transcription by inhibiting the binding of E2F1 to the GLUT1 promoter region, thereby inhibiting tumor progression and the Warburg effect (20).

*Glycolytic enzymes.* The activity and stability of glycolytic enzymes directly affect the entire glycolytic metabolic pathway, and they are categorized as rate-limiting enzymes according to whether they can affect the overall speed of the metabolic pathway. Hexokinase (HK) is the first rate-limiting enzyme in aerobic glycolysis, catalyzing the conversion of glucose to glucose-6-phosphate (G-6-P). It has four subtypes, HK1, HK2, HK3 and HK4 (11,26), of which HK2 is more dominant than the other subtypes in promoting aerobic glycolysis (27). The expression level of HK2 has been found to be significantly increased in a variety of cancer tissues, and the silencing of HK2 can effectively reduce the level of aerobic glycolysis and promote the transformation of the metabolic mode of cancer cells to oxidative phosphorylation (28-30). Phosphofructokinase-1 (PFK1) is the second rate-limiting enzyme in glycolysis, which catalyzes fructose-6-phosphate (F-6-P) to fructose-1,6-diphosphate (F-1,6-BP) through the use of ATP(31). PFK1 exists as three isoforms (PFK-M, PFK-P and PFK-L) in mammals, and the proportions of these isoforms may vary in tissues with varying metabolic needs (32). Fully activated PFK1 exists as a tetramer, and the formation and stabilization of tetramers largely affects the rate of glycolytic flux (33). The third rate-limiting enzyme in glycolysis is pyruvate kinase (PK), which catalyzes the dephosphorylation of phosphoenolpyruvic acid (PEP) to generate ATP and pyruvate, including the four subtypes of PKM1, PKM2, PKR and PKL (34). Previous research has demonstrated that PKM2 isoforms are highly upregulated in tumor cells and are associated with poor prognosis (35). There are two forms of PKM2: One is a tetramer, which is located in the cytoplasm, has high catalytic activity and can rapidly convert PEP to pyruvate, generating more glycolytic flux and ATP (36), while the other is a monomer or dimer that can translocate into the nucleus, has lower catalytic activity, and acts as a coactivator of several transcription factors (34,37).

In addition, the regulatory effects of enzymes that are not rate-limiting on glycolysis cannot be ignored. Phosphoglycerate kinase (PGK) mainly catalyzes the formation of ATP in the aerobic glycolysis pathway. It has two isoforms: PGK1 and PGK2. PGK1 is ubiquitously expressed in all cells and catalyzes the reversible transfer of phosphate groups from 1,3-bisphosphoglycerate (1,3-BPG) to adenosine diphosphate to generate 3-phosphate glyceric acid (3-PG) and ATP (38). PGK1 is associated with the occurrence and progression of various cancers, and it mediates the ATP produced by glycolysis for use by tumor cells (39). PGK1 and

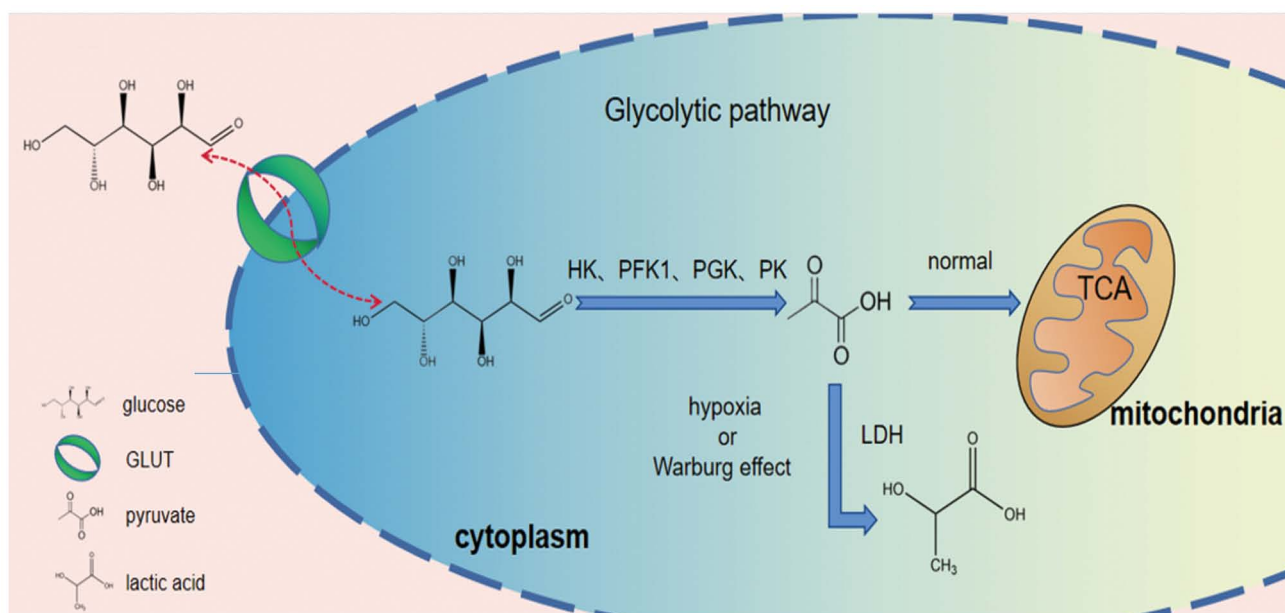


Figure 1. Glucose is transferred from extracellular to intracellular space under the mediation of GLUT. Subsequently, glucose is catalyzed by glycolytic enzymes in the cytoplasm to pyruvate, which is normally transferred to the mitochondria to enter the TCA. However, in hypoxic environments or when tumor cells exert the Warburg effect, pyruvate is catalyzed by LDH to produce lactate. This energy pathway change provides certain advantages for the occurrence and development of tumors. GLUT, glucose transporter; HK, hexokinase; PFK1, phosphofructokinase 1; PGK, phosphoglycerate kinase; PK, pyruvate kinase; LDH, lactate dehydrogenase; TCA, tricarboxylic acid cycle.

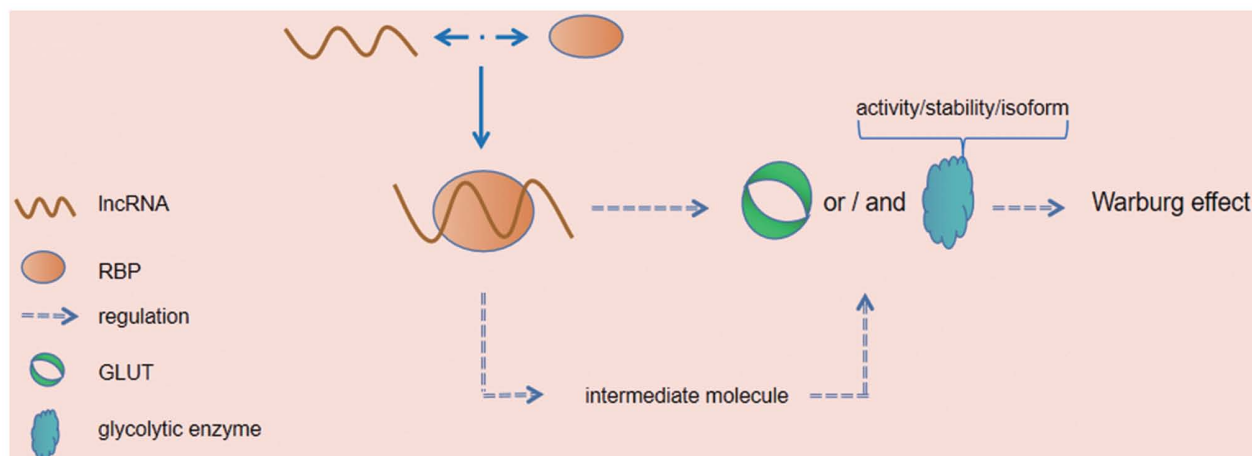


Figure 2. Following the binding of lncRNAs and RBPs, the interaction between them can affect GLUT and glycolytic enzymes, thereby regulating the Warburg effect. Among them, the activity, stability, and isoform changes of glycolytic enzymes are all involved in regulating the downstream Warburg effect. This regulatory mechanism can have a direct effect on GLUT and and/or glycolytic enzymes or indirectly regulate them by modulating their upstream molecules. lncRNA, long non-coding RNA; RBP, RNA binding protein; GLUT, glucose transporter.

PKM2 are the only two enzymes that control ATP production during aerobic glycolysis in cancer cells (40). The final conversion of pyruvate to lactate depends on lactate dehydrogenase A (LDHA). The abnormal expression and activation of LDHA are closely related to a variety of tumors, and the upregulation of LDHA promotes the malignant progression of tumors by increasing lactate production, accelerating glycolysis, regulating the production of reactive oxygen species, and regulating numerous cancer-related proteins (41).

**Glycolytic enzyme activity.** It is well known that phosphorylation is a main method of protein post-translational modification. By regulating the degree of protein phosphorylation, the activity of the protein can be significantly

affected, thereby participating in the regulation of intracellular biological effects. It has been reported that fibroblast growth factor receptor 1 (FGFR1) can directly phosphorylate LDHA, increasing the binding of LDHA to the substrate nicotinamide adenine dinucleotide dehydrogenase to enhance its enzymatic activity (42), and the intracellular kinase domain of FGFR1 can also phosphorylate PKM2, preventing F-1,6-BP binding to PKM2 and inhibiting active tetramer formation (43). In HCC, lncRNA HULC directly binds and interacts with LDHA and PKM2, and HULC functions as a linker molecule that enhances the binding of LDHA and PKM2 to FGFR1, and increases the phosphorylation levels of LDHA and PKM2 (44). The activity of LDHA is enhanced due to phosphorylation;

Table I. lncRNAs interact with RBP to regulate the reprogramming of glucose metabolism in tumor cells.

A, Regulation by direct action				
lncRNA	RBP	Target of action	Resulting effects on cancer	(Refs.)
CASC11	EIF4A3	Enhanced GLUT1 expression	Promotes HCC proliferation, migration and glucose metabolism	(19)
Gas6-AS1	E2F1	Inhibit GLUT1 transcription	Inhibition of LUAD progression and reprogramming of glucose metabolism	(20)
HULC	LDHA/PKM2	Enhanced LDHA/PKM2 phosphorylation	Promotes HCC progression and the Warburg effect	(44)
CASC8	FGFR1	Inhibits LDHA phosphorylation	Inhibits BCa cell growth and glycolysis	(45)
CRYBG3	LDHA	Enhance LDHA activity	Promotes LC progression and aerobic glycolysis	(46)
CASC9	IGF2BP2	Improve the stability of HK2mRNA	Promote GBM aerobic glycolysis	(52)
CDKN2B-AS1	IMP3	Improve the stability of HK2mRNA	Promotes glycolysis and tumor progression in cervical cancer cells	(53)
HCG22	HUR	Downregulation of PKM2 mRNA and protein levels	Inhibits BCa progression and glycolysis	(54)
LINC00470	FUS	Inhibits HK1 degradation	Promotes glycolysis in GBM cells and inhibits autophagy	(58)
KCNQ1OT1	HK2	Inhibits HK2 degradation	Promote the occurrence and aerobic glycolysis of CRC	(62)
AC020978	PKM2	Inhibits PKM2 degradation	Promotes NSCLC cell proliferation and glycolytic pathway	(63)
FEZF1AS1	PKM2	Inhibits PKM2 degradation	Promotes CRC proliferation, metastasis and glycolysis	(64)
PTCSC3	PGK1	Promotes PGK1 degradation	Inhibits PTC glycolysis and cell proliferation	(65)
LINC00926	STUB1/PGK1	Promotes PGK1 degradation	Inhibition of breast tumor growth, metastasis and Warburg effect	(67)
SNHG6	hnRNPA1	Increase PKM2/PKM1 ratio	Promote CRC aerobic glycolysis and tumor development	(70)
LNCAROD	SRSF3	Increase PKM2/PKM1 ratio	Increased aerobic glycolysis, malignant transformation and chemoresistance in HCC	(72)
SNHG14	Lin28A	Promote PKM2/GLUT1 expression	Promotes aerobic glycolysis and tumorigenesis in glioma	(73)
HNF4A-AS1	hnRNPU	Promote HK2/GLUT1 expression	Promotes NB progression and aerobic glycolysis	(77)
B, Regulation by indirect action				
lncRNA	RBP	Target of action	Resulting effects on cancer	(Refs.)
CASC9	HIF-1 $\alpha$	Increase the stability of HIF-1 $\alpha$	Promotes glycolysis and tumorigenesis in NPC cells	(89)
LINK-A	BRK/LRRK2	Activates HIF-1 $\alpha$ and prevents degradation	Promotes glycolytic reprogramming and tumorigenesis in TNBC	(90)
lincRNA-p21	VHL	Block HIF-1 $\alpha$ degradation	Promotes tumor growth and glycolysis	(91)
GHET1	VHL	Block HIF-1 $\alpha$ degradation	Promotes glycolysis and progression in ovarian cancer cells	(92)
EPB41L4A-AS1	HDAC2	Promote HIF-1 $\alpha$ degradation	Inhibits the Warburg effect of tumor cells	(93)
FILNC1	AUF1	Inhibit c-Myc transcription	Inhibits kidney cancer development and glycolysis	(101)

Table I. Continued.

B, Regulation by indirect action				
lncRNA	RBP	Target of action	Resulting effects on cancer	(Refs.)
LINC00261	IGF2BP1	Promotes c-Myc mRNA degradation	Inhibits glycolysis and proliferation in pancreatic cancer	(107)
FGF13-AS1	IGF2BP1	Promotes c-Myc mRNA degradation	Inhibits glycolysis and stemness in breast cancer cells	(78)
LINRIS	IGF2BP2	Prevent c-Myc mRNA degradation	Promotes CRC aerobic glycolysis and proliferation	(108)
UCA1	UPF1	Unknown	Promotes HCC growth and invasion and glycolysis	(109)
ZFAS1	IMP2	Unknown	Promotes CRC progression and glycolysis	(51)

CASC11, cancer susceptibility candidate 11; GLUT1, glucose transporter 1; HCC, hepatocellular carcinoma; E2F1, E2F transcription factor 1; LUAD, lung adenocarcinoma; HULC, highly upregulated in liver cancer; LDHA, lactate dehydrogenase A; PKM2, pyruvate kinase M2; CASC8, cancer susceptibility candidate 8; FGFR1, fibroblast growth factor receptor 1; BCa, bladder cancer; LC, lung cancer; CASC9, cancer susceptibility candidate 9; IGF2BP2 (IMP2), insulin-like growth factor 2 mRNA binding protein 2; HK2, hexokinase2; GBM, glioblastoma multiforme; IMP3, insulin-like growth factor 2 mRNA binding protein 3; HCG22, HLA complex group 22; HuR, human antigen R; FUS, fused in sarcoma; HK1, hexokinase1; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; FEZF1AS1, FEZF1 antisense RNA 1; PTCSC3, papillary thyroid cancer susceptibility candidate 3; PGK1, phosphoglycerate kinase 1; PTC, papillary thyroid carcinoma; STUB1, STIP1 homology and U-box containing protein 1; SNHG6, small nucleolar RNA host gene 6; hnRNPA1, heterogeneous nuclear ribonucleoprotein A1; PKM1, pyruvate kinase M1; SRSF3, serine-and arginine-rich splicing factor 3; HNF4A-AS1, HNF4A antisense RNA 1; hnRNPU, heterogeneous nuclear ribonucleoprotein U; NB, neuroblastoma; HIF-1 $\alpha$ , hypoxia-inducible factor-1 $\alpha$ ; NPC, nasopharyngeal carcinoma; LINK-A, long-intergenic non-coding RNA for kinase activation; BRK, tyrosine protein kinase 6; LRRK2, leucine-rich repeat kinase 2; TNBC, triple-negative breast cancer; VHL, von Hippel-Lindau; GHET1, gastric carcinoma high expressed transcript 1; HDAC2, histone deacetylase 2; FILNC1, Fox O-induced long non-coding RNA 1; AUF1, adenosine-uridine-rich binding factor 1; LINRIS, long intergenic non-coding RNA for IGF2BP2 stability; UCA1, urothelial cancer associated 1; UPF1, up-frameshift protein 1; ZFAS1, ZNF1 antisense RNA 1.

however, the activity of PKM2 is reduced due to the reduction of the tetrameric form, which ultimately contributes to the Warburg effect and cell proliferation (44). FGFR1 is a membrane receptor of the tyrosine kinase group and can also function as an RBP to interact with lncRNAs to regulate the Warburg effect (45). lncRNA CASC8 exerts a tumor suppressive effect by interacting with FGFR1. Mechanistically, when CASC8 binds to FGFR1, it inhibits the FGFR1-mediated phosphorylation of LDHA and attenuates the conversion of pyruvate to lactate, thereby inhibiting glycolysis and bladder cancer cell growth (45). In addition, it has been demonstrated that lncRNA CRYBG3 interacts with LDHA in lung cancer, and CRYBG3 specifically upregulates the activity of LDHA and promotes aerobic glycolysis and cell proliferation in tumor cells (46).

**Glycolytic enzyme stability.** In addition to changes in the activity of glycolytic enzymes, certain lncRNAs interact with RBPs to regulate the expression of glycolytic enzymes by affecting the mRNAs of the enzymes. N<sup>6</sup>-methyladenosine (M<sup>6</sup>A) is an mRNA modification that can regulate the metabolism of RNAs (mRNAs, miRNAs and lncRNAs) (47-49). Insulin-like growth factor 2 mRNA-binding protein (IGF2BP1/2/3, also known as IMP1/2/3) belongs to the K homology domain family and is one of the M<sup>6</sup>A readers involved in the occurrence and development of cancers by interacting with different RNAs (50,51). lncRNA CASC9 has a M<sup>6</sup>A site in glioblastoma multiforme (GBM), which is recognized by IGF2BP2 and enhances the stability of CASC9 (52).

CASC9 interacts with IGF2BP2 to form an IGF2BP2/CASC9 complex, which can bind to the M<sup>6</sup>A modification site of HK2, promote the expression of HK2 by improving the stability of HK2 mRNA, and ultimately promote the Warburg effect (52). The circular isoform of lncRNA CDKN2B-AS1, circCDKN2B-AS1, interacts with IMP3 (IGF2BP3) in cervical cancer, and the recruitment of IMP3 (IGF2BP3) to the 3'UTR of HK2 mRNA stabilizes HK2 mRNA and upregulates HK2 expression, promoting a malignant cell phenotype and aerobic glycolysis (53). In addition, lncRNA HCG22 binds and interacts with human antigen R (HUR) in bladder cancer; HUR can positively regulate the expression of polypyrimidine tract-binding protein 1 (PTBP1) (54), and studies have demonstrated that PTBP1 enhances the Warburg effect in certain types of cancer (55,56). When HCG22 is overexpressed, it promotes HUR protein degradation, thereby reducing the expression level of PTBP1 and blocking the Warburg effect mediated by PTBP1, and has been demonstrated that this is achieved by downregulating the mRNA and protein levels of PKM2 (54).

In addition to affecting the state of its mRNA, the stable expression of glycolytic enzymes is also the key to whether or not they will be degraded. It has been reported that >80% of protein degradation is related to the ubiquitin-proteasome pathway (57). For HK, the lncRNA LINC00470 activates protein kinase B (AKT) after interacting with fused in sarcoma protein in GBM (58), and the serine/threonine kinase AKT is a well-established regulator of glucose metabolism

that stimulates aerobic glycolysis in tumor cells (59-61). These three proteins work together to form a ternary complex. AKT has an enhanced activity due to its increased phosphorylation, and high levels of phosphorylated AKT can inhibit HK1 ubiquitination and attenuate the degradation rate of HK1 protein, thereby affecting the progress of glycolysis (58). In addition, lncRNA KCNQ1OT1 directly binds and interacts with HK2, inhibits the ubiquitination and subsequent degradation of HK2 through the proteasome pathway, and increases the stability of HK2, thereby promoting aerobic glycolysis and cell proliferation in colorectal cancer (CRC) (62). For PKM2, lncRNA AC020978 in non-small cell lung cancer and lncRNA FEZF1-AS1 in CRC both promote tumor progression and aerobic glycolysis, both of which directly bind to PKM2 in mechanism and maintain the stability of PKM2 protein by inhibiting ubiquitin-mediated proteasomal degradation (63,64). The role of PGK1 enzymes has been investigated in papillary thyroid carcinoma (PTC), where the expression of the lncRNA PTCSC3, a tumor suppressor, was found to be significantly downregulated. It was experimentally verified that PTCSC3 directly binds to PGK1, inhibits aerobic glycolysis, and inhibits tumor progression by promoting ubiquitin-mediated degradation of PGK1 (65). Additionally, the STIP1 homology and U-box containing protein 1 (STUB1) has been reported to be an E3 ubiquitin ligase that regulates ubiquitination of multiple substrates (66). In breast cancer cells, STUB1 and PGK1 function together as RBPs to specifically interact with the lncRNA LINC00926, resulting in an enhanced ability of STUB1 to mediate PGK1 ubiquitination, thereby reducing PGK1 expression. LINC00926 inhibits breast tumor growth and metastasis by inhibiting the PGK1-mediated Warburg effect and induces a switch in glucose metabolism from glycolysis to mitochondrial respiration (67).

*Glycolytic enzyme isoforms.* There are four isoforms of PK, of which PKR and PKL are expressed from the same gene under the control of two different promoters, while PKM1 and PKM2 are generated by the alternative splicing of the PKM gene transcript (68). PKM2 is highly upregulated in cancer cells, and it has been demonstrated that replacing PKM2 with PKM1 can markedly reduce lactate production in tumor cells and the overall tumor size, suggesting that the selection of PKM1 or PKM2 is directly related to the metabolic phenotype of the tumor (69).

Heterogeneous nuclear ribonucleoprotein (hnRNP) is one of the most crucial and classical regulators of alternative splicing. lncRNA SNHG6 is highly expressed in CRC, and it has been experimentally demonstrated that SNHG6 can interact with hnRNPA1, specifically target the 3'UTR of PKM pre-mRNA, and induce hnRNPA1-specific splicing of PKM pre-mRNA, leading to an increased ratio of PKM2/PKM1, which in turn enhances aerobic glycolysis in CRC cells and promotes tumor development (70). In addition, Ser/Arg-rich splicing factor 3 (SRSF3), known as an alternative splicing regulator, functions as an RBP in various cancer types to play oncogenic roles (71). SRSF3 has been reported to be a PKM splicer that induces the conversion of PKM from PKM1 to PKM2; it induces the conversion of PKM to PKM2 after directly binding to lncRNA LNCAROD in HCC, enhancing aerobic glycolysis, tumorigenesis and chemoresistance in HCC (72).

*Regulation of transporters and enzymes simultaneously.* In the process of lncRNAs binding to RBPs to regulate the tumor Warburg effect, certain studies have found that GLUT and glycolytic enzymes can be affected simultaneously. lncRNA SNHG14 interacts with RBP Lin28A with an enhanced stability in glioma cells. Stable SNHG14 promotes the degradation of downstream interferon regulatory factor 6 (IRF6) mRNA through the STAU1-mediated degradation pathway and inhibits the expression of IRF6 in cells and tissues, thereby disabling the effect of IRF6, which targets the GLUT1 and PKM2 promoters to repress their expression, and ultimately promoting aerobic glycolysis and cell proliferation in gliomas (73). Among these, IRF6, as a tumor suppressor, has the functions of regulating innate immunity, cell cycle arrest and tumor biological behavior (74-76). Additionally, hepatocyte nuclear factor 4 alpha (HNF4A) was identified in neuroblastoma (NB) as a transcription factor that promotes the expression of the glycolytic genes SLC2A1 (GLUT1) and HK2 (77). However, it was found that the expression of HNF4A in NB was regulated by the transcription factor, CCCTC-binding factor (CTCF). Mechanistically, lncRNA HNF4A-AS1 interacts with hnRNPU to promote hnRNPU-mediated CTCF transactivation, and CTCF then increases HNF4A transcription through epigenetic regulation and promotes the Warburg effect and tumor progression through the HNF4A-AS1/hnRNPU/CTCF axis (77).

### **3. lncRNAs interact with RBPs to regulate the reprogramming of glucose metabolism in tumor cells through indirect action**

*Regulation of upstream molecules.* In summary, the abnormal expression of GLUT and glycolytic enzymes can directly regulate the Warburg effect in tumor cells. However, there is also the indirect regulation of the Warburg effect by affecting the upstream molecules targeting GLUT and glycolytic enzymes. This chapter focuses on hypoxia inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) and c-Myc due to their central regulatory roles in cancer cell glycolysis (78).

Due to the rapid proliferation and expansion of cancer cells, there is a phenomenon of hypoxia in the core of tumor tissue, and this abnormal change in the microenvironment will cause continuous metabolic stress on tumor cells. HIF-1 $\alpha$  is a transcription factor that is active under specific hypoxic conditions and is a key molecule for cells to adapt to hypoxic conditions (79). It is hydroxylated at proline residues by prolyl hydroxylase under normoxic conditions, and hydroxylated HIF-1 $\alpha$  is recognized and bound by von Hippel-Lindau (VHL) proteins that function as ubiquitin E3 ligases, followed by rapid degradation via the ubiquitin-proteasome pathway (80-83). However, HIF-1 $\alpha$  exhibits an increased stability in hypoxia and binds to the hypoxia response element of target gene promoters, leading to the transcription of related genes involved in overcoming hypoxia effects (32). According to previous research, HIF-1 $\alpha$  is mainly involved in the regulation of the Warburg effect in the following aspects. First, HIF-1 $\alpha$  can promote the transcription of GLUT1, which promotes glycolysis by enhancing the uptake of glucose by tumor cells (84). Second, HIF-1 $\alpha$  can control the transcription of several glycolytic enzymes, such as HK2, PFK1, PKM2, LDHA, etc., by upregulating the

expression of these genes, thus further increasing the level of glycolysis (85,86). Finally, HIF-1 $\alpha$  can promote the expression of pyruvate dehydrogenase kinase (PDK1) and inhibit pyruvic dehydrogenase (PDH) activity, leading to the conversion of pyruvate to lactate and inhibiting the TCA (87,88). According to previous research, lncRNA CASC9 binds to HIF-1 $\alpha$  as an upstream activator of HIF-1 $\alpha$  in nasopharyngeal carcinoma, enhancing the stability of HIF-1 $\alpha$  and reprogramming cellular glucose metabolism (89). lncRNA LINK-A directly interacts with tyrosine protein kinase 6 (also known as breast tumor kinase) and leucine-rich repeat kinase 2 in triple-negative breast cancer, which activates HIF-1 $\alpha$  and prevents its degradation under normoxic conditions, promoting the enhanced Warburg effect (90). In addition, lncRNA lincRNA-p21 and lncRNA GHET1 both block VHL-mediated HIF-1 $\alpha$  degradation by interacting with VHL protein in tumors, thereby improving the protein stability and protein level of HIF-1 $\alpha$ , and accelerating aerobic glycolysis (91,92). The expression of VHL is also regulated by some indirect mechanisms. It has been reported that lncRNA EPB41L4A-AS1 is a repressor of the Warburg effect and interacts with histone deacetylase 2 (HDAC2). In a previous study, following the knockdown of EPB41L4A-AS1, it was found that the occupancy of HDAC2 on the VHL promoter was increased; histone modification then reduced the expression of VHL and finally activated the HIF-1 $\alpha$  pathway to promote glycolysis in tumor cells (93).

c-Myc is the most common oncogene in human carcinogenesis and is involved in the regulation of the cell cycle, cell survival, proliferation and metabolic reprogramming (94). It binds to almost all active promoters and most enhancers, thereby regulating the expression of key genes in the process of cell growth (95-97). The regulatory mechanisms of c-Myc in the Warburg effect are similar to those of HIF-1 $\alpha$ . Studies have indicated that c-Myc can promote the expression of GLUT1, HK2, PKM2 and LDHA, thereby increasing the glycolytic flux (87,98,99), increasing the cellular uptake of glucose and the production of pyruvate and lactate. c-Myc can also synergistically activate PDK1 with HIF-1 $\alpha$ , thereby downregulating PDH and inhibiting the aerobic oxidation of pyruvate, promoting lactate production, and increasing the acidity of the extracellular environment (100). It has been demonstrated that lncRNA FILNC1 is specifically expressed in the kidneys and that FILNC1 interacts with AU-rich elements/poly(U)-binding/degradation factor 1 (AUF1) during energy stress (101). AUF1 has been reported to bind to (A+U)-rich elements within the 3'UTR of c-Myc mRNA and promote its translation without affecting c-Myc mRNA levels (102). FILNC1 reduces c-Myc protein levels by sequestering AUF1 from binding to the c-Myc 3'-UTR; however, this regulatory circuit is dysregulated in renal cancer with a reduced FILNC1 expression (101). Additionally, IGF2BP1/2/3 all physically prevent the degradation of c-Myc mRNA by binding to a consensus sequence containing the 'GGAC' M<sup>6</sup>A core motif (103). lncRNA LINC00261, a widely reported tumor suppressor (104-106), interacts with IGF2BP1 in pancreatic cancer and attenuates the c-Myc-mediated Warburg effect by regulating c-Myc mRNA stability (107). Similarly, the interaction of lncRNA FGF13-AS1 with IGF2BP1 in breast cancer shortens the half-life of c-Myc mRNA and ultimately impairs c-Myc-associated glycolysis to inhibit tumor progression (78).

lncRNA LINRIS and IGF2BP2 bind and interact in CRC to ensure the stabilization of c-Myc mRNA by preventing the degradation of IGF2BP2, thereby maintaining the c-Myc-mediated Warburg effect and cell proliferation (108).

*Unknown target regulatory mechanisms.* Among studies on the regulation of glucose metabolism reprogramming following the binding of lncRNAs to RBPs, some did not involve a clear target for regulating the Warburg effect. Rather, changes in glucose consumption, extracellular acidification rates, and lactate production were experimentally demonstrated to explain their effects on the Warburg effect. In HCC tissues, lncRNA UCA1 binds to the tumor suppressor Up-frameshift protein 1 (UPF1), and their expression is inversely correlated. The knockdown of UPF1 has been found to increase the rate of glucose consumption and lactate production (109). In addition, it has been reported that the Obg-like ATPase 1 (OLA1) is an ATP hydrolase that binds to ATP through an amino acid site (110), which plays a crucial role in the production of lactate in tumor cells (111). The stability of lncRNA ZFAS1 is improved after binding to IGF2BP2 in CRC cells, and the binding of stable ZFAS1 to the OBG-type functional domain of OLA1 enhances its ATP hydrolysis ability, thereby promoting the accumulation of lactate and the release of ATP synthesis raw materials, activating the Warburg effect (51).

#### 4. Conclusions and future perspectives

Glucose metabolic reprogramming is one of the recognized metabolic features of tumor cells, and enhanced glycolysis produces an acidic and hypoxic microenvironment that promotes tumorigenesis, invasion and metastasis. lncRNAs interact with RBPs in a variety of tumor cells, directly or indirectly affecting the Warburg effect by regulating GLUTs, glycolytic enzymes, or their upstream molecules. However, there are still a number of studies that have not yet clearly defined the targets that regulate glycolysis in tumor cells, and further research is still required to elucidate the underlying molecular mechanisms. Interfering with the Warburg effect of tumor cells by affecting the expression of lncRNAs and RBPs or inhibiting GLUTs and glycolytic enzymes can cut off the energy supply, thereby interfering with tumor progression. This provides a potential novel direction and strategy for the targeted therapy of tumors. In the tumor glucose metabolism pathway, there are numerous different molecular targets to choose from to inhibit tumor growth and progression, which may contribute to the advancement of clinical treatment of patients and the improvement of prognosis.

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## Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

## Authors' contributions

WW and KW conceived the review. WW was involved in the collection of references. WW wrote the manuscript and constructed the figures. WW and KW checked and revised the manuscript. WW was responsible for the organization, revision and submission of this manuscript. Both authors have read and approved the final manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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