Long noncoding RNAs, glucose metabolism and cancer (Review)

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Abstract. Cancer is a serious and potentially life-threatening disease, which, despite numerous advances over several decades, remains a challenge to treat that challenging to detect at an early stage or treat during the later stages. Long noncoding RNAs are >200 nucleotides long and do not possess protein-coding capacity, instead regulating cellular processes, such as proliferation, differentiation, maturation, apoptosis, metastasis, and sugar metabolism. Several studies have shown the role of lncRNAs and glucose metabolism in regulating several key glycolytic enzymes and the activity of multiple functional signaling pathways during tumor progression. Thus, it is possible to further learn about the effects of lncRNA and glycolytic metabolism on tumor diagnosis, treatment, and prognosis through a thorough investigation of the lncRNA expression profiles and glycolytic metabolism in tumors. This may provide a novel strategy for improving the management of several types of cancer.

Contents

1. Introduction

Long noncoding RNAs (lncRNAs), sometimes known as competitive endogenous RNA (ceRNA), are a class of noncoding RNAs that are >200 nucleotides in length, which are involved in multiple cellular processes, such as proliferation, differentiation, maturation, apoptosis, metastasis, and metabolism (1-3). By targeting complementary miRNAs, ceRNAs can downregulate miRNA expression, indirectly regulating the expression of the downstream mRNA and thus affecting the behavior of a tumor cell (4). lncRNAs can bind to DNA, RNA, and proteins to form complexes that regulate transcription (5). A diseased state is ultimately brought on via the regulation of gene expression via various mechanisms, including mRNA stability and translation (6-8). It has been shown that lncRNAs can be categorized into different classes, which modulate tumor activity through differing functions. For example, they act as molecular sponges for miRNAs (9), modifiers and decoys for ribosomal proteins or ribonucleic acids (10), catalysts for gene transcription (11), gene methylation (12), protein kinase phosphorylation (13), and stabilizers of protein expression (14). lncRNAs can also act as coactivators of signaling factors as agonists. Additionally, they may alter the formation of tumors by sensitizing or desensitizing the cancerous cells to chemotherapeutic drugs. For example, the lncRNA LINC02525, which acts as a modifier of ribosomal proteins, can function as an oncogene by interacting with the ribosomal protein RPL35 to activate the translation of E2F1 and subsequently enhance the transcription of the GTPase-activating protein DEPDC1B to regulate the biological activity of neuroblastoma (NB) cells (15). Additionally, lincRNA-p21 acts as a gene transcription catalyst by mediating the binding of hnRNPK to promote transcription of its neighboring gene, cyclin-dependent kinase inhibitor 1A (*CDKN1A*), which encodes p21, and mediates the binding of hnRNPK to it, negatively regulating mRNA translation (10). lncRNAs can influence the transcription of genes on several chromosomes and can also be used as a decoy to trigger protein and RNA regulation (16). LINC00184 increases protein kinase phosphorylation and gene methylation, which increases the level of glycolysis in esophageal cancer (EC) cells by promoting *PTEN* methylation and *AKT* phosphorylation (17). Through the LINRIS/*IGF2BP2*/v-Myc avian myelocytomatosis viral oncogene homolog (*c-Myc*) axis, the lncRNA LINRIS can stabilize protein expression, prevent *IGF2BP2* degradation, and upregulate *Myc* expression to maintain glycolysis in colorectal cancer (CRC) cells (12). It was found that the *SNP rs11672691* risk allele at the regulatory region 19q13 locus upregulated the expression of transcription factors NK3 homeobox 1 (*NKX3.1*), Yin-Yang 1 (*YY1*), PCAT19-long through promoter-enhancer switching bifunctional regulatory elements in the SNP region, increased the

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expression of HNRNPAB-PCAT19-long ribonucleoprotein complex and cell cycle gene expression (18). Increased levels of the transcription factor homeobox A2 (*HOXA2*) and the carcinoembryonic antigen-related cell adhesion molecule 21 (*CEACAM21*) are also brought on by prostate cancer-associated transcript 19 (PCAT19) upregulation, which together promote prostate cancer (PCa) invasion (13,18). As a desensitizer of tumor-resistant cells, lncRNA differentiation antagonizing non-protein coding RNA (DANCR) exerts a sponging effect through the miR-125b-5p/hexokinase (HK)2 axis to down-regulate miR-124b-5p expression and thus enhances HK2 activity, desensitizing cisplatin-resistant CRC cells, while silencing DANCR exhibits the opposite effect, decreasing the resistance of CRC cells to cisplatin (9). LINC00504 functions as a coactivator of *c-Myc* and stimulates CRC glucose metabolism levels by increasing the recruitment of *c-Myc* to chromatin sites, which is how chromatin modifiers are used to modulate gene transcription (11). lncRNAs can regulate tumor apoptosis by affecting chromosomal gene transcription, post-transcription and the regulation of epigenetic mechanisms such as gene methylation, which results in lncRNAs acting as tumor suppressors or oncogenes, which provides new potential targets for improving tumor prognosis and metastasis (19).

The three primary metabolic pathways are glycolysis, pentose phosphate, and oxidative phosphorylation, of which, glycolysis is highly active in tumor cells (20). Otto Warburg, a German scientist, discovered the Warburg effect in the 1950s, which states that when oxygen levels are adequate, tumor cells do not undergo oxidative phosphorylation like normal cells but instead produce the required energy by aerobic glycolysis (21). A complex process of glucose metabolism in neoplastic cells contributes to the dysregulated lncRNA expression profiles in neoplasms. Regulation via lncRNAs can alter gene transcription levels, protein synthesis, and translation rates, affecting glucose metabolism in tumor cells. Several studies have been conducted to assess the specific molecular mechanisms of lncRNAs in tumor glucose metabolism. In these studies, it was found that a single lncRNA can exert a regulatory role in several types of cancer, often have differing effects. For example, potassium voltage-gated channel subfamily Q member 1 opposite strand/antisense transcript 1 (KCNQ1OT1) can promote the glycolysis of CRC cells through HK2 (22); in contrast, it can also compete with miR-34c-5p to increase aldolase A (ALDOA) activity and glycolysis levels in osteosarcoma (OS) cells (23). Similarly, LINC00504 increases glycolysis in ovarian cancer (OC) (24) and CRC (11) by increasing the activity of the glycolytic enzymes HK2, pyruvate dehydrogenase kinase 1 (PDK1), pyruvate kinase 2 (PKM2), and the expression levels of *c-Myc* in the corresponding tumor cells. In pituitary tumors (PT), urothelial cancer associated 1 (UCA1) accelerates HK2 and lactate dehydrogenase A (LDHA) activation to increase glycolysis (25). At the same time, in cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC) (26), UCA1 and HK2 expression are negatively correlated. It was found that several lncRNAs can regulate a single gene to influence tumor progression. *MYC* genes have a significant impact on the regulation of transcription. LncRNA GLCC1 (27) and LINC00504 (11) can regulate *c-Myc* to promote glycolysis of tumor cells and accelerate tumor growth, whereas LINC00261 (28) is negatively correlated with *c-Myc*. With MIR17HG being significantly upregulated in CRC (29) while acting as a tumor growth suppressor in OC (30), the effect of lncRNA expression varies in different tumors. As shown in Fig. 1, it was found that lncRNAs, including protein tyrosine phosphatase receptor type G antisense RNA 1 (PTPRG-AS1) (31), H19 (32), MIR210 host gene (MIR210HG) (33), MIR17HG (29), LINC00243 (34), and LINC00346 (35), promote the growth of tumor cells, altering the expression of key gluconeogenesis enzymes through sponging of miRNAs. Additionally, several signaling molecules are regulated by lncRNAs, such as transmembrane protein 161B antisense RNA 1 (TMEM161B-AS1) (36), high expression in hepatocellular carcinoma (HEIH) (37), lncENST (38), and LINC00261 (28), that can affect glycolysis and tumor cell activity (Fig. 2). The effects of lncRNAs and glycometabolism in cancer are summarized in this review.

2. The role of lncRNA and glycometabolism in digestive tract tumors

The majority of malignant tumors occur in the digestive system, which includes the esophagus, the stomach, the liver, the pancreas, and the colon (39). Their characteristics of slow diagnosis, challenging treatment, poor prognosis, and high mortality rates have become significant clinical issues that must be resolved. Numerous studies have shown that lncRNAs can target key enzymes and various signaling factors that affect glycolysis and are crucial for regulating digestive system tumor expression.

The role of lncRNA and glucose metabolism in EC. EC is a common, aggressive, malignant tumor with a poor prognosis worldwide. An ever-increasing number lncRNAs are being reported to be involved in the progression of EC. However, more research is required on lncRNAs and their potential molecular mechanisms for regulating EC glucose metabolism.

lncRNA and key glycolytic enzymes regulate EC glucose metabolism. A recent study found that PTPRG-AS1 upregulated PDK1 expression through a PTPRG-AS1/miR-599/PDK1 axis via sponging miR-599 (31), thereby promoting EC cell proliferation, migration, and glycolysis. The lncRNA actin γ 1 pseudogene (AGPG) is a novel stimulator of glycolysis and tumorigenesis. It regulates 6-phosphofructose-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3), negatively regulated by the P53 oncogene to enhance sugar metabolism and promote the progression of the cell cycle. Future treatments for EC may be tailored using AGPG, which targets an AGPG/P53/PFKFB3 axis (40).

lncRNA and signal molecules regulate EC glucose metabolism. It was found that LINC00184 could promote *PTEN* methylation and *AKT* phosphorylation by regulating the *PTEN/Akt* axis, subsequently promoting glycolysis and oxidative phosphorylation of mitochondria from EC cells (17). Upregulated expression of TMEM161b-AS1 improved a patient's prognosis. The TMEM161B-AS1/miR-23a-3p/hypoxia-inducible factor 1 subunit α inhibitor (*HIF1AN*) signaling axis offers a new alternative direction for the targeted treatment of ECs. It was shown that miR-23a-3p uptake by TMEM161B-AS1 was to enhance the expression of *HIF1AN* by inhibiting HK2, phosphofructokinase isoform (PFKM), LDHA, and *HIF1A* thereby attenuating EC reproduction, invasion, and glycolysis (36).

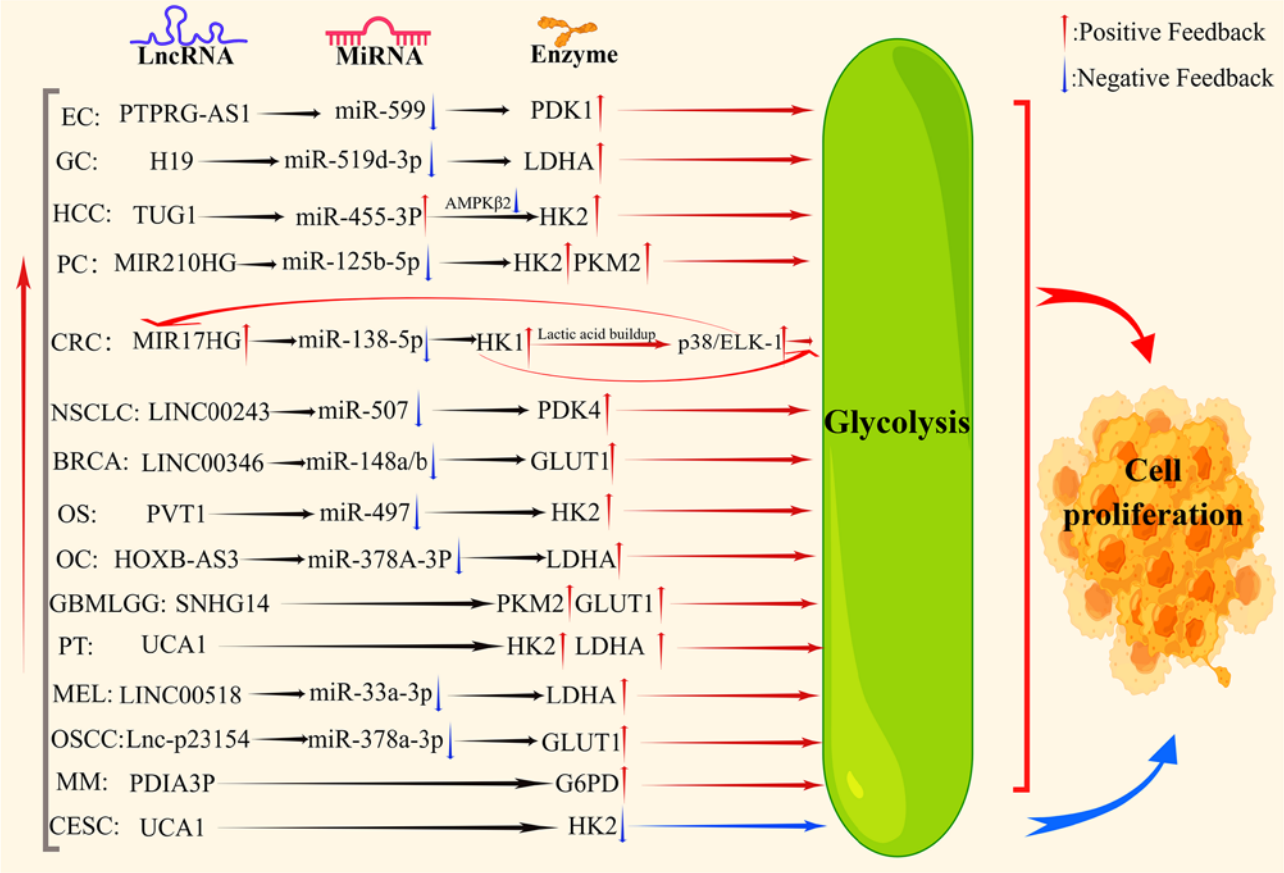

Figure 1. Schematic representation long noncoding RNA-mediated regulation of tumor glycolysis via enzymes. PTPRG-AS1, protein tyrosine phosphatase receptor type G antisense RNA 1; PDK1, pyruvate dehydrogenase kinase 1; H19, herein 19; LDHA, lactate dehydrogenase A; TUG1, taurine upregulated 1; HK2, hexokinase 2; PKM2, pyruvate kinase 2; GLUT1, glucose transporter type 1; PVT1, plasmacytoma transformation migration gene 1; HOXB-AS3, homeobox B antisense RNA 3; SNHG14, small nucleolar RNA host gene 14; UCA1, urothelial cancer associated 1; PDIA3P, protein disulfide isomerase family A member 3 pseudogene 1; G6PD, Glucose-6-phosphate dehydrogenase; EC, esophagus cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; PC, pancreatic cancer; CRC, colorectal cancer; NSCLC, Non-small cell lung cancer; BRCA, invasive breast carcinoma; OS, osteosarcoma; OC, ovarian cancer; GBMLGG, glioma; PT, pituitary tumor; MEL, melanoma; OSCC, oral squamous cell carcinoma; MM, multiple myeloma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma.

The role of lncRNA and glucose metabolism in gastric cancer (GC). GC is ranked the fifth most common type of cancer worldwide and the third leading cause of death in patients with high cancer risk. Most patients with GC have a poor survival rate, with a tendency for their 5-year survival rate to be <50% (41).

lncRNA and key glycolytic enzymes regulate GC glucose metabolism. Sun *et al* (32) found that lncRNA H19 promotes GC cell proliferation by regulating a miR-519d-3p/LDHA axis and promoting glycolysis. Pei *et al* (42) found that small nucleolar RNA host gene (SNHG) 7 was upregulated in GC cisplatin-resistant cells that were resistant to cisplatin, and that knocking down SNHG7 could successfully inhibit the expression of LDHA and sensitize cisplatin-resistant cells. miR-34a is negatively correlated with SNHG7, which can target LDHA and knockdown lncRNA to downregulate the expression of cisplatin-resistant GC cells and inhibit GC glucose metabolism. As a result, SNHG7 can reduce the sensitivity to cisplatin in GC cells through a miR-34a/LDHA axis. Similarly, Hu *et al* (43) showed that lncRNA HAGLR desensitizes GC5-Fu-resistant cells by inhibiting the miR-338-3p/LDHA-glycolytic axis via sponging. Qian *et al* (44) found that the lncRNA distal-less homeobox six antisense RNA 1 (DLX6-AS1) may target and precisely promote GC glycolysis through direct contact with miR-4290 and PDK1, enhancing its malignant biological activity. Deng *et al* (45) showed that LINC00242 could regulate the miR-1-3P/Glucose-6-phosphate dehydrogenase (G6PD) axis and promote the glycolytic effect of GC. Recent studies have found that the expression of lncRNA VAL was significantly higher in GC, indicating a poor prognosis. Biological function tests showed that VAL promoted the rapid progression of GC. The direct binding of VAL to PKM2 increases PKM2 kinase activity, promoting glycolysis in GC cells. Additionally, it can inhibit PKM2 from interacting with Parkin and inhibits the glycation of PKM2 (46). The lncRNA muscle layer antisense RNA 1(MSC-AS1) promotes GC cell proliferation and glycolysis by enhancing the expression of PFKFB3 (47).

lncRNA and signal molecules regulate GC glucose metabolism. Xu *et al* (48) reported that lncRNA heart and neural crest derivatives expressed two antisense RNA 1 (HAND2-AS1) inhibited the activity of a lncRNA HAND2-AS1/miR-184/*HIF3A* signaling axis in gastric adenocarcinoma (AGS) tissues and cells, which in turn down-regulated hypoxia-induced AGS glycolysis. Qian *et al* (49) found that LINC01391 inhibits GC invasion, migration,

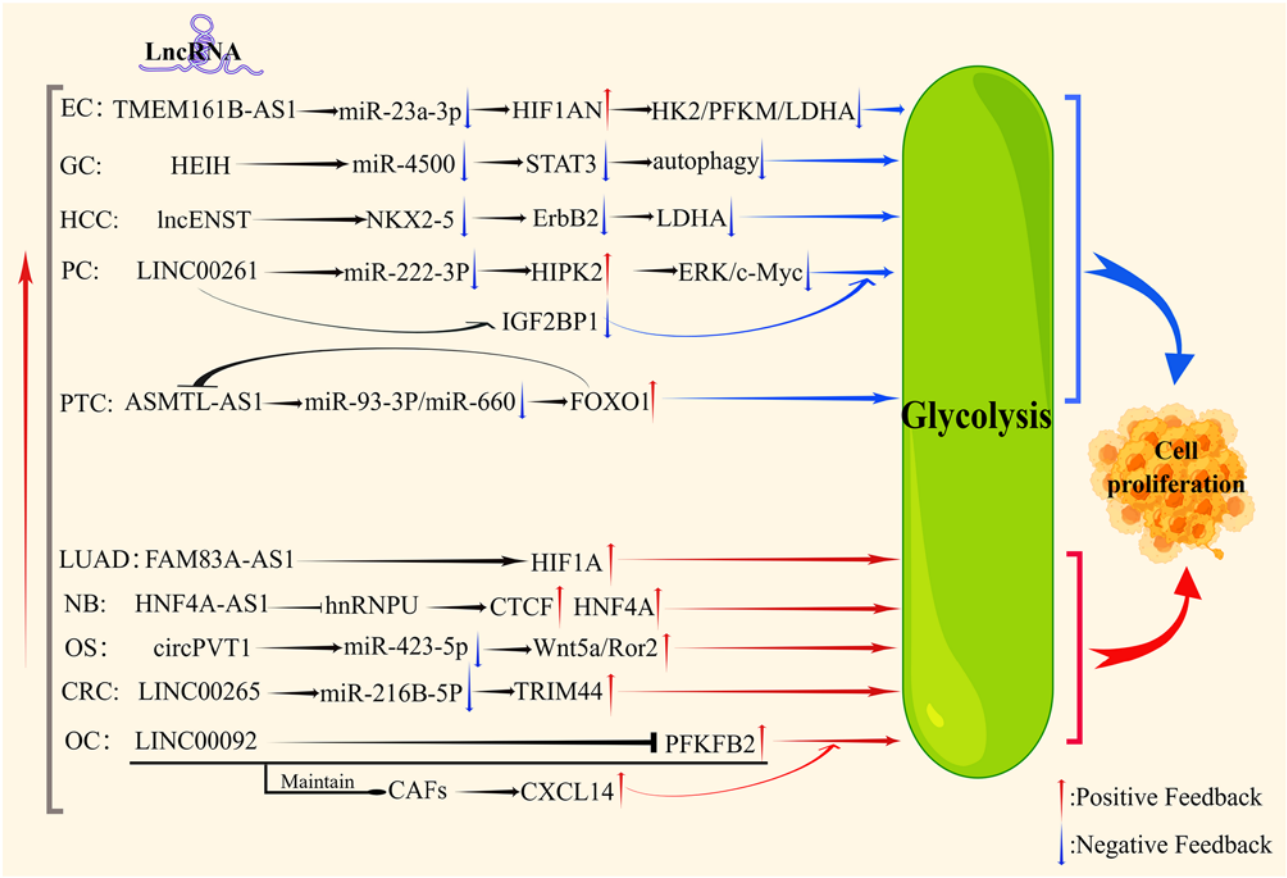

Figure 2. Schematic representation of long noncoding RNA-mediated regulation of tumor glycolysis via various signaling molecules. TMEM161B-AS1, transmembrane protein 161B antisense RNA 1; HIF1AN, hypoxia inducible factor 1 subunit alpha inhibitor; PFKM, phosphofructokinase isoform; HK2, hexokinase 2; LDHA, lactate dehydrogenase A; HEIH, high expression in hepatocellular carcinoma; STAT3, signal transducer and activator of transcription 3; Nkx2-5, homeobox protein Nkx-2.5; ERK, extracellular regulated protein kinases; HIPK2, homeodomain-interacting protein kinase 2; IGF2BP1, insulin-like growth factor 2 mRNA-binding proteins 1; ASMTL-AS1, acetylserotonin O-methyltransferase like antisense RNA 1; FOXO1, forkhead box O1; FAM83A-AS1, sequence similarity family 83 member A-antisense ribonucleic acid 1; HIF1A, hypoxia inducible factor 1 subunit alpha; HNF4A-AS1, hepatocyte nuclear factor 4 alpha antisense RNA 1; CTCF, CCCTC-binding factor; Wnt5a, Wnt family member 5A; Ror2, receptor tyrosine kinase like orphan receptor 2; TRIM44, *tripartite motif 44*; PFKFB2, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2; CAF, Cancer-associated fibroblasts; CXCL14, C-X-C motif chemokine 14; EC, esophagus cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; PC, pancreatic cancer; PTC, papillary thyroid carcinoma; LUAD, lung adenocarcinoma; NB, neuroblastoma; OS, osteosarcoma; CRC, colorectal cancer; OC, ovarian cancer.

and aerobic glycolysis by targeting a miR-12116/CKLF-like MARVEL transmembrane domain containing 2 (*CMTM2*) axis after downregulating miR-12116 expression and upregulating the effect of *CMTM2* expression. Yan *et al* (50) found that insulin growth factor 2 antisense (IGF2-AS) gene knockout could inhibit glycolysis and promote apoptosis of GC cells through its sponging effect. It was also revealed that the IGF2-AS absorbed miR-195 to inhibit the expression of cAMP-responsive element binding protein 1 (CREB1). Additionally, it has been found that miR-506 can target *STAT3* expression and inhibit GC cell occurrence and progression. LncRNA-nuclear paraspeckle assembly transcript 1 (NEAT1) and miR-506 are negatively correlated. Through the NEAT1/miR-506/*STAT3* axis, the endogenous NEAT1 sponge can promote the progression of GC cells and glucose metabolism after absorbing miR-506 (51). Similarly, miR-4500 absorption by HEIH sponges inhibits *STAT3*-mediated autophagy and promotes the progression of GC malignancy and glycolysis (37). Sun *et al* (52) showed that LINC00152 downregulates miR-139-5p in GC cells. Since miR-139-5P inhibits glycolysis in GC cells by suppressing the expression of AMP-activated α1 catalytic subunit (*PRKAA1*), LINC00152 promotes *PRKAA1* by upregulating miR-139-5P expression to accelerate glycolysis in GC cells via a sponging effect. Li *et al* (53) found that paeonol may inhibit the expression of LINC00665 and mitogen-activated protein kinase 1 (*MAPK1*) expression via the LINC00665/miR-665/*MAPK1* axis, preventing the proliferation, migration, invasion, and glycolysis of apatinib-resistant GC cells while promoting apoptosis.

The role of lncRNA and glucose metabolism in hepatocellular carcinoma (HCC). HCC is among the most prevalent malignancies worldwide, particularly in East Asia and Africa. The high prevalence of these diseases is caused by the lack of monitoring and treatment options (54). Below is a summary of recent research on the role of lncRNA in regulating aerobic glycolysis in HCC.

lncRNAs and key glycolytic enzymes regulate glucose metabolism in HCC. PKM2 was found to be essential, and E2F1-activated SNHG1 regulates the miR-326/PKM2 axis to promote PKM2 expression, glycolysis, and HCC cell proliferation (55). The orphan nuclear receptor Nur77 regulates

the Nur77-WFDC21P-PFKP/PKM2 axis by transcriptionally activating the lncRNA WAP four-disulfide core domain 21 pseudogenes (WFDC21P), which suppresses PFKP and PKM2 and impedes HCC glycolysis (56). LDHA and PKM2 are more readily bound to the fibroblast growth factor receptor type 1 by the lncRNA highly upregulated in liver cancer (HULC), resulting in their phosphorylation and facilitating glycolysis (57). By inhibiting forkhead box M1 (*FOXM1*) transactivation through *STAT3* and regulating glucose transporter Type 1 (GLUT1) by competing with *STAT3*, lncRNA SLC2A1-AS1 deactivates HCC cells by interfering with the *FOXM1*/GLUT1 axis and inhibits aerobic glycolysis in HCC cells (58). *AMPKβ2*, a downstream marker gene of miR-455-3P, was found to be downregulated to stimulate the enzymatic protein activity of HK2, and TUG1 was found to activate HK2 and promote cell proliferation, metastasis, and glycolysis by upregulating the expression of miR-455-3p through the TUG1/miR-455-3p/*AMPKβ2* axis (59). The inactivation of GLUT1 and HK2, caused by genistein-induced downregulation of *HIF1A*, promotes the apoptosis of HCC aerobic glycolytic cells and the antitumor effect of sorafenib on HCC cells (60). According to a study, aspirin can target the inhibition of aerobic glycolysis and PFKFB3 overexpression in HCC cells, sensitizing sorafenib-resistant HCC cells. The findings provide a strong theoretical basis for the targeted treatment of sorafenib-resistant HCC cells and the eradication of HCC cells with aspirin and sorafenib (61).

lncRNAs and signaling molecules regulate glucose metabolism in HCC. A previous study reported that the Warburg effect is mediated by human epidermal growth factor receptor (*ErbB*) 2, which activates heat shock factor 1 before upregulating LDHA (62). Its promoter may interact negatively with the transcription factor *Nkx2-5*. Inhibiting the Warburg effect in HCC cells, lncENST directly binds to and activates the transcription factor *Nkx2-5* through an *Nkx2-5*/*ErbB2* axis. This inhibits *ErbB2* gene transcription and downregulates *ErbB2* protein expression (38). HOX transcript antisense RNA (HOTAIR) regulates a miR-130a-3p/*HIF1A* axis on miR-130a-3p uptake, resulting in high expression of *HIF1A*, which inhibits glycolysis in hypoxia-induced HCC cells (63). Regulating GSK3β and Wnt/β catenin signaling and promoting HCC, SNHG5 promotors (64). In HCC cells, lncRNA cyclin-dependent kinase inhibitor 2B antisense RNA 1 (CDKN2B-AS1) sponge let-7c-5p promotes upregulation of nucleosomal assembly protein 1 like 1SS-mediated *PI3K*/*Akt*/*mTOR* axis-stimulated glycolysis (65). While NEAT1 is the primary transcriptional target of *mTOR*, it can also control the lncRNA transcriptome in HCC. When activated in cancer, *mTORC1* inhibits NEAT1_2 expression while facilitating mRNA splicing and the expression of key glycolytic enzymes, which promotes HCC glucose metabolism and cell proliferation (66). By controlling the *MAPK*/extracellular regulated protein kinases (*ERK*) pathway, hypoxia-inducible lncRNA neuropeptide S receptor 1 antisense RNA 1 was also found to promote the proliferation and glycolysis of HCC cells (67). The target gene of the lncRNA Fiveprime to Xist (FTX) is the peroxisome proliferator-activated receptor γ (*PPARγ*), and FTX functions downstream of PPAR. Through overexpression of the FTX/*PPARγ* axis, FTX promotes activation of the *PPARγ* pathway, which attenuates the expression of tumor necrosis factor-α (TNFα), leptin, and PDK1, regulating GLUT4, PDK1, and PFKL in HCC cells, and maintains increased glycolysis in HCC (68). Additionally, the progression of HCC may be aided by the regulation of Bcl-2-related protein A1 (*BCL2A1*) expression by the lncRNA POU3F3 adjacent noncoding transcript 1 (PANTR1) via sponging of miR-587 (69).

The role of lncRNAs and glucose metabolism in pancreatic cancer (PC). PC is a highly lethal malignancy that is often diagnosed in the first instance as advanced PC, and thus has a poor prognosis, with an overall 5-year survival rate of <6% (70,71). By 2030, PDAC is predicted to be the second leading cause of cancer-related death, and is refractory to most current treatment strategies (72). There are few functional targets identified for the management of PC and their underlying mechanisms remain to be determined. The following is a summary of the known findings.

lncRNAs and key glycolytic enzymes regulate PC glucose metabolism. The lncRNA MIR210HG was found to be upregulated in PC and is a key oncogenic regulator of PC invasiveness and glycolysis. Through the MIR210HG/miR-125b-5p/HK2/PKM2 axis, MIR210HG and miR-125b-5p bind competitively to target HK2/PKM2 expression, enhancing PC cell invasion and glycolysis (33).

lncRNAs and signaling molecules regulate PC glucose metabolism. According to recent studies, homeodomain-interacting protein kinase 2 (*HIPK2*) inhibits PC glycolysis through the *ERK*/*c-Myc* signaling pathway. At the same time, LINC00261 activates the *HIPK2*/*ERK* pathway through the sponging of miR-222-3P and blocking *IGF2BP1* from inhibiting *c-Myc*-mediated glycolysis, which inhibits PC cell proliferation (28). lncRNA-targeted regulation of PC drug resistance continues to be a significant clinical challenge. It has been found that the lncRNA (HIF1A-AS1) induces Y box-binding protein 1 (YB1) phosphorylation and translation activation of *HIF1A* through the HIF1A-AS1/*HIF1A* axis, desensitizing gemcitabine-resistant PC cells and promoting aerobic glycolysis, providing an efficient target for GEM therapy (73).

The role of lncRNA and glucose metabolism in CRC. CRC is one of the most prevalent cancers of the digestive system worldwide, the fourth most common form of cancer in the United States, after breast cancer, lung cancer, and PCa, and the second leading cause of cancer-related death, after lung cancer, in terms of cancer mortality worldwide (74,75). Meanwhile, in the 21st century, CRC is rising in the cancer spectrum and is in the top five of the most common cancers in China (76). Patients with CRC have a 5-year overall survival rate of ~64% (74). Several studies have shown that lncRNAs and glucose metabolism significantly impact colon cancer development, progression, and outcomes.

lncRNAs and key glycolytic enzymes regulate CRC glucose metabolism. The activity of key enzymes such as HK1 (29), HK2 (77), PKM1 (78), and PKM2 (14) are crucial for glucose metabolism in CRC cells. Poor survival is correlated with high MIR17HG expression. In CRC cells, MIR17HG as a ceRNA binds miR-138-5p to regulate the expression of HK1, resulting in glycolysis, aggressive cell behaviors, and CRC liver metastasis. The *p38*/*ELK-1* axis

is subsequently activated by lactic acid accumulated during glycolysis. The transcriptional expression of MIR17HG from CRC cells, thus, continuously enhances CRC progression (29). Additionally, HK1 can be promoted by the interaction between lncARSR and miR-34a-5p to increase the aerobic glycolysis of CRC (79). KCNQ1OT1 and HK2 expression are positively correlated. Overexpression of KCNQ1OT1 upregulates HK2 protein expression at the post-transcriptional level, which increases aerobic glycolysis and cell proliferation in CRC (22). Similarly, lncSLCC1 increases HK2 expression. The risk allele *SNP rs6695584* promotes lncSLCC1 expression by interacting with the transcription factor BATF and upregulated lncSLCC1 interacts with aryl hydrocarbon receptor to transcriptionally activate HK2 expression to promote CRC progression (77). Additionally, miR-125b-5p was targeted to regulate HK2 to inhibit CRC progression and was negatively correlated with lncRNA DANCR. Through competitive inhibition of the HK2 3'-UTR by a miR-125b-5p/HK2 axis, endogenous DANCR was targeted by miR-125b-5p, desensitizing cisplatin-resistant cells and thus increasing glycolysis (9). It was found that the lncRNA HOXB-AS3 encodes a 53-amino acid polypeptide that inhibits the production of PKM, which hnRNP A1 mediates, and thereby aerobic glucose metabolism in CRC (78). By binding to PKM2 and increasing protein stability, Fez family zinc finger protein 1 antisense ribonucleic acid 1 (FEZF1-AS1) promotes PK activity and lactate production. Additionally, *STAT3* expression is disrupted by down-regulated FEZF1-AS1, which has an impact on downstream proteins (14). lncRNAs have been shown to promote the progression of CRC by increasing the PKM2/PKM1 ratio. If SNHG6 is upregulated in CRC, SNHG6-induced hnRNPA1 specifically splices PKM mRNA, increasing the PKM2/PKM1 ratio and enhancing aerobic glycolysis in CRC cells (80). Similarly, miR-137 attenuates glycolysis in CRC cells. It sensitizes 5-FU/cisplatin-resistant cells by blocking PKM conversion from PKM1 to PKM2. However, miR-137 binding and inhibition by the lncRNA X-inactive-specific transcript (XIST) blocks PKM2 to PKM1 conversion through an XIST/miR-137/PKM axis, which increases the PKM2/PKM1 ratio and enhances glycolysis and chemotherapy resistance in CRC (81). It has been demonstrated that traditional Chinese medicines can regulate lncRNA and key glycolysis enzymes, exerting an antitumor effect. In millet bran, ferulic acid (FA) and p-coumaric acid (P-CA) have anti-cancer properties and can synergistically inhibit tumor growth. lncRNA 495810 positively regulates PKM2. A candidate way for nutritional intervention and treatment of CRC is provided by FA and P-CA, which inhibit lncRNA 495810 and PKM2 to block aerobic glycolysis in CRC (82).

lncRNAs and signaling molecules regulate CRC glucose metabolism. By regulating a *HIF1A*/pituitary tumor transformation 3 pseudogene (PTTG3P)/YES1 associated transcriptional regulator (*YAP1*) axis, the lncRNA PTTG3P has been found to increase macrophage proliferation, glycolysis, and M2 polarization (83). LINC00265 sponging inhibits miR-216B-5P, which in-turn promotes CRC glycolysis by increasing the expression of tripartite motif 44 (*TRIM44*) through regulation of a miR-216B-5P/*TRIM44* axis (84). Similarly, miR-20b-5p is sponged by collagen type IV α2 chain antisense RNA 1 (COL4A2-AS1) to increase HIF1A expression, promoting CRC cell proliferation and glycolysis (85). CRC cells cannot exist without *Myc* oncogene-mediated signaling pathways. For example, the lncRNA LINRIS stabilizes *IGF2BP2* to prevent *IGF2BP2* degradation, which can maintain *Myc*-mediated glycolysis through a LINRIS/*IGF2BP2*/*Myc* axis and support the *in vitro* and *in vivo* proliferation of CRC cells (12). Heat shock protein 90 (HSP90)-binding lncRNA GLCC1 stimulates aerobic glycolysis of CRC cells by stabilizing *c-Myc* protein through a GLCC1/*c-Myc*/LDHA axis and thus increasing the expression of LDHA (27). The c-Mycoactivator LINC00504 increases *c-Myc* recruitment to chromatin sites and increases *c-Myc* transcriptional activation to increase CRC glucose metabolism levels. LINC00504 functions in the pentose phosphate pathway (PPP), which produces nicotinamide adenine dinucleotide (NADPH) to induce redox reactions, increasing the supply of energy for cell growth, and increasing citrate levels. In addition to promoting glycolysis, LINC00504 also promotes G6PD activity. Expression of enzymes of the PPP, glucose absorption, glycolysis, and the tricarboxylic acid (TCA) cycle is promoted by LIN00504, which is a key gene regulator for enhancing glucose metabolism in CRC (11). RAD51-AS1 sponges miR-29b/c-3p to indirectly upregulate N-myc downstream-regulated gene 2 (*NDRG2*) expression, thus impeding CRC cell progression (86). It was also shown that sponging of miR-874-3P by MCF2L-AS1 increased the expression of *FOXM1* through a miR-874-3P/*FOXM1* axis, promoting CRC cell growth, invasion, and glycolysis (87). Additionally, through a miR-124/MyO6 axis and mir-188/TAB3 axis, respectively, HNF1A-AS1 and ZEB2-AS1 facilitate CRC cell migration, invasion, and glycolysis (88,89). A significant clinical issue in CRC is oxaliplatin (L-OHP) resistance. According to certain research, lncRNAs can encode proteins that subtly contribute to CRC resistance. The lncRNA-AP-encoded short peptide PEP-AP can decrease PPP activity, sensitize L-OHP-resistant CRC, and prevent the expression of transaldolase 1 (TALDO1). As a result, PEP-AP could be considered as a sensitizer for individualized treatment of L-OHP-resistant CRC (90).

3. The role of lncRNA and glucose metabolism in other tumors

lncRNAs are crucial for regulating glucose metabolism in several types of cancer, including thyroid cancer (TC), lung cancer (LC), breast invasive carcinoma (BRCa), NB, OS, CESC, OC, glioma, PT, melanoma, oral squamous cell carcinoma, and multiple myeloma, amongst others (25,91-98). Table I lists certain lncRNAs that regulate tumor glycolysis and their identified roles.

lncRNAs and key glycolytic enzymes regulate tumor glucose metabolism. It was found that hypoxia inhibited LINC00671 and *STAT3*, the latter of which is a transcription factor regulated by the *STAT3*/LINC00671/LDHA axis, downregulated the production of LDHA, and inhibited the glycolytic and malignant biological activities of TC (99). Non-small cell lung cancer (NSCLC) cells proliferate and undergo glycolysis due to binding and inhibition of miR-507 via LINC00243 through a LINC00243/miR-507/PDK4 axis (34). Additionally, m^6 A methyltransferase-like 3 (*METTL3*) may promote NSCLC

Table I. Regulation of tumor glycolytic-related lncRNAs.

First author, year	Cancer type	lncRNA	Repressed miRNA	Target enzymes involved in glucose metabolism	Potential value	Role	(Refs.)
Liu *et al*, 2020	Pituitary tumor	UCA1	-	HK2 and LDHA	-	Promotes glycolysis in pituitary cancer cells	(25)
Hong *et al*, 2021	Glioma cell	LINC01138	miR-375	-	-	Promotes aerobic glycolysis to enhance the biological activity of glioma cells.	(91)
Zhang *et al*, 2019	Glioblastoma	SNHG9	miR-199a-5p	-	Associated with low survival rates in patients with glioma	Promotes aerobic glycolysis and cell proliferation	(92)
Lu *et al*, 2020	Glioma cell	SNHG14	-	PKM2 and GLUT1	-	Promotes glycolysis in tumor cells	(93)
Liu *et al*, 2019	Glioma cell	LINC00689	miR-338-3p	PKM2	-	Promotes glycolysis in tumors	(94)
He *et al*, 2018	Glioma cells, Glioblastoma -associated stromal cells	UCA1	miR-182	PFKFB2	-	Promotes glycolysis and glioma cell invasion	(95)
Liu *et al*, 2021	Melanoma	LINC00518	miR-33a-3p	LDHA	Provides a potential way to improve treatment outcomes of melanoma radiotherapy	Promotes tumor glycolysis and reduces sensitivity to melanoma radiotherapy	(96)
Wang *et al*, 2018	Oral squamous cell carcinoma	Lnc-p23154	miR-378a-3p	GLUT1	-	Promotes the metastasis of tumor cells	(97)
Yang *et al*, 2018	Multiple myeloma	PDIA3P	-	G6PD	Potential therapeutic target	Promotes tumor cell growth and tolerance to drugs	(98)

UCA1, urothelial cancer associated 1; HK2, hexokinase 2; LDHA, lactate dehydrogenase A; SNHG, small nucleolar RNA host gene; PKM2, pyruvate kinase 2; GLUT1,glucose transporter type 1; PFKFB2, 6-phosphofructose-2-kinase/fructose-2,6-bisphosphatase 2; G6PD, Glucose-6-phosphate dehydrogenase; PDIA3P, protein disulfide isomerase family A member 3 pseudogene 1; lncRNA, long non-coding RNA; miRNA, microRNA.

progression and glucose metabolism by increasing the stability of ABHD11-AS1 (100). Through the LINC00346-miR-148a/b-GLUT1 axis, LINC00346 downregulates miR-148a/b, promoting GLUT1 expression and thus, glycolysis in BRCA cells (35). The expression of glycolysis-related enzymes is critical for the survival of OS cells. The lncRNA plasmacytoma transformation migration gene 1 (PVT1) promotes OS glycolysis and increases HK2 expression through the binding and inhibition of miR-497 through the miR-497/HK2 axis (101). Furthermore, TUG1 also promotes OS glycolysis by upregulating HK2 expression (102). ALDOA expression is upregulated in the KCNQ1OT1/miR-34c-5p/ALDOA axis due to competitive interactions between KCNQ1OT1 and miR-34c-5p, which promote OS progression and glucose metabolism (103). The study of CESC found that inhibiting the UCA1/HK2/glycolysis pathway by downregulating

HK2 expression decreased the levels of glycolysis in CESC, increasing the radiosensitivity of CESC cells (26). It was also discovered that HOXB-AS3 functions in OC as a ceRNA to bind and inhibit miR-378A-3P, promoting LDHA expression and enhancing glycolytic, proliferative, and metastatic activities in OC (104).

lncRNAs and signaling molecules regulate tumor glucose metabolism. It has been found that acetylserotonin O-methyltransferase like antisense RNA 1 (ASMTL-AS1) upregulates the expression of forkhead box O1 (*FOXO1*) and inhibits glycolysis in papillary thyroid carcinoma (PTC) through an ASMTL-AS1/miR-93-3P/miR-660/*FOXO1* axis. A positive feedback loop created by the recombination of *FOXO1* and ASMTL-AS1 can further inhibit the occurrence and progression of PTC (105). It was also shown that the lncRNA sequence similarity family 83 member A-antisense ribonucleic acid 1 (FAM83A-AS1) upregulated *HIF1A* expression through a *HIF1A*/glycolytic axis to accelerate the progression of lung adenocarcinoma (106). Hepatocyte nuclear factor 4 α antisense RNA 1 (HNF4A-AS1) binds to heterogeneous nuclear ribonucleoprotein U (hnRNPU) through an HNF4A-AS1/hnRNPU/CCCTC-binding factor (CTCF) axis, which transactivates CTCF upregulates HNF4A expression, and promotes aerobic glycolysis and NB cell invasion (107). To activate Wnt family member 5A (*Wnt5a*)/receptor tyrosine kinase-like orphan receptor 2 (*Ror2*) signaling and promote OS glycolysis and cell proliferation, circPVT1 binds and inhibits miR-423-5p through the circPVT1-miR-423-5p-*Wnt5a*/*Ror2* axis (108). It was found that LINC00092 and 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2 (PFKFB2) together promoted glycolysis in OC metastasis, which in turn maintained the characteristics of cancer-associated fibroblasts in the tumor microenvironment. In addition, the chemokine CXCL14 promoted OC metastasis *in vivo* and *in vitro*, forming a positive feedback loop that regulated the biological activity of OC (109). The HIPPO pathway regulates cell proliferation and cell invasion. LINC00857 upregulates the expression of the oncogene *YAPA1* through a LINC00857/miR-486-5p/*YAP1* axis, which binds to the miR-486-5p pathway, a pathway that inactivates the HIPPO pathway to enhance OC cell proliferation and glycolysis (110). Another study found that LINC00504 promoted the activation of glycolytic enzymes PDK1, PKM2, and HK2 by sponging miR-1244. This enhanced OC cell proliferation and aerobic glycolysis (24). RNA-binding signal transduction-associated protein 3 (KHDRBS3) can promote glycolysis through the gene claudin (*CLDN6*), which is associated with chemoresistance and a key player in several types of cancer. Studies have shown that MIR17HG can inhibit paclitaxel by downregulating the expression of KHDRBS3 and *CLDN6* by targeting the KHDRBS3/MIR17HG/*CLDN6* axis. Paclitaxel cell resistance and glycolysis are novel approaches to treating OC-resistant cells (30).

4. Conclusions and future perspectives

lncRNAs participate in transport, in the activity of key enzymes, in the regulation of miRNAs, in the regulation of various signaling pathways, and in the regulation of tumor energy metabolism, thus having a broad impact on the malignant properties of cancerous cells. Tumor occurrence and progression are highly correlated with glucose metabolism. Blocking glycolysis or the pentose phosphate pathway can effectively inhibit the proliferation of tumor cells and even result in their death. Therefore, glycolysis-related enzymes may be a novel therapeutic target. However, additional research is required to determine the underlying mechanism of lncRNA regulation of energy metabolism in different types of tumors. For example, it is unknown whether the identified transcription factors and their derived lncRNAs can target and coordinate the regulation of tumor progression. Further research is required to determine how different transcription factors, via lncRNAs, regulate tumor glucose metabolism directly, indirectly, cooperatively, or antagonistically and whether lncRNAs can establish a specific relationship to regulate the expression of tumors jointly. The mechanism of targeted and precise regulation of tumor drug resistance via the interaction between lncRNAs and drugs also needs to be studied. Further research is required to fully understand how different transcription factors regulate tumor expression in the microenvironment under both hypoxic and normoxic conditions. lncRNAs can act as sponges that bind to miRNAs to inhibit the regulatory effect of said miRNAs on their target mRNAs. The discovery of the ceRNA mechanism, which reduces the inhibitory effect of miRNAs on target genes, opens novel avenues for further investigation into the lncRNAs. This review may assist in understanding the molecular mechanisms of tumor energy metabolism regulation and offer a fresh perspective for future studies on tumor diagnosis and targeted therapy.

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Authors' contributions

XH contributed to drafting of the manuscript. ZZ and XC were involved in writing the paper and revising it critically for important intellectual content. XW reviewed and edited the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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