Involvement of lncRNAs in the regulation of aerobic glycolysis in hepatocellular carcinoma: Main functions, regulatory mechanisms and potential therapeutic implications (Review)

QIONGQING HUANG[1*], ZHENGUI LIANG[1*], QIQI HUANG[1*], XUEYU LI[2], JINGJING XIA[1], LINING HUANG[1], LIN BING HUANG[1] and CHAO OU[1]

[1]Department of Clinical Laboratory, Guangxi Medical University Cancer Hospital, Nanning, Guangxi 530021, P.R. China; [2]Experimental Research Department, Guangxi Medical University Cancer Hospital, Nanning, Guangxi 530021, P.R. China

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Abstract. Even under aerobic conditions, tumor cells can reprogram their metabolism to preferentially metabolize glucose into lactic acid. This abnormal metabolic pattern, known as the 'Warburg' effect or aerobic glycolysis, promotes cancer progression. Long non-coding RNAs (lncRNAs) are RNAs that are >200 nucleotides in length and do not have protein-coding capabilities. However, these RNAs play a key role in tumor development. There is increasing evidence to indicate that lncRNAs regulate glucose metabolism in tumor cells by affecting metabolic enzymes and some signaling pathways, thereby regulating the occurrence and progression of hepatocellular carcinoma (HCC). Therefore, it is crucial to understand which lncRNAs play a regulatory role in HCC glycolysis and to determine the related molecular mechanisms. The present review summarized and discussed the functions of lncRNAs, focusing on the regulatory mechanisms of lncRNAs in the process of glycolysis in HCC. In addition, the present review suggests the importance of lncRNAs as future therapeutic targets for antitumor cell metabolism.

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Correspondence to: Professor Chao Ou, Department of Clinical Laboratory, Guangxi Medical University Cancer Hospital, 71 Hedi Road, Nanning, Guangxi 530021, P.R. China
E-mail: ouchaogx@163.com

*Contributed equally

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1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide and the third most common cause of cancer-related mortality (1). The prognosis of patients with HCC remains unsatisfactory, despite the fact that various treatment strategies have been developed. HCC is a highly aggressive tumor. Frequent intrahepatic and distant metastases are the main reasons for the high recurrence rate and the low survival rate of patients with liver cancer following surgery (2). Therefore, in-depth studies on the developmental mechanisms of HCC are urgently required to identify safer and more effective therapeutic strategies for patients with HCC in order to prevent tumor recurrence and improve the survival rate of patients.

Normal cells rely on mitochondrial oxidative phosphorylation to provide energy for growth and differentiation under well-oxygenated conditions. In tumors and other proliferating or developing cells, even in the presence of oxygen and fully functioning mitochondria, the cells opt to undergo cellular metabolism and acquire an energy supply in the form of glycolysis, which leads to a marked increase in the rate of glucose uptake into the cells and promotes the production of large amounts of lactic acid. This phenomenon is known as the 'Warburg' effect or 'aerobic glycolysis' (3).

In glycolysis, when glucose is metabolized to lactate, only two ATPs are generated per glucose molecule, whereas the oxidative phosphorylation of a glucose molecule following complete oxidation can generate up to 36 ATPs for cellular energy supply, and cancer cells tend to favor glycolysis. This appears to be a 'disadvantageous' metabolic pattern, with the inefficient production of ATP. Indeed, the preference of tumors for glycolysis as their primary metabolic energy source represents an adaptive response to the

environmental growth constraints commonly encountered in cancer development. Firstly, aerobic glycolysis provides the free energy or co-factors (for example ATP, NADPH and NADH) required for sustained cancer cell proliferation (4). Secondly, glycolysis metabolizes one molecule of glucose 10-100-fold more rapidly than the complete oxidation of one molecule of glucose in the mitochondria. These two different strategies of metabolizing glucose produce comparable amounts of ATP in any given time period (5). Therefore, a plausible explanation is that glycolytic metabolism occurs more rapidly than oxidative phosphorylation (OXPHOS) and ATP production is rapid enough to compensate for the insufficient amount of ATP produced (6,7). Thirdly, using glycolytic metabolism, tumor cells escape oxidative stress and are protected from reactive oxygen species-induced damage (8). In fact, the liver is one of the largest metabolic organs and a center for gluconeogenesis. Aerobic glycolysis affects the progression of HCC, including the maintenance of cell proliferation, the induction of immune escape, invasion and metastasis, and the promotion of angiogenesis and tumor resistance (9,10).

RNA sequencing techniques and transcriptional profiling have demonstrated that although the human genome is universally transcribed, only ~2% of RNAs code for proteins (11,12). Even if they do not code for proteins, long non-coding RNAs (lncRNAs) are not functionless 'noise sequences'. lncRNAs can be involved in biological activities, including tumor growth, metastasis and metabolism (13-15).

In recent years, lncRNAs have been found to play a key role in the pathogenesis of cancers, including HCC. Understanding the novel regulatory roles of lncRNAs in glucose metabolism, particularly in HCC, could provide new insight into the underlying mechanisms of cancer onset and progression, which could ultimately lead to the identification of novel therapeutic targets. Therefore, in the present review, the major factors affecting the function of lncRNAs in HCC were briefly discussed and the mechanisms through which lncRNAs regulate HCC progression through glycolysis were summarized.

2. Overview of lncRNAs

High-throughput sequencing technologies and computing platforms have demonstrated that ~75% of the human genome can be transcribed into RNAs, of which 74% are encoded as non-protein coding RNAs (ncRNAs). Although not translated, ncRNAs play a regulatory role in the developmental and pathophysiological stages of human cells. According to the length of RNAs, ncRNAs can be mainly divided into small ncRNAs and lncRNAs. Among ncRNAs, those with >200 nucleotides are classified as lncRNAs. They are mostly transcribed by RNA polymerase II (pol II) and include various types of intergenic transcripts, enhancer RNAs and positive or antisense transcripts that overlap with other genes. lncRNAs can be classified according to four factors as follows: Genomic localization and influence on DNA sequence, functional mechanism and targeting mechanisms (16). lncRNAs have different subcellular localizations in cells, and the unique subcellular localization is closely related to the function of interacting molecules, post-transcriptional or co-transcriptional regulatory modifications and external stimuli.

3. Major factors affecting the function of lncRNAs in HCC

In HCC, lncRNAs can play a key role as oncogenes/tumor suppressor gene, and the main factors affecting the function of lncRNAs are the following: Epigenetic modification, selective splicing, transcriptional regulation, binding to RNAs and the encoding of small peptides (Fig. 1).

Epigenetic modification. Common epigenetic modifications in HCC progression include DNA methylation and histone modification (17). The regulation of epigenetic modification determines the function of lncRNAs. lncRNAs can recruit some chromatin remodeling complexes to mediate gene silencing and thus play a role in promoting or suppressing HCC. For example, linc00441 has been shown to recruit DNA methyltransferase (DNMT)3A for methylation, inducing the silencing of its neighboring gene, RB1, and thereby promoting the proliferation of HCC cells (18). In addition, DNMT1 and DNMT3 induce the hypermethylation of the MEG3 promoter of the tumor suppressor lncRNA, reducing MEG3 expression and leading to apoptotic resistance and tumor growth in HCC cells (19). Of note, Zhou *et al* (20) reported that lncRNA ID2-AS1 inhibited HCC tumor metastasis by blocking histone deacetylase 8.

Alternative splicing. Different forms of selective splicing of lncRNA precursors (pre-lncRNAs) generate different isoforms of lncRNAs, which may enable them to perform different functions in HCC. For example, lncRNA PXN-AS1 can be spliced into several different isoforms, among which the PXN-AS1-L isoform inhibits apoptosis in myeloid leukemia in a PXN-dependent manner (21). However, another isoform (PXN-AS1-IR3) promotes HCC metastasis by inducing transcriptional activation of MYC (22). In addition, the lncRNA NEAT1 can be alternatively spliced to produce two isoforms, NEAT1_1 and NEAT1_2. It has been found that the low expression of NEAT1_2 is significantly associated with the overall survival of patients with HCC. Follow-up data suggest that NEAT1_2, but not NEAT1_1, mediates mTORC1 signaling to control aerobic glycolysis in HCC cells, contributing to the Warburg effect and HCC development (23).

Transcriptional regulation. lncRNAs are subject to different transcriptional regulations, which markedly affect the cancer- or cancer-suppressive functions of lncRNAs. A number of tumor suppressor genes or oncogene transcription factors, including p53, hypoxia inducible factor-1α (HIF-1α) and myelocytomatosis (myc) have been shown to induce the transcription of lncRNA genes. For example, myc is a key proto-oncogene, and in HCC, lncRNA linc00176, which is transcribed by myc, has been found to play a role in promoting cell proliferation and survival by inhibiting cancer cell cycle arrest and cell necrosis (24). Another study demonstrated that HIF-1α binds to the promoter region of lncRNA RAET1K to activate its transcription, thereby enhancing its cancer-promoting effect in HCC (25). However, MEG3 has been identified to function as a tumor suppressor gene in hepatoma cells by interacting with tumor suppressor p53 protein to activate p53-mediated transcriptional activity and affect the expression of certain p53 target genes (26).

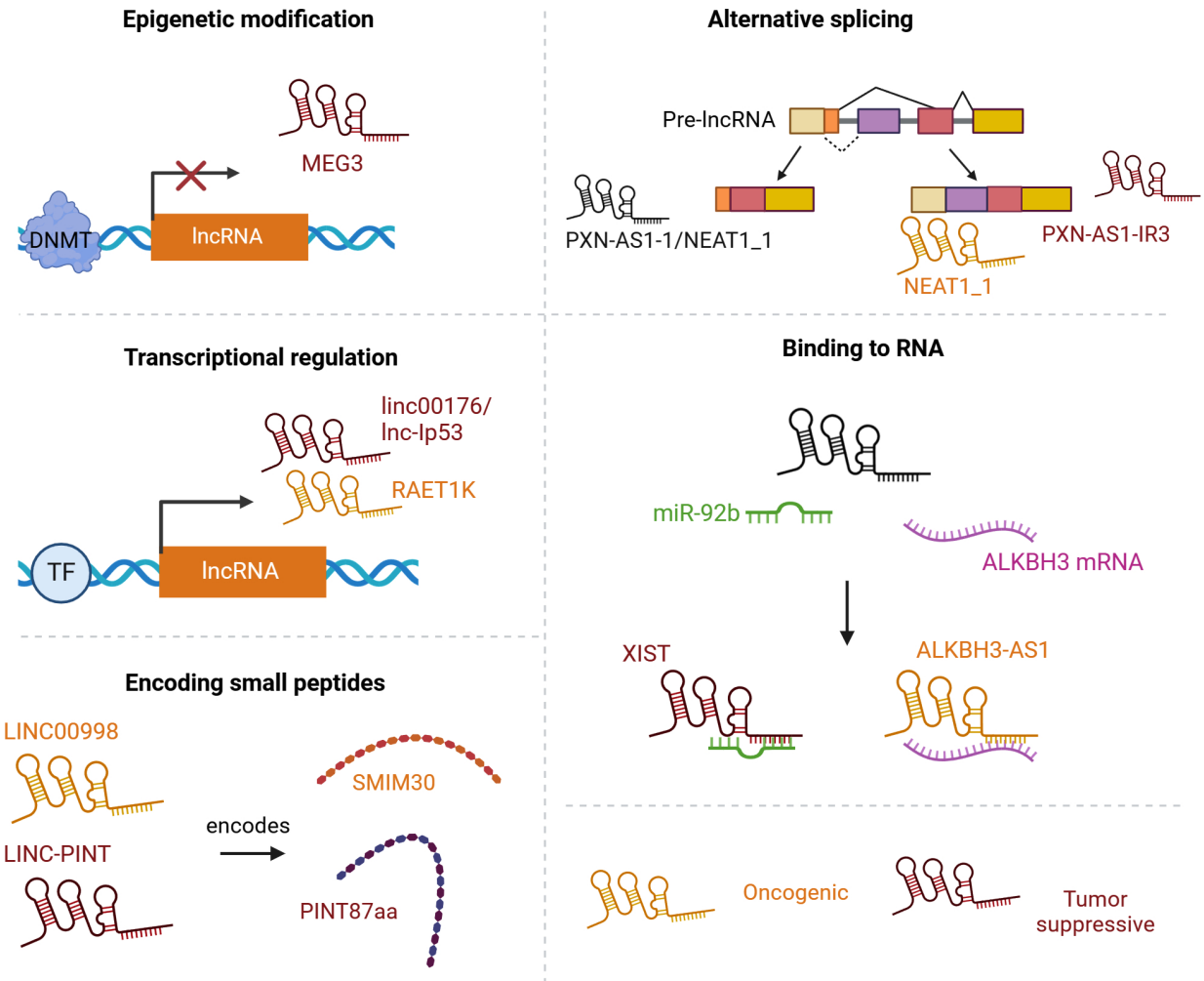

Figure 1. Functional mechanisms of lncRNA in HCC. DNMT, DNA Methyltransferase; MEG3, maternally expressed 3; RAET1K, retinoic acid early transcript 1K; miR-92b, microRNA 92b; ALKBH3: AlkB Homolog 3, alpha-ketoglutarate dependent dioxygenase; ALKBH3-AS1, ALKBH3 antisense RNA 1; XIST, X inactive specific transcript; LINC-PINT, long intergenic non-protein coding RNA, P53-induced transcript; SMIM30, small integral membrane protein 30.

Binding to RNAs. The binding of lncRNAs to RNAs is another key factor in determining their role in cancer. ALKBH3-AS1 is a carcinogenic lncRNA, which directly binds ALKBH3 mRNA in HCC cells, upregulates the expression level of ALKBH3, and promotes the proliferation of cancer cells (27). In addition to directly regulating mRNAs, lncRNAs also affect the expression of their target genes by controlling microRNA (miRNA or miR) expression. For example, it has been demonstrated that lncRNA XIST binds miR-92b as a sponge in liver cancer tissues, preventing miR-92b from binding to its downstream target Smad7 mRNA, thereby inhibiting the proliferation and metastasis of HCC (28).

Encoding small peptides. Encoded small peptides play a crucial role in cancer development and determine the functions of lncRNAs in cancer. SMIM30, encoded by LINC00998 in HCC, has been found to be associated with a low survival rate of patients with HCC and is able to promote the development of HCC by inducing SRC/YES1 membrane anchoring and MAPK pathway activation (29). By contrast, LINC-PINT encodes a PINT87aa micropeptide that binds to the transcription factor, FOXM1, as a potential anticancer micropeptide, while promoting cancer cell senescence (30). A recent correlative study using ribosome analysis methods found that a 99-aa peptide termed KRASIM encoded by lncRNA NCBP2-AS2 bound to KRAS proteins to inhibit ERK signaling, thereby inhibiting the growth of HCC cells (31).

4. Interaction between lncRNAs, glycolysis and HCC progression

Aerobic glycolysis is strongly associated with the progression of HCC. Aerobic glycolysis in HCC cells has been reported to be closely related to their sustained proliferation, invasive metastasis, the induction of stem cell activity and the generation of therapeutic resistance. In the aerobic glycolytic metabolism of HCC cells, an increase in the glycolytic flux of the cancer cells, accompanied by an increase in intermediate metabolites, provides sufficient energy and metabolites for the biosynthetic molecules required for the sustained proliferation of the cancer cells. As previously demonstrated, in xenograft tumors, the growth rate of HCC tumors was reduced by ~50% by decreasing the aerobic glycolytic enzyme, hexokinase 2 (HK2) (32). The production of large amounts of lactate and H^+ in aerobic glycolysis leads to the acidification of the extracellular environment,

induces the transformation of cancer cell epithelial cells into mesenchymal cells, and promotes the invasion and metastasis of tumor cells. It has been found that the highly metastatic HCC cell lines, MHCC97H and LM3, exhibit higher levels of aerobic glycolysis compared with those with a lesser invasive ability (33). Increased lactate levels further enhance the stemness of tumor stem cells, and the elevated lactylation of H3 histone effectively promotes the oncogenicity of HCC stem cells (34). Furthermore, the substantial production of lactic acid and hydrogen ions (H^+) during aerobic glycolysis leads to acidification of the tumor microenvironment, promoting immunosuppression and facilitating tumor immune evasion, as well as conferring resistance to immunotherapy (35). Therefore, targeting glycolytic metabolic pathways and controlling lactate levels may be an effective strategy with which to prevent or attenuate the progression of HCC.

lncRNAs involved in the regulation of glycolysis in HCC. In the tumor microenvironment, some lncRNAs can affect proliferation, metastasis and drug resistance in HCC by promoting or inhibiting aerobic glycolysis in tumor cells. For example, the knockdown of NPSR1-AS1 in HCC cells has been shown to reduce their glycolytic metabolism and abolish their tumorigenic potential. This suggests that NPSR1-AS1 has glycolysis-dependent tumorigenic activity in HCC (36). It has been demonstrated that overexpression of lncRNA RP11-620J15.3 in HCC suggests that it functions as a competitive endogenous RNA to upregulate glucose-6-phosphate isomerase via sponge-binding to miR-326 and promoting aerobic glycolysis, which in turn promotes HCC cell proliferation and metastasis (37). In addition to promoting tumor progression, targeting changes in cancer cell metabolism is currently providing new insight into tumor drug therapy. Tretinoin is a widely known compound capable of inhibiting the development of HCC. Zhang *et al* (38) demonstrated that lncRNA MBNL1-AS1 reduced the sensitivity of HCC cells to tretinoin by inhibiting miR-708-5p-mediated glycolysis. This finding revealed an effective therapeutic target for the treatment of HCC. The majority of the lncRNAs involved in glycolysis in HCC are summarized in Table I and are discussed below.

Glycolysis-promoting lncRNAs

Taurine upregulated gene 1 (TUG1). TUG1 has been found to function as an oncogenic lncRNA that is abnormally upregulated in the majority of cancers, including HCC tissues (64). Its overexpression has been found to be associated with the promotion of glycolysis and has been studied in HCC. Partially, TUG1 mediates its biological function by segregating with miRNAs. The overexpression of TUG1 has been shown to be significantly associated with HK2, and luciferase reporter gene-based assays have revealed that the TUG1/miR-455-3p/AMPKβ2 axis affects HCC cell growth, metastasis and glycolysis through the regulation of HK2 (40). SIX1 is a therapeutic target in HCC and directly regulates lactate levels in cancer cells, which in turn affects tumor cell proliferation, apoptosis and metastasis (65). Lu *et al* (39) found that the overexpression of TUG1 impaired the miR-524-5p mimic-mediated inhibition of SIX1 expression, and suppressed glucose uptake, LDHA activity, lactate levels and ATP levels. This suggests that the TCG1/miR-524-5p/SIX1 axis plays a key role in glycolysis, invasion and metastasis in HCC.

HOX transcriptional antisense intergenic RNA (HOTAIR). HOTAIR is a new class of oncogenic lncRNA often involved in regulating chromatin remodeling and epigenetic changes (66). Previous research has indicated that HOTAIR is highly expressed in a variety of malignant tumors and is involved in cell proliferation, metastasis, DNA repair and metabolism (67). As previously demonstrated in HCC, HOTAIR promotes glycolysis through the upregulation of glucose transporter (GLUT)1 and the activation of the mTOR signaling pathway (42). In addition, has been revealed to promote glycolysis in HCC under hypoxic conditions by targeting and inhibiting miR-130a-3p (41).

Urothelial carcinoma associated 1 (UCA1). The lncRNA UCA1 was originally identified in human bladder cancer. It has an aberrant expression in embryogenesis and in a wide range of cancerous tissues and cells, and plays a role in tumor growth and glycolysis (68). The expression of UCA1 has been found to be higher in HCC tissues than in paracancerous tissues. Upwardly mobile coding protein 1 (UPF1) is an evolutionarily conserved and ubiquitously expressed phosphoprotein that promotes cellular processes through G1/S (69). RIP experiments have revealed that UPF1 specifically binds to UCA1, and the downregulation of UPF1 significantly upregulates the expression level of UCA1 and effectively increases the rate of lactate production in HCC (70).

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1). TCF7L2 has been identified to be an effector of the Wnt signaling pathway and directly binds to several genes which play a key role in the regulation of glucose metabolism. In addition, genome-wide association studies have identified single nucleotide polymorphisms in the TCF7L2 gene associated with diabetes mellitus (71). It has been previously indicated that MALAT1 plays a pivotal role in the regulation of HCC cell proliferation, migration, and metastasis (72). Furthermore, MALAT1 has been found to regulate the expression of glycolytic genes in HCC by increasing the translation of the transcription factor, TCF7L2, which increases lactate and glucose fluxes (43). In addition, gluconeogenesis, a major component of normal hepatocyte glucose metabolism, is negatively regulated by MALAT1.

Glycolysis-inhibiting lncRNAs

LINC00659. Member 1 of 10 of the solute carrier family (SLC10A1) encodes Na^+-taurine bile acid cotransporter peptide (73). The expression of SLC10A1 in tumor tissues has been shown to be lower than that in normal tissues, and it has been found to be associated with the poor survival of patients with HCC (74). SLC10A1 has also been demonstrated to inhibit glycolysis in HCC cells through rates of glucose utilization, lactic acid production and extracellular acidification (75). The transfection of pcDNA3.1LINC00659 can upregulate the expression of SLC10A1 in HCC cells. Similarly, seahorse experiments have revealed that an increase in the oxygen consumption rate and a decrease in the extracellular acidification rate of HepG2 and Huh7 cells induced by the overexpression of LINC00659 can be partially reversed by co-transfection with sh-SLC10A1. These results suggested

Table I. Role of lncRNAs in the regulation of glycolysis in HCC.

Regulation of glycolysis	lncRNAs	Target	Function of HCC	(Refs.)
Promote	NPSR1-AS1	MAPK/ERK	Promoting proliferation	(36)
Promote	RP11-620J15.3	miR-326/GPI	Promoting proliferation and metastasis, invasion	(37)
Promote	MBNL1-AS1	miR-708-5p/HK2	Promoting resistance to tripterine and metastasis, invasion	(38)
Promote	TUG1	miR-524-5p/SIX1; miR-455-3p/AMPKβ2/HK2	Promoting proliferation and invasion	(39, 40)
Promote	HOTAIR	miR-130a-3p/HIF1α/ mTOR/GLUT1	Promoting proliferation	(41, 42)
Promote	MALAT1	TCF7L2	Promoting proliferation	(43)
Promote	lncMMPA	miR-548 s/ALDH1A3	Promoting proliferation	(44)
Promote	Ftx	PPARγ	Promoting proliferation and metastasis, invasion	(45)
Promote	SNHG6	BOP1	Promoting proliferation	(46)
Promote	FTO-IT1	GLUT1/PKM2/c-myc	Promoting proliferation	(47)
Promote	SOX2OT	PKM2	Promoting metastasis and invasion	(48)
Promote	miR4458HG	IGF2BP2	Promoting proliferation	(49)
Promote	NR2F1-AS1	miR-140/HK2	Promoting invasion	(50)
Promote	PANTR1	miR-587/BCL2A1	Promoting proliferation and invasion	(51)
Promote	SLC2A1-AS1	STAT3/FOXM1/GLUT1	Promoting proliferation and metasis	(52)
Promote	FIRRE	CREB/PFKFB4	Promoting proliferation	(53)
Promote	LINC01572	miR-195-5p/PFKFB4/ PI3K-AKT	Promoting proliferation and metastasis, invasion	(54)
Promote	ZFPM2-AS1	miR-18b-5p/PKM	Promoting proliferation, Metastasis, cancer stem macrophage polarization and infiltration	(55)
Promote	SNHG1	miR-326/PKM2	Promoting proliferation	(56)
Promote	CERS6-AS1	miR-30b-3p/MDM2/p53	Promoting proliferation and invasion	(57)
Promote	MNX1-AS1	PKM2	Promoting proliferation	(58)
Promote	UPK1A-AS1	HIF-1α	Promoting proliferation	(59)
Inhibit	NEAT1	mTORC1	Inhibiting proliferation	(23)
Inhibit	LINC00659	FUS/SLC10A1	Inhibiting proliferation and metastasis	(60)
Inhibit	LINC01554	PKM2, Akt/mTOR	Inhibiting proliferation	(61)
Inhibit	WFDC21P	Nur77	Inhibiting proliferation and metastasis	(62)
Inhibit	NONHSAT024276	PTBP1/(PKM1/PKM2)	Inhibiting proliferation and metastasis	(63)

HCC, hepatocellular carcinoma; NPSR1-AS1, NPSR1 antisense RNA 1; MBNL1-AS1, MBNL1 antisense RNA 1; TUG1, taurine upregulated 1; HOTAIR, HOX transcript antisense RNA; MALAT1, metastasis associated lung adenocarcinoma transcript 1; FTX, five prime to Xist; SNHG6, small nucleolar RNA host gene 6; FTO-IT1, FTO intronic transcript 1; SOX2-OT, SOX2 overlapping transcript; MIR4458HG, MIR4458 host gene; NR2F1-AS1, NR2F1 antisense RNA 1; PANTR1, POU3F3 adjacent non-coding transcript 1; FIRRE, firre intergenic repeating RNA element; LINC01572, long intergenic non-protein coding RNA 1572; ZFPM2-AS1, ZFPM2 antisense RNA 1; SNHG1, small nucleolar RNA host gene 1; CERS6-AS1, CERS6 antisense RNA 1; MNX1-AS1, MNX1 antisense RNA 1; UPK1A-AS1, UPK1A antisense RNA 1; NEAT1, nuclear paraspeckle assembly transcript 1; LINC00659, long intergenic non-protein coding RNA 659; LINC01554, long intergenic non-protein coding RNA 1554; WFDC21P, WAP four-disulfide core domain 21.

that LINC00659 inhibits the aerobic glycolysis of HCC cells by modulating SLC10A1. Thus, LINC00659 is a potential therapeutic target in HCC (60).

LINC01554. LINC01554 is a tumor suppressor lncRNA and inhibits aerobic glycolysis in HCC (61). The primary target of LINC01554 is pyruvate kinase M2 (PKM2), which is the late rate-limiting enzyme of aerobic glycolysis. *In vitro* ubiquitination experiments demonstrated enhanced PKM2 degradation mediated by ubiquitination in LINC01554 cells compared with controls. In LINC01554-KO cells, the ubiquitination-mediated degradation of PKM2 by LINC01554 was significantly attenuated. This resulted in a reduced glucose consumption, lactate production and pyruvate production, and in increased ATP levels. LINC01554 has the characteristic of weakening the advantage of cancer cells in acquiring high glycolysis; therefore, LINC01554 functions as a tumor suppressor in HCC and may be used as a potential therapeutic target in patients with HCC.

5. lncRNAs affect glycolysis by regulating transporter proteins, enzymes and signaling pathways in HCC

Dysregulated lncRNAs in HCC are involved in an altered cancer metabolism and are considered to play a key role in regulating the dysregulation of transporter proteins, metabolic enzymes and related signaling pathways in tumors that are dependent on high rates of glycolysis (Fig. 2).

lncRNAs regulate glycosylation-related transporters and enzymes

GLUT. Often cancer cells exhibit a higher glucose uptake, and GLUT proteins play a crucial role in the transmembrane transport of glucose. GLUT proteins can be classified into three isoforms. GLUT1, a facilitator of glucose transporter proteins, is highly expressed in a variety of human cancers, including lung cancer (76), colorectal cancer (77), prostate cancer (78) and HCC (89). GLUT1 has also been shown to be associated with a poor patient prognosis and plays a role in glycolysis in cancer. It has been demonstrated that lncRNAs can regulate glycolysis by affecting GLUT1 expression, thereby influencing the development of HCC. For example, a previous study found that SLC2A1-AS1-mediated the downregulation of GLUT1 and significantly inhibited glycolysis in HCC (52). Another study demonstrated that lncRNA FTO-IT1 promoted glycolysis and progression in HCC by regulating FTO-mediated N^6-methyladenosine modification on GLUT1 (47). Furthermore, it has been revealed that lncRNA HOTAIR promotes glycolysis by upregulating GLUT1 and activating the mTOR signaling pathway (42). GLUT has emerged as a target for cancer therapy in recent years due to the dependence of tumor cell growth on extracellular glucose (80).

HK2. HK catalyzes the first step in glycolytic metabolism, catalyzing the formation of glucose-6-phosphate. It is considered to be a key regulator of cellular energy metabolism and contributes to the Warburg effect by promoting intracellular glucose uptake (81-83). HK2 has often been reported to be highly expressed in HCC cells and induces tumor development by promoting glycolysis. The lncRNA TUG1 has been shown to be significantly associated with HK2 overexpression and the poor prognosis of patients with HCC. It has also been demonstrated that TUG1 positively regulates HK2 expression by binding to miR-455-3p, which promotes glycolysis in tumor cells, and accelerates tumor growth and metastasis (40). In addition, MBNL1-AS1 and NR2F1-AS1 have been reported to positively regulate the expression level of HK2, which promotes aerobic glycolysis in HCC cells, and contributes to cancer cell proliferation, migration and resistance to therapeutic drugs (38,50). Therefore, an in-depth study of HK2 may provide insight into the tumorigenesis and progression of HCC, and may lead to the development of novel therapeutics.

Lactate dehydrogenase (LDH) A. LDHA is a member of the LDH family, which is the rate-limiting enzyme for the interconversion of pyruvate and lactate in the glycolytic pathway. LDHA is upregulated in a number of types of cancer and is associated with the clinicopathological features and prognosis of patients (84,85). The lncRNA RAET1K has been found to be positively associated with the expression of LDHA in cells and regulate its activity, contributing to increased levels of glycolysis, thereby promoting cell proliferation and invasion (25).

PKM2. PK functions as the final rate-limiting enzyme of glycolysis, converting phosphoenolpyruvate to pyruvate. PKM2 is one of the four isozymes of PK and plays a crucial role in cancer development (86). lncRNAs can participate in the regulation of aerobic glycolysis by affecting the expression of PKM2, thereby influencing HCC progression. For example, the lncRNA SOX2OT has been shown to promote PKM2-mediated glycolytic activation by targeting the binding to miR-122-5p, increasing its expression level and promoting the metastasis of HCC cells (48). In addition, the lncRNA SNHG1 has been revealed to function as a molecular sponge for miR-326, isolating the interaction of miR-326 with PKM2, and promoting PKM2 expression. The activation of PKM2 expression is one of the mechanisms through which SNHG1 promotes glycolysis and HCC cell proliferation (56). NONHSAT024276, a potential oncogene for HCC, directly binds to polypyrimidine bundle-binding protein 1 (PTBP1), increases the ratio of M1 to M2 isoforms of PKM1/PKM2 and blocks PTBP1/PKM-mediated glycolysis to inhibit cancer cell proliferation and migration (63).

6-Phosphofructo-2-kinase/fructose-2,6-biphosphatase4 (PFKFB4). PFKFB4, a member of the PFKFB family, which has been identified to be a key regulator of glycolysis, controls the synthesis and degradation of fructose-2,6-bisphosphate (F-2,6-BP) (87). It has been recently revealed that lncRNAs are involved in the regulation of PFKFB4 expression in tumor tissues and that they play a key role in tumor glycolysis. The high expression of the lncRNA FIRRE has been shown to be associated with malignant clinical features and with the poor survival of patients with HCC. Mechanistically, FIRRE promotes HCC cell proliferation and glycolysis by facilitating PFKFB4 transcription and expression, mainly through cAMP-responsive element-binding protein (53). Another study confirmed that LINC01572 is aberrantly upregulated in HCC tissues, particularly in patients with type 2 diabetes. Mechanistically, LINC01572 increases the level of PFKFB4 by competitively inhibiting miR-195-5p, thereby enhancing glycolysis and triggering HCC development (54).

lncRNAs regulate glycolysis-related signaling pathways p53 signaling pathway. p53 (also known as TP53) is a well-known tumor suppressor gene. It has been demonstrated that lncRNAs, as functional components of the p53 pathway, may play a regulatory role in this pathway. lncRNA CERS6-AS1 can sponge miR-30b-3p to elevate MDM2, which promotes MDM2-mediated ubiquitin-dependent degradation of the p53 oncogene, and facilitates glycolysis in HCC cells (57). On the contrary, the interaction between p53 and lncRNA can promote cancer by influencing glycolytic enzymes. p53 forms a complex with the lncRNA CUDR, which binds to the promoter region of PKM2 to enhance PKM2 expression, phosphorylation and polymer formation, and, ultimately, p53 accelerates the growth of the HCC cell line, Hep3B, by lengthening telomeres through a cascade of reactions that promotes HCC development (88).

c-Myc signaling pathway. c-Myc is a transcription factor, mainly found in the nucleus, that has been implicated in the development and progression of cancer. c-Myc, as a major

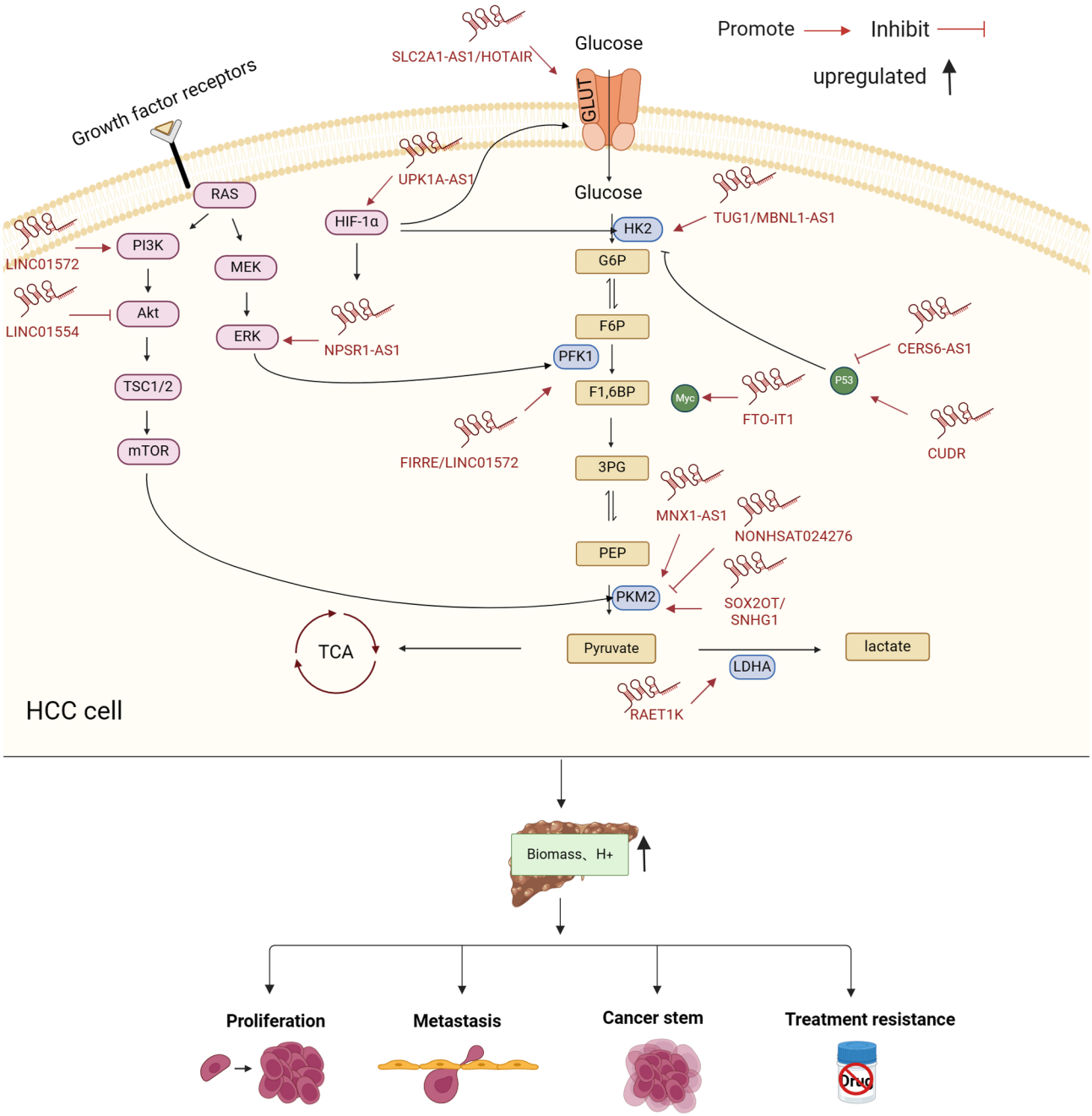

Figure 2. lncRNAs affect glycolysis in HCC by regulating glycolytic enzymes, transporter proteins and related pathways. RAS, reliability availability and serviceability; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; TSC1/2, tuberous sclerosis complex 1/2; mTOR, mammalian target of rapamycin; MEK, mitogen-activated extracellular signal-regulated kinase; ERK, extracellular regulated protein kinases; HIF-1α, hypoxia inducible factor-1α; GLUT1, glucose transporter type 1; HK2, hexokinase 2; G6P, glucose-6-phosphatase G-6-pase; F6P, fructose 6-phosphate; PFK1, phosphofructokinase-1; F1,6-BP, fructose 1,6-bisphosphate; 3PG, 3-phosphoglycerate; PEP, phosphoenolpyruvate; PKM2, pyruvate kinase isozyme typeM2; LDHA, lactate dehydrogenase A; Myc, v-myc avian myelocytomatosis viral oncogene homolog; ATP, adenosine 5'-triphosphate; H^+, hydrogen; HOTAIR, HOX transcript antisense RNA; UPK1A-AS1, UPK1A antisense RNA 1; NPSR1-AS1, NPSR1 antisense RNA 1; FIRRE, firre intergenic repeating RNA element; TUG1, long non-coding RNA taurine-upregulated gene 1; FTO-IT1, FTO intronic transcript 1; SNHG1, small nucleolar RNA host gene 1.

regulator of aerobic glycolysis, can regulate aerobic glycolysis by directly activating glycolytic enzymes (89). In addition to a large number of coding genes, lncRNAs function as downstream targets of c-Myc and participate in glycolysis in cancer cells. lncRNA FTO-IT1 has been shown to enhance glycolysis in HCC by inducing the stabilization of FTO mRNA, leading to the overexpression of c-Myc. Moreover, c-Myc has been found to regulate the expression of FTO-IT1 by binding to its promoter region under low glucose conditions, forming a positive feedback loop between c-Myc and FTO-IT1 (47). Wu *et al* (58) also demonstrated that MNX1-AS1, a c-Myc target gene, was upregulated in HCC, promoting aerobic glycolysis and tumorigenesis.

HIF-1α signaling pathway. When tumor cells continue to proliferate and expand to a certain limit, vascular hypoxia leads to the appearance of HIF, and HIF-1α plays a key role as a member of the aerobic glycolysis and lactate pathways (90). In hypoxic environments, NPSR1-AS1 induces the activation

of the MAPK/ERK pathway in HCC cells, which promotes the proliferation and glycolysis of HCC cells (36). The overexpression of lncRNA UPK1A-AS1 has been reported to significantly increase the stability of the HIF-1α ubiquitin-modified expression of upregulated glycolysis-related genes, thereby promoting glycolysis levels in HCC cells (59).

Phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR signaling pathway. The dysregulation of the PI3K/AKT/mTOR pathway is a prevalent occurrence in the majority of human cancers. In HCC, this signaling cascade plays a crucial role in facilitating glucose metabolism, tumor metastasis, and resistance to drugs (91-93). It has been demonstrated that lncRNA is a regulator of PI3K/AKT/mTOR signaling in a variety of cancer types, and can indirectly affect the expression of enzymes by regulating this pathway. In HCC tissues and cell lines, the upregulation of LINC01572 increases the expression of the glycolytic enzyme, PFKFB4, by activating PI3K/AKT signaling, thereby enhancing glycolysis and triggering HCC malignancy (54). mTOR is a serine/threonine kinase. It has been previously shown that the upregulation of lncRNA HOTAIR can induce the glycolysis of HCC cells by activating the mTOR signaling pathway (42). By contrast, LINC01554, a novel oncogene in HCC, has been identified to inhibit the AKT/mTOR signaling pathway and eliminate aerobic glycolysis in HCC cells, thereby suppressing tumor growth (61).

In summary, lncRNAs mediate changes in the expression of glycolysis-associated transporter proteins, enzymes and signaling pathways in HCCs, affecting the level of tumor aerobic glycolysis, and thus cancer formation and progression. Therefore, these glycolysis-associated lncRNAs have gradually become key targets for cancer research, and the inhibition of these lncRNAs is critical for controlling tumor development. Follow-up studies should continue to explore the mechanisms of the lncRNA regulation of glycolysis to provide new directions for cancer treatment.

6. Conclusions and future perspectives

Although there have been major breakthroughs in the study of malignant tumors, HCC remains a lethal disease. Due to the high aggressiveness of HCC, this type of cancer is very likely to metastasize, and the majority of cases are diagnosed in the middle and late stages; thus, the option of surgical treatment is only <40%, which is reflected in the low long-term survival rate of patients with HCC (94). Therefore, the influence of other molecular therapeutic targets on the progression and mechanism of HCC may have a key impact on the prevention and control of HCC and the long-term survival rate of patients.

Cancer cells are metabolically active, and they can alternate between glycolysis and mitochondrial OXPHOS in response to nutritional stress caused by environmental changes (95). Therefore, blocking the glycolytic pathway in tumor cells or inducing the transformation of cancer cells from aerobic glycolytic to mitochondrial OXPHOS may lead to novel approaches for the treatment of HCC. The present review focused on the effects of lncRNAs on HCC progression, and their specific functions and mechanisms in cancer metabolic pathways. In terms of the mechanisms, lncRNAs significantly affect the process of glucose metabolism mainly through glycolytic-related transporters, metabolic enzymes or related signaling pathways, and thus participate in the progression of HCC. lncRNAs are involved in the regulation of glucose metabolism in tumor cells, which suggests that lncRNAs, related glycolytic regulatory factors, may become novel targets for cancer therapy.

In the current stage of HCC research, clinical trials involving lncRNAs primarily focus on exosomal lncRNAs that can serve as detectable biomarkers (96). lncRNAs can participate in tumor cell metabolism through different mechanisms, which may have extensive therapeutic significance and may provide new insight into the treatment of HCC. Therefore, the role of lncRNAs in regulating aerobic glycolysis should be carefully considered when considering the development of future therapeutic drugs and methods. Further studies on lncRNAs inhibitors may provide strategies with which to block the progression of HCC. These may include: i) Targeting lncRNAs capable of regulating glycolytic enzymes; ii) targeting lncRNAs that regulate the glucose transporter GLUT to inhibit glucose uptake; and iii) lncRNAs that target glycolysis-related regulatory factors or signaling pathways. Therefore, the further in-depth exploration of the mechanisms of lncRNAs in HCC glycolysis may aid in the development of more effective therapeutic strategies with which to inhibit tumor progression.

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Authors' contributions

CO designed the present review. QioH wrote the manuscript. ZL and QiqH was involved in article revision. XL, JX, LH and LBH surveyed the literature and contributed to the revisions. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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