Review Article
Non-coding RNAs: emerging regulators of glucose metabolism in hepatocellular carcinoma

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Abstract: Reprogramming of metabolism is one of the hallmarks of cancer, among which glucose metabolism dysfunction is the most prominent feature. The glucose metabolism of tumor cells is significantly different from that of normal cells. Glucose metabolism reprogramming of hepatocellular carcinoma (HCC) has become an important research hotspot in the field of HCC, a variety of tumor metabolic interventions have been applied clinically. Moreover, various Non-coding RNAs (ncRNAs) including microRNAs (miRNAs), long non-coding (lncRNAs) as well as circular RNAs (circRNAs), have recently been proved to play potential roles in glucose metabolism. This review summarizes the effects of ncRNAs on HCC that participate in glucose metabolism and discuss the related mechanisms to find potential and effective targeted treatments for HCC.

Keywords: Hepatocellular carcinoma, glucose metabolism, glycolysis, non-coding RNA, microRNAs, long non-coding RNAs, circular RNAs

Introduction

Liver cancer is the sixth highest-incidence cancer and it is also the 4th most deadly cancer with easy metastasis and poor prognosis. There were approximately 850,000 new cases and 780,000 deaths of liver cancer occurred in 2018. HCC accounts for 75% to 85% of primary liver cancer and more than half of the world's HCC cases occur in China [1].

For early-stage HCC, a comprehensive treatment plan is mainly based on surgery, combined with transcatheter arterial chemoembolization (TACE) and radiofrequency ablation [2]. However, it is regrettable that most patients have reached an advanced stage or distant metastasis at the first diagnosis, that losing the opportunity for surgery. As for advanced HCC, there is no standard treatment, and the 5-year survival rate of HCC is 3% to 5% [3].

Despite the unremitting efforts of researchers, the key molecular mechanism of HCC development remains inconclusive, limiting the progression of therapeutic regimens. Recently, multiple lines of evidence have shown that metabolic reprogramming is closely related to the occurrence and development of HCC, among which glucose metabolism reprogramming is one of the most prominent features [4]. The mechanisms of glucose metabolic reprogramming often involve gene mutations, especially C-MYC and P53 [5, 6]. While changes in the expression or activity of glucose metabolism genes and related glucose metabolism enzymes also have global effects [7].

Non-coding RNAs (ncRNAs) are RNA transcribed from DNA and unable to encode proteins, which account for the majority of RNAs (**Figure 1**). With the improvement and maturity of ncRNAs identification technology, the crucial role of ncRNAs in tumorigenesis has been increasingly recognized. They participate in almost all biological functions, including proliferation, apoptosis, migration, invasion, EMT, cancer stem cells and drug resistance [8, 9].

Multiple lines of evidence have manifested that ncRNAs, mainly miRNAs, lncRNAs and circular RNAs (circRNAs) may play pivotal roles in repro-
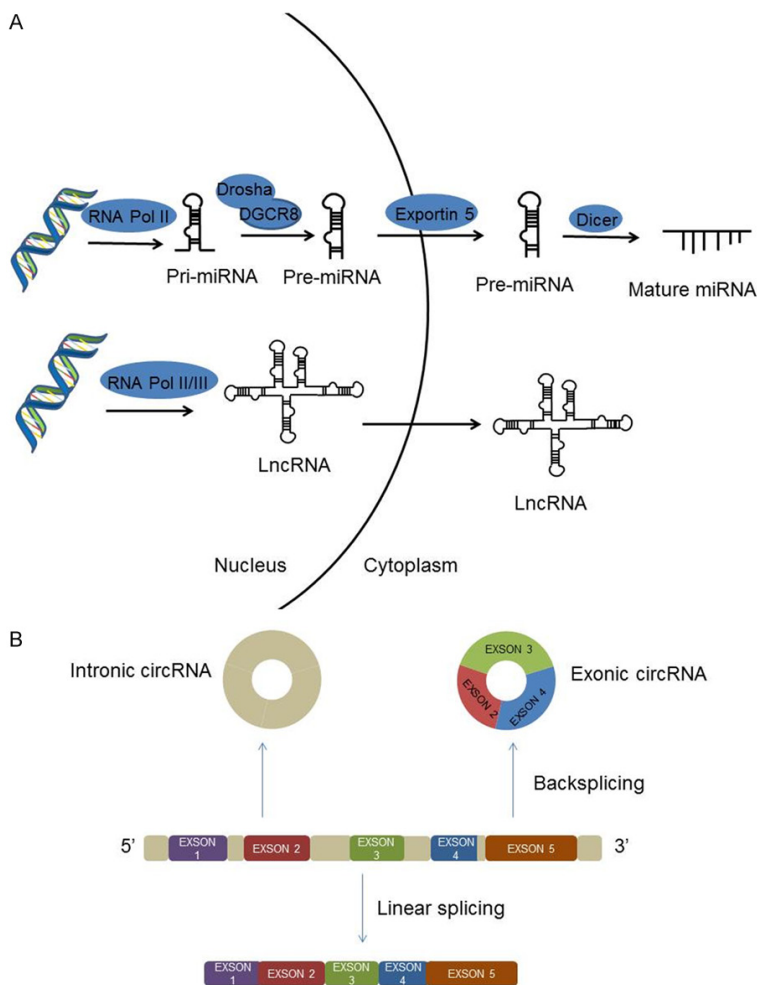
Figure 1. A. The biogenesis of ncRNAs. miRNAs are transcribed into pri-miRNA under the help of RNA Polymerase II, pri-miRNA is processed into a pre-miRNA by Drosha/DGCR8 in the nucleus, and then transported to the cytoplasm via Exportin-5, pre-miRNA is further cleaved by Dicer to form mature miRNA. lncRNAs are transcribed by RNA Polymerase II or III. B. CircRNAs formed by exon circularization.

these specific mRNAs by either mRNA cleavage or translational repression [10-12]. In recent years, more and more studies have found that miRNAs are involved in the regulation of glucose metabolism, including glycolytic pathway, pentose phosphate pathway (PPP) and gluconeogenesis. Here we discuss the role of miRNAs on glucose metabolism of HCC. The related studies' contents are summarized in **Table 1**.

MiRNAs involved in aerobic glycolysis

Aerobic glycolysis also called the "Warburg effect", which preference for tumor cells acquire energy through glycolysis rather than oxidative phosphorylation even in the sufficient aerobic and mitochondrial function [13]. Glycolysis also provides raw materials for other anabolic [13]. Furthermore, aerobic glycolysis can produce a large amount of lactic acid and creating an acidic microenvironment, which is conducive to tumor cell invasion and metastasis [15]. Therefore, inhibition of aerobic glycolysis may be a promising anti-tumor therapy [16-19].

gramming glucose metabolism, including glycolytic pathway, pentose phosphate pathway (PPP) and gluconeogenesis via altering the expression or activity of the glucose metabolism genes and related glucose metabolism enzymes (**Figure 2**) and regulating the activation of various signaling pathways (**Figure 3**).

MiRNAs

MiRNAs are a class of ncRNAs that about 22 nt in length. MiRNAs completely or incompletely combine with the 3' untranslated regions (3'-UTR) of the target genes, leading to direct degradation or blocked translation of the target genes, thereby decreasing the expression of

The regulation of glycolysis is mainly through manipulating the activity of the rate-controlling enzymes (key enzymes), including hexokinase (HK), 6-phosphate fructokinase (PFK) and pyruvate kinase (PK). Hypoxia-inducible factors (HIFs), particularly HIF-1α is a crucial mediator of hypoxia response, promoting glycolysis process to adapt cancer cells to hypoxic environment [20]. On the one hand, emerging studies demonstrated that alters miRNAs expression profiles may orchestrate the glycolytic pathway of HCC cells by regulating the expression of glycolysis-related enzymes, including HK, PFK, PK, HIFs. On the other hand, different glucose levels also alter the level of miRNAs. For example, the expression of miR-483-3p is low under
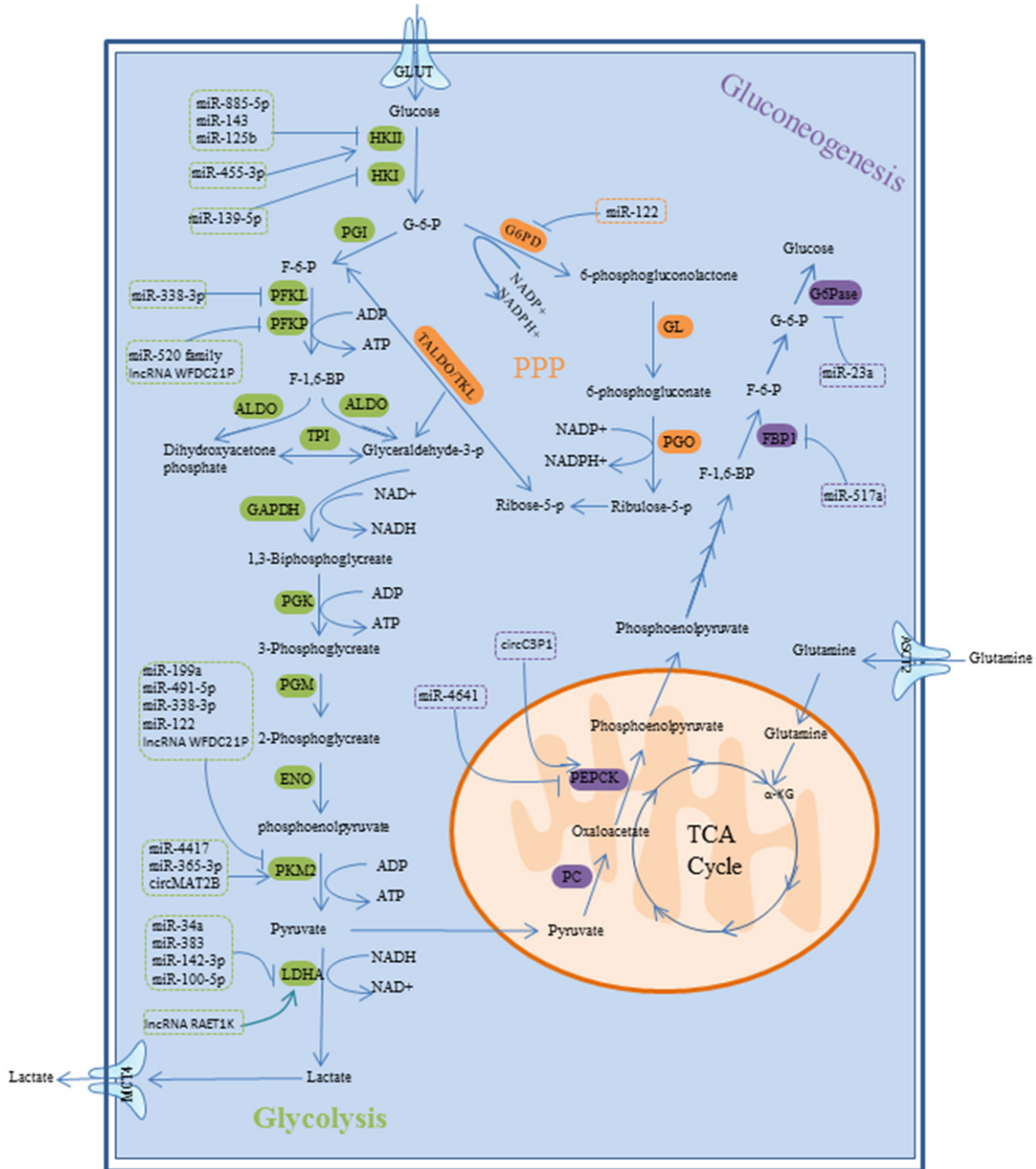
Figure 2. Glycolysis pathway, PPP and gluconeogenesis pathway of HCC, and the role of ncRNAs in glucose metabolism via regulating rate-controlling enzyme and GLUT.

low glucose, while under high glucose conditions, the expression of miR-483-3p increases and inhibits apoptosis [21].

MiRNAs and HK: HK is the first rate-limiting enzymes of aerobic glycolysis, which catalysis phosphorylation of glucose to glucose 6-phosphate [22]. The overexpression of HK has been highlighted in HCC cells. On the contrary, sup-

pression of HK expression may induce HCC cells apoptosis. Therefore, it is considered to be a vital molecule in the glycolysis pathway and has been proposed as a therapeutic target for cancer.

In mammals, there are four hexokinase isoforms, HKI, HKII, HKIII, and HKIV. On the one hand, miRNAs weaken glycolysis of HCC by
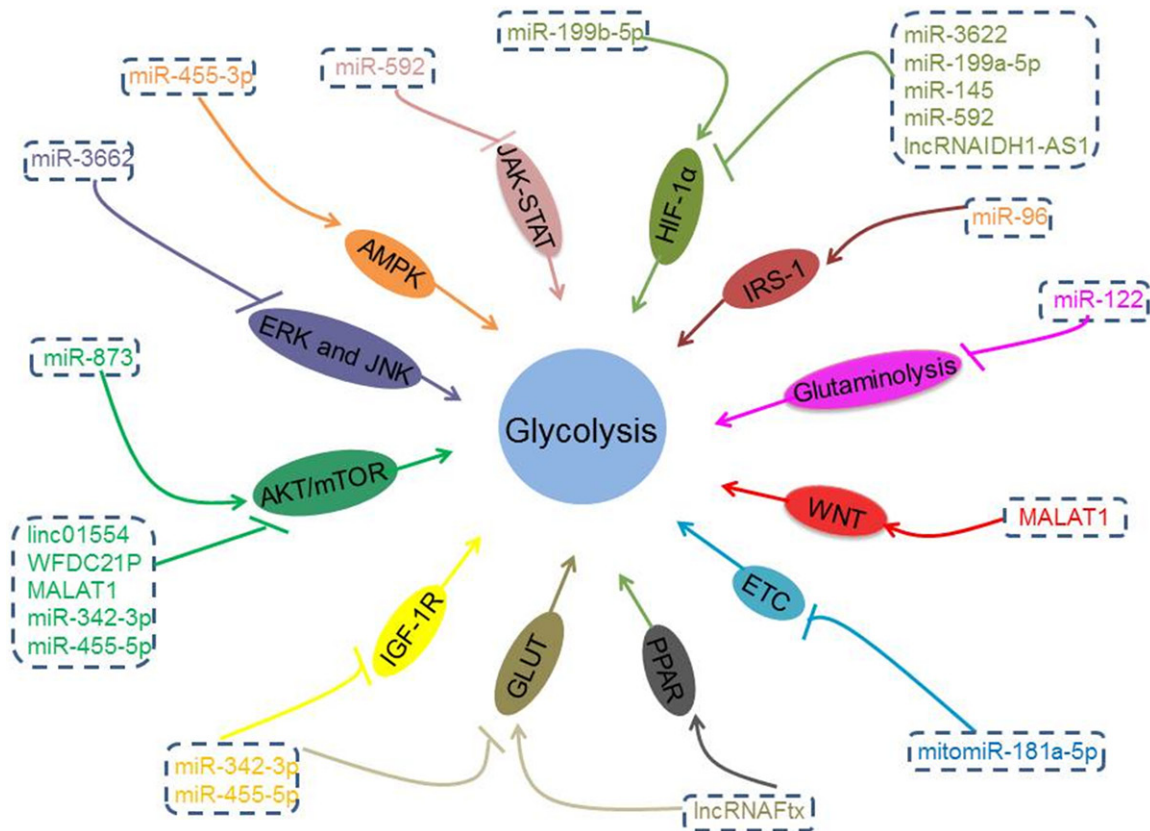
Figure 3. NcRNAs may play an important role in regulating glucose metabolism of HCC through different signal pathways and mechanisms.

directly targeting HKII expressions. For instance, miR-885-5p, miR-143 and miR-125b have proved plays a decisive role in limiting glycolysis in HCC cells by targeting HKII, thereby inhibiting the HCC growth [23-25]. On the other hand, miRNAs elevate glycolysis of HCC by stabilizing HKII expression. For example, miR-455-3p induces cell proliferation, metastasis and glycolysis by increasing HKII expression, which is achieved by stabilizing HKII protein through proteasome. Mir-455-3-p directly targets the 3'UTR of AMP-activated protein kinase subunit beta 2 (AMPKβ2), an important role in the AMPK pathway. Suppress AMPKβ2 expression has been shown to induced p-mTOR, Snail and HKII expressions, leading to enhanced cell glycolysis [26].

Furthermore, HKI has also been found to be involved in the regulation of glycolysis. MiR-139-5p negative regulate HKI and 6-phospho-fructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) expression by directly targeting the ETS1, which is a transcription factor and bound

to the promoters of the HKI and PFKFB3 genes [27].

MiRNAs and PFK: PFK, the second rate-limiting enzyme in glycolysis that catalyzes fructose-6-phosphate to fructose-1,6-bisphosphate [28]. Mammals have three PFK isoforms: liver (PFKL), muscle (PFKM) and platelet (PFKP). Expression of PFKP was significantly up-regulated in a variety of cancers, including brain cancer, pancreatic cancer, breast cancer and HCC [29-31].

Recently, several miRNAs have been shown to be involved in regulating glycolysis of HCC by altering the expression of PFK. For instance, miR-520 family, including miR-520a-3p, miR-520b, and miR-520e are indicated to inhibited glycolysis by target the 3'UTR of PFKP in HCC. On the contrary, inhibit the expression of miR-520a/b/e was notably potentiated the rate of glycolysis [32]. MiR-338-3p dampens glycolysis by directly interacted with PFKL. MiR-338-3p act as a tumor suppressor was down-regulated

Table 1. MiRNAs involved in glucose metabolism in HCC

Glucose metabolism	microRNA	Effect	Target	Mechanism	Reference
glycolytic pathway	miR-885-5p	Decrease	HKII	-	[23]
	miR-143	Decrease	HKII	-	[24]
	miR-125b	Decrease	-	Inhibit HKII	[25]
	miR-455-3p	Increase	AMPKβ2	stabilizes HKII protein active AMPK pathway	[26]
	miR-139-5p	Decrease	ETS1	Inhibit HKI and PFKFB3 expression	[27]
	miR-520 family	Decrease	PFKP	-	[32]
	miR-338-3p	Decrease	PFKL	-	[33]
	miR-139-5p	Decrease	PKM2	-	[27]
	miR-199a	Decrease	PKM2	-	[36]
	miR-491-5p	Decrease	PKM2	-	[37]
	miR-338-3p	Decrease	PKM2	-	[38]
	miR-122	Decrease	PKM2	-	[39]
	miR-4417	Increase	-	Promote PKM2 phosphorylation	[40]
	miR-365a-3p	Increase	-	Inhibit PKM2 degradation	[41]
	miR-374b	Decrease	hnRNPA1	Inhibit PKM2 expression	[42]
	miR-142-3p	Decrease	LDHA	-	[44]
	miR-383	Decrease	LDHA	-	[45]
	miR-34a	Decrease	LDHA	-	[46]
	miR-100-5p	Decrease	LDHA	-	[47]
	miR-592	Decrease	WSB1	Disrupting HIF-1α stabilization	[51]
	miR-199a-5p	Decrease	HIF-1α	-	[52]
	miR-3662	Decrease	HIF-1α	Inactivate ERK and JNK	[53]
	miR-145	Decrease	-	Inhibit HIF-1α and PDK1 expression	[54]
	miR-873	Increase	NDFIP1	Active AKT/mTOR	[56]
	miR-199b-5p	Decrease	-	Up-regulates HIF-1α transcription through overexpression of NPAS2	[57]
	mitomiR-181a-5p	Decrease	-	Impair electron transport chain	[59]
	miR-342-3p	Decrease	IGF-1R	Downregulate GLUT1 Inactivate PI3K/AKT	[61]
	miR-455-5p	Decrease	IGF-1R	Downregulate GLUT1 Inactivate PI3K/AK	[62]
	miR-129-5p	Decrease	PDK4	-	[55]
pentose phosphate pathway	miR-122	Decrease	G6PD	-	[65]
gluconeogenesis	miR-4641	Decrease	PCK1	-	[69]
	miR-517a	Decrease	FBP1	-	[72]
	miR-23a	Decrease	G6PC PGC-1α	-	[74]
	miR-96	Increase	IRS-1	-	[76]
	miR-122	Increase	-	Promoted glutaminolysis	[78]

"-": unknown. Abbreviations: HCC: Hepatocellular carcinoma; HK: Hexokinase; PFK: 6-phosphate fructokinase; PK: Pyruvate kinase; HIFs: Hypoxia-inducible factors; AMPKβ2: AMP-activated protein kinase subunit beta 2; PFKFB3: 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PKM2: Pyruvate kinase M2; LDHA: Lactate dehydrogenase A; IGF-1R: Insulin-like growth factor-1 receptor; GLUT: Glucose transporters; PDK4: Pyruvate dehydrogenase kinase 4; PEPCK: Phosphoenolpyruvate carboxylase; FBP1: Fructose 1,6-bisphosphatase; G6PC: Glucose 6-phosphatase; PGC-1α: Peroxisome proliferator-activated receptor gamma, coactivator 1 alpha; IRS-1: Insulin receptor substrate 1.

in HCC, while, the expression of miR-338-3p was increased after HCC cells treatment with 125I irradiation, which was considered as a potential strategy for HCC. The up-regulated miR-338-3p elevates the suppression of PFKL expression, thereby inhibiting glycolysis of HCC [33].

Moreover, miRNAs can regulate PFKFB to inhibit glycolysis. For instance, miR-139-5p reduced the expression of HKI and PFKFB3, thereby inhibiting aerobic glycolysis [27]. PFKFB is an allosteric activator of PFK1 and an effective stimulator of glycolysis. PFKFB3 is related to many aspects of tumorigenesis and development. And recent studies also found that PFKFB3 regulates immune response and the sensitivity of sorafenib in HCC [17, 34].

MiRNAs and PK: PK is the last rate-limiting enzyme in glycolysis, which transfers phosphate group from phosphoenolpyruvate to adenosine diphosphate (ADP) to produce pyruvate ATP [35]. So it is not surprising that miRNAs can regulate glycolysis and the progression of HCC through manipulating PKM2 expression. For example, miR-199a, miR-491-5p, miR-338-3p, and miR-122 act as a tumor suppressor that induces apoptosis, growth arrest and suppresses glycolysis of HCC cells by direct binding to 3'UTR of PKM2, which is one of isozymes of pyruvate kinase PK, and is universally expressed in embryonic development, tissue repair, and tumors [36-39].

Several miRNAs act as cancer-promoting factors by promoting PKM2 activation. For example, miR-4417 could promote the phosphorylation of PKM2 and facilitates the proliferation and glycolysis of HCC cells [40]. miR-365a-3p dampens PKM2 degradation and provokes Akt/mTOR signaling pathway activation via targeting linc01554, and thereby accelerates glycolytic of HCC cells [41].

MiRNAs not only manipulates the proliferation, metastasis and invasion of HCC through regulating PKM2, but also regulates the drug sensitivity of HCC. MiR-374b reverses the sensitivity of sorafenib-resistant HCC cells to sorafenib by counteracting PKM2-mediated glycolysis pathway via binding to the 3'-UTR of hnRNPA1, which is a RNA-binding protein [42]. It provides new ideas for the treatment of sorafenib resistance.

MiRNAs and lactate dehydrogenase: Lactate dehydrogenase A (LDHA) catalyzes the last key step of glycolysis, catalyzing lactate dehydrogenation to pyruvate. Down-regulation of LDHA expression notably inhibits the proliferation, invasion and migration of HCC cells [43]. Several miRNAs act as tumor suppressors, and decrease the expression of LDHA by binding to the 3'-UTR of LDHA mRNA, thereby inhibiting aerobic glycolysis. For instance, miR-142-3p, miR-383, miR-34a and miR-100-5p inhibit aerobic glycolysis and cell proliferation of HCC by targeting the 3'-UTR of LDHA [44-47].

MiRNAs and HIF-1α: Emerging data have indicated that hypoxia of cancer cells is the initial factor for malignant transformation and even metastasis of tumors, and also one of the key factors that lead to the resistance of tumor cells to radiochemotherapy [48]. Among them, hypoxia-inducible factor-1 alpha (HIF-1α) is an important transcriptional regulator under hypoxia, which has the function of promoting tumor angiogenesis and glucose metabolism, affecting tumor cell proliferation [49]. Under the induction of HIF-1α, glycolytic-related enzyme expression increased, which further increase glycolytic activity, thus improve the imbalance between energy supply and energy consumption caused by hypoxia in tumors [50].

Several miRNAs have been demonstrated to deceased the efficacy of glycolysis by suppressing HIF-1α expression. For instance, miR-592 disrupts HIF-1α protein stabilization and inhibited glycolysis in HCC cells via targeting WSB1 mRNA [51]. Moreover, WSB1 negatively regulates JAK-STAT signaling pathway. MiR-199a-5p inhibits glycolysis by directly targets HIF-1α [52]. Interestingly, HIF-1α overexpression can in turn inhibit the abundance of miR-199a-5p under hypoxic environment. miR-3662 directly targets HIF-1α, and negatively regulates the activation of ERK and JNK signaling pathways in HCC, thereby dampened glycolysis [53]. miR-145 attenuates the expression of HIF-1α and PDK1, opposing glycolysis and suppress cell survival of HCC cells [54].

Other mechanisms: MiR-129-5p targets the mitochondrial matrix protein pyruvate dehydrogenase kinase 4 (PDK4), which diminished phosphorylation of the E1α subunit of pyruvate dehydrogenase (PDH) complex and hinders glycolysis [55].

MiR-873 promotes the Warburg effect through activating AKT/mTOR signaling pathway via targeting NDFIP1, which triggers metabolic shift and NDFIP1 was shown to suppress the PTEN/AKT signaling pathway activation [56].

MiRNAs also involved in glycolysis of HCC by regulating circadian gene expression. For example, miR-199b-5p prevents glycolysis via inhibiting NPAS2 expression, which is a circadian gene and notable boosts glycolysis through elevating the transcription of HIF-1α and downregulated the expression of PGC-1α [57]. Numerous studies have indicated that the consequences of circadian rhythm disturbances are related to many diseases, including obesity, type 2 diabetes and cancer [58]. Additionally, NPAS2 promoted glycolysis by heterodimeric with BMAL1, another core circadian rhythm factor, which regulates the expression of a variety of target genes including glycolysis in HCC cells [57].

MitomiR-181a-5p damages mitochondrial function and accelerates glycolysis in HCC by regulating the electron transport chain (ETC) [59]. MitomiRs refers to miRNAs located in the mitochondria. It is well known that mitochondria are the site of oxidative phosphorylation and adenosine triphosphate (ATP) production, and the explanation of the mechanism of oxidative phosphorylation is mainly based on the electron transport chain [60]. So it is not surprising that dampened ECT can inhibit oxidative phosphorylation and promotes glycolysis in HCC.

miR-342-3p and miR-455-5p attenuate glycolysis of HCC cells by target insulin-like growth factor-1 receptor (IGF-1R), which has been verified to activates the intracellular AKT signaling pathway, then up-regulates the expression of GLUT1 on the plasma membrane and enhances glycolysis in HCC cells [61, 62].

MiRNAs involved in PPP

The PPP is also known as hexose phosphate bypass, which is a glucose catabolic pathway commonly found in animals, plants and microorganisms. In addition to providing energy, the PPP provides a variety of raw materials for anabolic metabolism, for example, NADPH and ribose-5-phosphate. Therefore, the PPP is an important multifunctional metabolic pathway [63, 64].

Multiple lines of evidence indicated that miRNAs participate in PPP by altering G6PD expression. G6PD is a rate-limiting enzyme of the PPP, and its expression is significantly up-regulated in HCC. MiR-122 plays a tumor suppressive role in HCC and dampens PPP process by targeting G6PD [65].

MiRNAs involved in gluconeogenesis

Gluconeogenesis is the process by which an organism converts a variety of non-carbohydrate carbon substrates into free glucose. In mammals, the liver is the main organ of gluconeogenesis that ensures the blood sugar levels are normal. It has been reported that gluconeogenesis pathway is reduced in HCC. Additionally, Metformin was originally considered as an oral hypoglycemic agent. Recently, metformin has attracted people's attention due to its anti-tumor therapeutic effect in inhibiting liver gluconeogenesis [22].

Gluconeogenesis and glycolysis are coordinated, glycolysis is extremely active in HCC cells, and thereby the activity of gluconeogenesis is inhibited accordingly. Gluconeogenesis appears to be the reverse reaction of glycolysis, because the seven steps of gluconeogenesis are all reverse reactions of glycolysis and are catalyzed by the same enzymes. But there are three steps in glycolysis, which are irreversible reactions, and these three steps must be bypassed during gluconeogenesis [66].

These three steps are bypassed by the following three rate-controlling enzymes: phosphoenolpyruvate carboxykinase (PEPCK), Fructose 1,6-bisphosphatase (FBP1), and glucose 6-phosphatase (G6Pase) [67]. They can not only affect the overall speed of the entire metabolic pathway but also change the direction of metabolism.

Emerging evident verified that miRNAs play critical roles in gluconeogenesis of HCC by influencing the expression of the rate-controlling enzyme, including PEPCK, FBP1 and G6PC.

MiRNAs and PEPCK: PEPCK is the first rate-controlling enzyme of gluconeogenesis, which catalyzes the irreversible reaction of phosphoenolpyruvate (PEP) and HCO3- to oxaloacetate (OAA) and inorganic phosphoric acid. It is the first and most important reaction in the pro-

cess of gluconeogenesis [68]. Accumulating evidence has indicated that PCK1 overexpression could block the glycolysis process and initiate the gluconeogenesis process by potentiating PEPCK expression.

MiR-4641 attenuates the expression of PEPCK by targeting PCK1, thereby inhibiting gluconeogenesis and promoting the growth and migration of HCC cells [69]. PCK1 is the coding gene of PEPCK and is widely involved in metabolic and biological processes such as glucose metabolism, lipid metabolism, diabetes, and tumor cell proliferation and apoptosis [70].

MiRNAs and FBP1: FBP1 is the second rate-controlling enzyme of the gluconeogenesis process. It hydrolyzes fructose 1,6-diphosphate (FDP) to phosphoric acid and fructose 6-diphosphate (F6P) [67]. The expression of FBP1 was suppressed in various cancers. In addition, HCC patients with low FBP1 expression have a higher malignant classification, including tumor enlargement, poor differentiation, impaired gluconeogenesis and enhanced glycolysis [71]. Therefore, FBP1 is expected to become a reliable prognostic marker for HCC patients.

MiR-517a inhibits gluconeogenesis, promotes glycolysis of HCC via directly targeting FBP1 [72]. MiR-517a was dominantly overexpressed and FBP1 expression was significantly lower in HCC cells and tissues. Ectopic expression of FBP1 upregulates gluconeogenesis and weaken miR-517a induced cell proliferation.

MiRNAs and G6Pase: G6Pase is the last rate-controlling enzyme of the gluconeogenesis process, which catalyzes glucose 6 phosphates to glucose [67]. G6Pase expression is significantly decreased in HCC cell lines and clinical tissue, G6Pase expression also correlated with tumor grade in HCCs. Moreover, G6Pase deficiency leads to glycogen storage disease type-Ia (GSD-Ia), while HCC is a long-term complication of GSD-Ia. Restore G6Pase expression normalizes glucose homeostasis and prevents the development of HCC in the initial stage [73].

Recently, several miRNAs have been proved to reduce gluconeogenesis of HCC by suppressing the expression of G6Pase. Wang et al. showed that miR-23a inhibits gluconeogenesis and promotes HCC progression by targeting G6PC, which is encoding the key gluconeogenic enzymes

G6Pase, thereby suppressing the expression of G6Pase [74]. Moreover, miR-23a inhibits gluconeogenesis via targeting peroxisome proliferator-activated receptor gamma, coactivator 1 alpha (PGC-1α), which has been demonstrated to accelerate hepatic gluconeogenesis in previous studies [75].

Other mechanisms: Jeong et al. found that miR-96 is up-regulated in mitochondrial dysfunction HCC cells and exhibit insulin resistance. Furthermore, mitochondrial dysfunction induced miR-96 overexpression, increase the level of gluconeogenesis in HCC cells via targeting the 3'UTR of Insulin receptor substrate 1 (IRS-1), which resulted in inhibition of gluconeogenesis in HCC cells [76].

It has been affirmed that mammalian cells utilize glutamine (Gln) as an alternative energy source of glucose and as an anaplerotic source for biomass generation. Glutamine-derived oxaloacetate is converted to PEP by PEPCK2, and then participates in the gluconeogenesis and other biosynthesis pathways [77]. Some miRNA can regulate gluconeogenesis by altering glutamine metabolism. For example, the level of miR-122 is reduced in HCC, and its expression is negative correlates with malignant classification. Silence miR-122 expression promoted glutaminolysis but suppressed gluconeogenesis in the mouse model. In contrast, ectopic expression of miR-122 promotes gluconeogenesis [78].

LncRNAs

LncRNAs refers to transcripts longer than 200 nucleotide units and is not involved in protein-coding [79]. LncRNAs regulations are diverse, which have been shown to regulate almost every step of gene expression. LncRNAs may serve as signals, decoys, guides or scaffolds. They also act as "sponge" or competing endogenous RNAs (ceRNAs) through the combination of their complementary miRNA response elements (MREs) and the primary miRNAs, playing a positive or negative role in the processing and expression of mature mRNAs, thereby indirectly participating in a variety of physiological process [80].

Growing researches have reported that lncRNAs play an important role in various tumors, including HCC. Although lncRNAs have been exten-

Table 2. LncRNAs and circRNAs involved in glucose metabolism in HCC

Glucose metabolism	LncRNA/ circRNA	Effect	Target	Mechanism	Signaling pathway	Reference
glycolysis	linc01554	Decrease	-	Promote PKM2 ubiquitination	Inactive Akt/mTOR	[42]
	lncRNA Ftx	Increase	-	Promote GLUT	active PPARγ	[85]
	lncRNA WFDC21P	Decrease	-	Suppress PFKP and PKM2 transcription	-	[86]
	linc-RoR	Decrease	miR-145	Inhibit HIF-1α and PDK1 expression	-	[54]
	lncRNAIDH1-AS1	Decrease	-	Inhibit HIF-1α expression	-	[89]
	lncRNA RAET1K	Increase	miR-100-5p	Increase LDHA expression	-	[47]
gluconeogenesis	MALAT1	Decrease	-	Enhance TCF7L2 translation	Active Wnt and mTOR pathway	[90]
glycolysis	circMAT2B	Increase	-	Promote PKM2 expression	-	[39]
gluconeogenesis	circC3P1	Increase	miR-4641	Promote PCK1 expression	-	[69]

"-": unknown. Abbreviations: HCC: Hepatocellular carcinoma; PKM2: Pyruvate kinase M2; HIFs: Hypoxia-inducible factors; GLUT: Glucose transporters; PPARγ: Peroxisome proliferator-activated receptor γ; PFKP: the platelet isoform of phosphofructokinase; PDK1: Pyruvate dehydrogenase kinase; LDHA: Lactate dehydrogenase A; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; TCF7L2: Transcription factor 7 like 2.

sively studied in regulating gene expression, the role of lncRNAs in glucose metabolism is not yet clear. The related research contents are listed in **Table 2**.

LncRNAs involved in glycolytic pathway

An increasing number of studies have verified that lncRNAs could influence the glycolysis pathway in a variety of tumors by regulating the expression and activation of glycolytic enzymes. We summarize the influence of lncRNAs on glycolytic pathway and related mechanisms, including PI3K/Akt/mTOR pathway, PPARγ, PFK/PKM2, and HIF-1α, so as to find potential and effective targeted therapies for HCC.

LncRNAs and PI3K/Akt/mTOR pathway: The PI3K/AKT/mTOR pathway is an intracellular signaling pathway that is often activated in various types of cancer cells, and its regulatory role in the process of glycolysis has been emphasized in HCC [81].

Linc01554 diminished the rate of glycolytic by accelerating PKM2 degradation and suppresses Akt/mTOR signaling pathway activation. Linc01554 is highly expressed in liver, while it is frequently down-regulated in HCC in the level of protein mRNA and DNA contrast with adjacent normal tissues. Moreover, silence linc01554 was significantly associated with aggressive clinicopathological features [41]. Furthermore, overexpression of linc01554 in combination with Akt inhibitor MK2206 exhibits a synergistic effect compared with used each alone, which shed new light on introducing Akt inhibitor to HCC treatment.

LncRNAs and PPARγ: Peroxisome proliferator-activated receptor γ (PPARγ) belongs to the family of PPARs, which plays a crucial regulatory role in cell differentiation, proliferation, metabolism and tumorigenesis [82]. Currently, PPARγ is the most extensively researched subtype. It has been demonstrated that ectopic expression of PPARγ inhibits WNT/β-catenin pathway and then downregulates PDK1, thus suppressed glycolysis [83].

LncRNA Ftx facilitates glucose consumption through promotes GLUT, including GUL1 and GUL4, and inhibits tumor necrosis factor (TNF) α and leptin expression via targeting PPARγ in HCC cells [84]. Furthermore, lncRNA Ftx potentiates glycolysis of HCC via directly targeting PPARγ, which elevating the activity and expression of glycolytic enzymes (LDH and PFKL) and decreases the activity of Krebs-cycle-associated molecules (TNFα, leptin and PDK1).

LncRNAs and PFK/PKM2: LncRNA WFDC21P diminished glycolysis via decreasing the expression and activity of PFKP and PKM2 [85]. Moreover, lncRNA WFDC21P is positively regulated by Nur77, which is a member of the orphan nuclear receptor NR4A family. Nur77 is down-regulated in HCC and shows the ability to inhibit glycolysis and promotes gluconeogenesis by stabilizing PEPCK1 [86]. Additionally, Linc01554 diminished the rate of glycolytic by accelerating PKM2 degradation [41]. LncRNA Ftx contributes to glycolysis of HCC via enhancing the activity and expression of PFKL [84].

LncRNA and HIF-1α: Recently, Takahashi et al. uncover linc-RoR knockdown significantly decreased HIF-1α expression as well as PDK1

expression, especially under hypoxia stress. Linc-RoR is a hypoxia-responsive lncRNAs, and thereby cancer cells release a large amount of linc-RoR under hypoxia context, facilitating cell survival in recipient cells by promoting glycolysis. In detail, Linc-RoR severs as a miRNA "sponge" to limit miR-145, which attenuates the expression of HIF-1α and PDK1, opposing glycolysis and suppress cell survival of HCC cells [54].

LncRNAIDH1-AS1 potentiates the activity of isocitrate dehydrogenase 1 and augments the production of α-ketoglutarate under normoxia, attenuating the expression of HIF-1α and inhibits glycolysis. Furthermore, MYC-dependent inhibition of lncRNAIDH1-AS1, induction of the Warburg effect by HIF1α [87].

Additionally, HIF1α boosting lncRNA RAET1K expression and facilitates glycolysis by binding to the promoter region of lncRNA RAET1K, and lncRNA RAET1K sponge miR-100-5p, which directly binging to LDHA and significantly inhibits glycolysis [47].

LncRNAs involved in gluconeogenesis

LncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) acts as an oncogene in HCC. MALAT1 potentiated glycolytic and attenuated gluconeogenesis by enhancing the expression of Transcription factor 7 like 2 (TCF7L2) [88]. TCF7L2 is one of the earliest genes to be found and deeply studied and TCF7L2 transcription factor strongly activates the Wnt signaling pathway. And gluconeogenesis has been shown to be negatively regulated by TCF7L2 [89].

Moreover, MALAT1 activates the mTORC1 pathway by increasing phosphorylation of eIF4E binding protein (4EBP1) and enhancing the expression and function of the splicing oncoprotein SRSF1. 4EBP1 is an important downstream effector of mTORC1 pathway, and SRSF1 has been reported to activate mTOR and protein translation. Both the Wnt and mTOR signaling pathways have been suggested to play a negative regulator role in gluconeogenesis program of HCC [90].

CircRNAs

CircRNAs, a group of endogenous ncRNAs with covalently closed continuous circular structure formed by exon circularization [91]. However, circRNAs were considered to be caused by splicing errors and without function in the previous. Due to the rapid development of high-throughput sequencing, increasingly circRNAs have been discovered and proved to be involved in a variety of biological processes.

The potential functions of circRNAs include: a) served as "miRNA sponge", inhibit the function of the target miRNAs, one circRNAs may "sponge" multiple mRNAs; b) regulate the splicing of pre-mRNA, thereby affecting protein production; c) interact with proteins; d) translated into protein or polypeptide; e) Regulate the expression of parental genes [92].

Emerging evidence indicates that changes in circRNA expression profiles play pivotal roles in the initiation and development of various cancers, including breast cancer [93], colon cancer [94], gastric cancer [95] and HCC [96]. Even though various studies have highlight miRNAs and lncRNAs partly account for glucose reprogram of HCC, it was very limited research about circRNAs was involved in metabolic regulation in HCC. Recently, Li et al. found that circRNA MAT2B promotes glycolysis and endows HCC cells with clinical aggressiveness under hypoxic [38]. Mechanistically, circMAT2B promotes glycolysis and HCC progression via increasing the abundance of the miR-338-3p, which subsequently blocking PKM2. Moreover, circRNA circC3P1 has been proved to promote the gluconeogenesis process and suppress HCC growth and metastasis through miR-4641/PCK1 pathway [69]. CircC3P1 enhancing the expression of PCK1 by sponging miR-4641 in HCC. PCK1 is the coding gene of PEPCK, which is a rate-controlling enzyme of gluconeogenesis.

Conclusion and future directions

Glucose is the main nutritional component of the animal body, and a unique source of fuel for some organizations to generate and sustain biological function. The reprogramming of glucose metabolism is one of the hallmarks of HCC. This reprogramming is caused by various factors and is closely related to the initiation, development and poor prognosis of HCC. The glucose metabolic differences between HCC and normal cells may become potential new targets. Some related drugs are already undergoing clinical trials and are expected to be used in clinical later (**Table 3**).

Table 3. Glucose metabolism targets and drugs which are in preclinical and clinical development for anti-tumor therapy

Target	Drug	Status	References
GLUTs	Phloretin	Preclinical	[99, 100]
	Fasentin	Preclinical	[101]
	STF-31	Preclinical	[102]
	WZB117	Preclinical	[103]
	Ritonavir	Phase III	[104]
	Silybin	Phase I	[105]
HKII	2-Deoxy-D-glucose	Phase II	[106, 107]
	Lonidamine	Phase II	[108]
	Genistein-27	Preclinical	[109]
	Benserazide	Preclinical	[110]
	Resveratrol	Phase I	[111]
	Astragalin	Preclinical	[25]
	Chrysin	Preclinical	[112]
PDK	Dichloroacetate	Phase I	[113-115]
LDHA	Oxamate	Preclinical	[116]
	FX11	Preclinical	[117]
	Quinoline-3-sulfonamide	Preclinical	[118]
	GNE-140	Preclinical	[119]
	PSTMB	Preclinical	[120]
PKM2	Shikonin	Preclinical	[121]
	Benserazide	Preclinical	[122]
PFKFB	3PO	Preclinical	[123]
	PFK158	Preclinical	[124]
GAPDH	Bromopyruvate	Preclinical	[125]
IDH	Enasidenib	Approved	[126]
	Ivosedinib	Approved	[127]
	DS-1001b	Preclinical	[128]
	Olutasidenib	Preclinical	[129]
	GSK864	Preclinical	[130]
	BAY1436032	Preclinical	[131]
	HMS-101	Preclinical	[132]
	I-8	Preclinical	[133]

Abbreviations: GLUT: Glucose transporters; HK: Hexokinase; PDK: Pyruvate dehydrogenase kinase; LDHA: Lactate dehydrogenase A; PKM2: Pyruvate kinase M2; PFKFB3: 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; GAPGH: glyceraldehyde-3-phosphate dehydrogenase; IDH: Isocitrate dehydrogenase.

Extensive studies have demonstrated the functions of ncRNAs in glucose reprogramming. It provides us a novel perspective of tumorigenesis and potential therapeutic targets. In addition, the aberrant expression of glucose metabolism related ncRNAs may be serving as biomarkers for the diagnosis or prognosis of HCC. Moreover, some ncRNA-based therapeutics for other diseases has been used in clinical treatment. Although these ncRNAs may only serve as a fine-tuning mechanism, the synergistic effect of multiple ncRNAs may lead to specific major metabolic changes in glucose metabolism in HCC. For example, Tang et al. synthesizes an artificial lncRNA (AlncRNA) that could target multiple sorafenib-resistance-related miRNAs simultaneously, including miR-21, miR-153, miR-216a, miR-217, and miR-494, restore the sensitivity of drug-resistant HCC cells to sorafenib again [97]. It brings a bright research prospect that ncRNAs combined with the glucose-metabolism-related-enzyme inhibitors would be a better choice than utilized inhibitors alone in the battle against HCC.

However, there are still some difficulties remain to be overcome. First, researches on glucose-metabolism-related ncRNAs are still very limited, especially in lncRNAs and circRNAs, which urgently needed to be explored. Second, how to efficiently deliver ncRNA molecules to the target is the biggest problem facing in their clinical application. There are several major problems with ncRNA compounds delivery: 1) Naked single-stranded RNA molecules are easily degraded by nucleases in the physiological environment; 2) RNA molecules are immunogenic and activate the immune system; 3) ncRNAs are biological macromolecules, and they are negatively charged, making it difficult to cross the cell membrane into cells; 4) The toxic effects of ncRNAs are unknown and may overlap the toxicity of existing chemotherapy drugs. 5) Liver is the site where the drug is acting and the site where the drug is metabolized. The amount of medicine, adverse reactions, and treatment of adverse reactions in patients with HCC need attention [98]. Therefore, it is necessary to design a suitable ncRNA de-

livery method or delivery vector to deliver ncRNAs to the target site to fully realize its huge disease treatment potential.

After decades of searching for ncRNA-based therapeutics, some ncRNA-based therapeutics has been approved for disease treatment. The development of ncRNA-based therapeutics in the future will focus on three aspects: 1) explore more ncRNA molecules that are critical for different glucose metabolism steps. 2) develop chemical modification technology for nucleic acid therapeutics to further improve the efficiency of ncRNA-based therapeutics; 3) develop diverse delivery systems for different types of ncRNA-based therapeutics based on the size and mechanism of action of ncRNAs; 4) combining ncRNA-based therapeutics with a variety of other drugs, such as combining ncRNAs with gene-editing tools, including CRISPR/Cas9-gRNA, antibodies, small molecules, or chemotherapeutics to maximize the effect of HCC treatment; 5) design individualized ncRNA-based therapeutics according to the etiology classification of patients by using gene sequencing technology.

Taken together, ncRNA-based therapies in orchestrates glucose metabolism of HCC have promising prospects. However, the evidence for the practical clinical application of ncRNAs is still very limited and desirable for further investigation.

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Disclosure of conflict of interest

None.

Abbreviations

HCC, Hepatocellular carcinoma; ncRNA, Noncoding RNA; miRNA, MicroRNA; lncRNA, Long noncoding RNA; circRNA, Circular RNA; TACE, Transcatheter arterial chemoembolization; GLUT, Glucose transporters; PPP, Pentose phosphate pathway; ATP, Adenosine triphosphate; HBP, Hexosamine biosynthetic pathway; HK, Hexokinase; PFK, 6-phosphate fructokinase; PK, Pyruvate kinase; HIFs, Hypoxia-inducible factors; VDAC, Voltage-dependent anion channel 1; 3'-UTR, 3'-untranslated region; AMPKβ2, AMP-activated protein kinase subunit beta 2; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; ADP, Adenosine diphosphate; PKM2, Pyruvate kinase M2; LDHA, Lactate dehydrogenase A; SOCS, Suppressor of cytokine signaling; ETC, Electron transport chain; IGF-1R, Insulin-like growth factor-1 receptor; PDK4, Pyruvate dehydrogenase kinase 4; PDH, Pyruvate dehydrogenase; PEPCK, Phosphoenolpyruvate carboxylase; FBP1, Fructose 1,6-bisphosphatase; G6PC, Glucose 6-phosphatase; GSD-Ia, Glycogen storage disease type-Ia; PGC-1α, Peroxisome proliferator-activated receptor gamma, coactivator 1 alpha; FDP, Fructose 1,6-diphosphate; PEP, Phosphoenolpyruvate; OAA, Oxaloacetate; TCA, Tricarboxylic acid; IRS-1, Insulin receptor substrate 1; Gln, Glutamine; PPARγ, Peroxisome proliferator-activated receptor γ; TNF, Tumor necrosis factor; MALAT1, Metastasis-associated lung adenocarcinoma transcript 1; TCF7L2, Transcription factor 7 like 2; 4EBP1, eIF4E binding protein; gRNA, Guide RNA.

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