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**Reprogramming of glucose metabolism in hepatocellular carcinoma: Progress and prospects**

Shang RZ *et al*. Aerobic glycolysis in hepatocellular carcinoma

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**Abstract**

Hepatocellular carcinoma (HCC) is one of the most lethal cancers, and its rate of incidence is rising annually. Despite the progress in diagnosis and treatment, the overall prognoses of HCC patients remain dismal due to the difficulties in early diagnosis and the high level of tumor invasion, metastasis and recurrence. It is urgent to explore the underlying mechanism of HCC carcinogenesis and progression to find out the specific biomarkers for HCC early diagnosis and the promising target for HCC chemotherapy. Recently, the reprogramming of cancer metabolism has been identified as a hallmark of cancer. The shift from the oxidative phosphorylation metabolic pathway to the glycolysis pathway in HCC meets the demands of rapid cell proliferation and offers a favorable microenvironment for tumor progression. Such metabolic reprogramming could be considered as a critical link between the different HCC genotypes and phenotypes. The regulation of metabolic reprogramming in cancer is complex and may occur via genetic mutations and epigenetic modulations including oncogenes, tumor suppressor genes, signaling pathways, noncoding RNAs, and glycolytic enzymes etc. Understanding the regulatory mechanisms of glycolysis in HCC may enrich our knowledge of hepatocellular carcinogenesis and provide important foundations in the search for novel diagnostic biomarkers and promising therapeutic targets for HCC.

**Key words:** Hepatocellular carcinoma; Metabolic reprogramming; Aerobic glycolysis; Glucose metabolism; Noncoding RNAs

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**Core tip:** The reprogramming of glucose metabolism is one of the peculiar characteristics of cancer cells. This paper addresses the regulatory mechanism of glucose metabolism in hepatocellular carcinoma (HCC) and prospects its future application for HCC treatment.

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**INTRODUCTION**

Hepatocellular carcinoma is the second leading cause of cancer-related death in the world, responsible for approximately 700000 deaths annually[1]. Although many treatment options have been developed and used in the clinic, including hepatic resection, local ablation, liver transplantation and molecular targeted therapies, patients’ prognoses remain poor[2]. Etiological studies of HCC revealed that hepatitis viruses, alcohol and aflatoxin might be the main risk factors for HCC[3]. In different areas of the world, HCC caused by these risk factors alone or together exhibits great diversity in genotype and phenotype, which impede the research of HCC. One remarkable feature of HCC is the alteration of glucose metabolism, which may be a critical link between the different HCC genotypes and phenotypes. Thus, a thorough understanding of cancer metabolism may offer promising therapeutic strategies for HCC in the future.

As early as the 1950s, Otto Heinrich Warburg first characterized cancer cell metabolism. Cancer cells principally use the glycolysis pathway to metabolize glucose and generate ATP whether there is sufficient oxygen present. This phenomenon now referred to as the “Warburg effect” was described and lead to a wave of investigation of cancer metabolism over several decades[4]. In the 1980s, the availability of 18F-deoxyglucose positron emission tomography (FDG-PET) pushed the study of tumor metabolism to the climax[5]. Observations from FDG-PET scanning revealed that approximately 50%-70% ATP was generated by glycolysis in different tumor types[6-8]. The application of FDG-PET was also recently involved in the detection and monitoring of metastasis and the recurrence of HCC and for prediction of patient’s prognosis[9-12]. Moreover, recent studies of metabolomics offer new mechanistic insights into aerobic glycolysis and provide promising individualized therapeutic strategies by targeting the Warburg effect for treatment of HCC[13,14].

In this article, we will review the recent investigations of glucose metabolism in HCC and summarize the regulation methods of metabolic reprogramming. Moreover, we will describe the development of therapy by targeting cancer metabolism.

**Reprogramming of glucose metabolism-related enzymes and transporting proteins in HCC**

As previously described, tumor cells rely on the aerobic glycolysis pathway to consume glucose and generate ATP, which is a rapid but low-efficiency metabolic process[15]. To meet the demands of energy, biosynthesis and redox for tumor progression, cancer cells reprogram their metabolic related enzymes and transporting proteins to facilitate increased glucose uptake, acceleration of glycolysis and metabolic end-product excretion (Figure 1).

The initial step of glycolysis is the transportation of glucose across the plasma membrane into the cytoplasm, which depends on the family of glucose transporters (GLUTs)[16]. Much evidence has shown that GLUT1-4, particularly GLUT1, are often aberrantly expressed in different cancer types and significantly influence cancer glucose metabolism[17-21]. Amann *et al*[22] observed that both mRNA and protein expression levels of GLUT1 were significantly up-regulated in HCC, and this plays a critical role in glucose transport, glycolysis and tumor progression in HCC cells. Daskalow *et al*[23] analyzed GLUT2 expression in 60 HCC samples and revealed the over-expression of GLUT2 in HCC. Another study demonstrated that positive GLUT2 predicts worse prognosis in HCC patients[24]. To the best of our knowledge, studies of GLUT3 and GLUT4 in HCC have not been conducted.

Several glycolysis-related key enzymes have been demonstrated to participate glycolysis and carcinogenesis in HCC. Hexokinase (HK) family members catalyze the first key step of glycolysis in which glucose is phosphorylated to become glucose 6-phosphate (G-6-P). In the HK family, HK2 shows the highest affinity for glucose and is up-regulated in HCC and correlated with poor prognosis[25]. PET-CT scans showed that over-expression of HK2 promotes the uptake of 18FDG in HCC cells[26], which suggested that HK2 has a critical role in HCC glycolysis. The latest study showed that HKDC1, a newly discovered HK family member, was up-regulated in HCC with poorer prognosis and inhibited HCC cellular proliferating and migration in vitro, probably by repression of the Wnt/beta-catenin pathway[27]. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) may also play an important role in HCC glycolysis. GAPDH used to be regarded as a stably expressed gene and was commonly used as a reference gene in the past. Recent studies have reported the aberrant expression of GAPDH in malignancies and raised the concern that it may play a role in tumor glycolysis[28]. Gong *et al*[29] showed that increased expression of GAPDH promoted glycolysis and tumor progression in HCC. Moreover, GAPDH was able to affect glycolysis *via* regulating metabolism-related pathways such as the mammalian target of rapamycin (mTOR)-complex1 (mTOR-C1) signaling pathway[30]. Pyruvate kinases (PKs) catalyze the last step of glycolysis to produce ATP and pyruvate, which regulates the influx of the glycolysis pathway together with HK and phosphofructokinase-1 (PFK-1). PKs contain 4 isoforms (PKL, PKR, PKM1 and PKM2) that are encoded by the PKL and PKM genes. PKL and PKR are mainly expressed in liver cells and erythrocytes, respectively, whereas PKM1 is constitutively expressed in normal cells. The over-expression of PKM2 was frequently observed in malignances and predicts worse prognosis[31,32]. A recent study demonstrated that the expression of PKM2 is up-regulated in HCC and is a predictor of survival and recurrence[33]. Dong *et al*[34] revealed the oncogenic role of PKM2 in HCC proliferation by its regulation of the expression of HIF-1α and Bcl-xL. Another study further observed that PKM2 effects on cell growth depend on a glucose rather than glutaminolysis pathways by using PKM2 knockdown-sensitive HCC cells. Additionally, the switching from PKL to PKM2 was reported to promote the rate of glucose uptake and increase the oxidative stress in hepatocarcinogenesis[35]. Lactate dehydrogenase (LDH) catalyzes the conversion of pyruvate to lactate. Up-regulation of the LDHA subunit in cancers has been noticed due to its role in promoting glycolysis and reducing the oxygen dependency of cancer cells[36,37]. A recent study has indicated that LDHA is up-regulated in HCC cells and promotes tumor growth and metastasis[38]. A series of clinical studies assessed the serum levels of LDH in HCC patients who were treated with hepatic resection[39,40], transarterial chemoembolization (TACE)[41,42] and sorafenib[43,44] and found a similar conclusion that LDH may be an easily obtained biomarker for prognosis prediction and treatment selection for HCC patients.

Activation of the glycolysis pathway in cancer cells not only provides sufficient ATP for tumor progression but also produces acid by-products such as lactate. To avoid apoptosis caused by the accumulation of acids in cells, the monocarboxylate transporters (MCTs) are up-regulated in cancer cells to speed up the export of lactate into the extracellular milieu. Aberrant expression of isoforms MCT1, MCT2 and MCT4 was frequently observed in many cancers including colorectal carcinoma[45], glioblastoma[46] and gallbladder cancer[47]. The role of over-expressed MCT4 in HCC has been illustrated. It is associated with HCC progression and poor prognosis[48,49]. The latest study observed the reduced expression of MCT1 and MCT2 in HCC[50]. However, the data from another study showed that MCT1 was over-expressed in HCC cells which facilitates the lactate exporting and promotes HCC glycolysis[51]. Therefore, further studies are still needed to illuminate the specific role of MCT1 and MCT2 in HCC glycolysis and progression.

**regulatory mechanism of glucose metabolic reprogramming**

***Oncogenes and tumor suppressor genes involved in glucose metabolic reprogramming during carcinogenesis***

Oncogenes are a number of important genes which are over-expressed or mutated in cancer cells that triggered the tumor initiation and maintained the tumor progression. Based on the biological functions, oncogenes are usually classified as growth factors, receptor tyrosine kinases, cytoplasmic tyrosine kinase, regulatory GTPase and transcription factors. The activation of oncogenes is complex and may be attributed to the genetic mutations and the tumor microenvironment. Hypoxic microenvironment is a crucial factor in the activation of some oncogenes. The lack of sufficient blood supply in rapidly proliferating tumor cells leads to hypoxia. HIF-1 is a key transcription factor that is activated in response to oxygen deprivation. In cancer cells, HIF-1 promotes glycolysis by activating glycolytic enzymes[52]. Over-expression of HIF-1 was observed in HCC samples[53] and was shown to promote cell proliferation and resistance to apoptosis by up-regulating FOXM1 expression[54]. [Hamaguchi](http://www.ncbi.nlm.nih.gov/pubmed/?term=Hamaguchi%20T%5BAuthor%5D&cauthor=true&cauthor_uid=18813785) *et al*[55] analyzed 22 glycolysis-related genes in HCC samples and identified 10 potential transcriptional targets of HIF-1α including HK1, HK2, GAPDH and PKM. Interestingly, several studies showed that HIF-1 could be activated by Ras[56] and membrane type-1 matrix metalloproteinase[57] under normoxic conditions, which may provide new insights into cancer glycolysis regulation beyond the hypoxic microenvironment. Myc is another crucial oncogene involved in the Warburg effect. As a vital transcription factor, Myc was first linked with glucose metabolism through its transactivation of LDHA expression[58]. A series of glycolytic enzymes were subsequently identified as direct targets of Myc, including GLUT1 and HK2[59,60]. Moreover, the interplay between Myc and HIF-1 has also been observed, which indicates that Myc may play a complementary role in cancer metabolism under non-hypoxic conditions[61,62]. CD147 (Basigin) is a transmembrane protein that is highly expressed in tumors. A number of studies have shown that CD147 is a “Warburg oncogene” due to its pivotal role in promoting glycolysis and inhibiting oxidative phosphorylation in cancer cells[63,64]. In HCC, CD147 was reported to reprogram glucose metabolism by facilitating lactate export, mediated by MCT1, and promoting glucose uptake by up-regulating GLUT1 expression[51]. Recently, some newly discovered oncogenes were also reported to play important roles in HCC glycolysis. For instance, PIM1 is involved in both aerobic and anaerobic glycolysis by targeting GLUT1 and PKM2[65].

Likewise, tumor suppressor genes also have a great influence on cancer glycolysis. The role of the p53 tumor suppressor gene in cancer metabolism could be summarized as promoting oxidative phosphorylation and reducing glycolysis. The effect of p53 on glycolysis mainly depends on the reduced expression of glucose transporters[66]. Recently, we investigated the role of the tumor suppressor gene Ras-related associated with diabetes (RRAD) in HCC. We found RRAD could suppress the invasion, migration and aerobic glycolysis in HCC cells and identified GLUT1 and HK2 as potential targets for RRAD[67]. Our results were recently verified by Yan *et al*[68] (Table 1).

***Signaling pathways involved in glucometabolic reprogramming***

**AMPK pathway:** The AMP-activated protein kinase (AMPK) is ubiquitously expressed in eukaryotes and acts as an energy status sensor and regulator of energy homeostasis[69]. The activation of AMPK by energetic stress promotes the switching from glycolysis to oxidative phosphorylation. This switching inhibits the “Warburg effect” in rapidly proliferating cells, including tumor cells to spare glucose and restore energy homeostasis[70]. At the same time, the activation of AMPK shuts down the synthesis of RNA, DNA, protein and lipid to inhibit the cell proliferation and growth. The downstream effect of AMPK activation on cancer metabolism has been well established. mTOR is a crucial downstream modulator of AMPK signaling in cancer cells. AMPK inhibits the activity of mTOR either directly or by reducing the activity of the mTOR-activating GTP-binding protein, Rheb, via activation of the Tuberous sclerosis complex 2 (TSC2)[71-73]. Inactivation of mTOR suppresses the expression of HIF-1α, a key regulator of glycolysis, as mentioned previously[52,74]. Recently, several reviews highlighted the regulatory role of AMPK on GLUT4 membrane translocation and GLUT1 activation in skeletal muscle cells and other normal cells[69,75]. In HCC, AMPK signaling pathway was reported to participate in the ciliary neurotrophic factor (CNTF) induced GLUT4 translocation and glucose uptake[76]. Considering the effect of AMPK on the inhibition of glucose uptake in transformed cells, further investigations are greatly needed to clarify the role of AMPK on glucose transporters and glycolytic enzymes in cancer cells.

**PI3K/Akt/mTOR pathway:** The PI3K/Akt pathway is one of the most frequently activated signaling pathways in human cancers including HCC. The PI3K/Akt pathway can be activated by mutated tumor suppressor genes, signaling from receptor tyrosine kinases, or by the PI3K components[77]. The activation of the PI3K/Akt pathway is involved in cell proliferation, cell survival, cell cycle progression and cancer metabolism[78]. Regulation of glucose metabolism by PI3K/Akt signaling is mediated by glycolytic enzymes. Firstly, PI3K/Akt promotes glucose uptake in cells by increasing the membrane translocation and expression of GLUT4[79,80]. In addition, PI3K/Akt promotes glycolysis by activating HK and by the binding of HK2 to the voltage-dependent anion channel (VDAC) in mitochondria[81,82]. Moreover, PI3K/Akt could regulate glycolytic enzymes indirectly by regulating the expression of AMPK and HIF-1[83,84].

***Noncoding RNAs involved in glucose metabolism***

Noncoding RNAs are functional RNAs that are not transcribed into proteins. In the past, noncoding RNAs have been regarded as the “noise” in transcription processes. However, accumulating evidence has suggested the indispensable role of noncoding RNAs in various biological processes including gene transcription and translation. Noncoding RNAs, especially microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) are also reported to be involved in the Warburg effect. The regulatory mechanism of noncoding RNAs in aerobic glycolysis consists of the following two aspects: the regulation of glycolytic enzyme expression and the activation of glycolysis-related oncogenic pathways (Table 2).

Noncoding RNAs were reported to regulate glucose uptake in cancer cells by targeting expression of GLUTs. MicroRNA-340, which increases the glucose uptake and lactate secretion by increasing the expression of GLUT1, was decreased in oral squamous cell carcinoma[85]. [Yamasaki](http://www.ncbi.nlm.nih.gov/pubmed/?term=Yamasaki%20T%5BAuthor%5D&cauthor=true&cauthor_uid=23889809) *et al*[86] evaluated the role of microRNA-1291 in renal cell carcinoma and found that reduced expression of miR-1291 promotes cancer cell proliferation and invasion and migration by direct targeting of SLCA1/GLUT1. [Chen](http://www.ncbi.nlm.nih.gov/pubmed/?term=Chen%20B%5BAuthor%5D&cauthor=true&cauthor_uid=25304371) *et al*[87] demonstrated that miR-22 regulates GLUT1 expression and inhibits the proliferation and invasion of breast cancer. MicroRNA-144 was also reported to mediate the metabolic shift by regulating GLUT1 expression in lung and ovarian cancers[88,89]. Moreover, miR-195-5p inhibits the glucose uptake by down-regulating GLUT3 expression and thus reduces proliferation in bladder cancer cells[90]. The expression of GLUT4 is also regulated by microRNAs, including miR-113[91] and miR-223[92]. MicroRNA-143 is a key regulator of HK2 in cancer. Studies have shown that miR-143 negatively regulates the expression of HK2 and thus modulates glycolysis in colon cancer[93], lung cancer[94] and head and neck squamous cell carcinoma[95]. In breast cancer cells, HK2 was regulated by the miR-155/miR-143 cascade at the post-transcriptional level[96]. Burchard *et al*[97] showed the up-regulation of miR-122 reduced lactate production and increased oxygen consumption in HCC. A subsequent study further demonstrated that miR-122 reduced the expression of PKM2 and thus repressed glycolytic activities[98]. Other microRNAs, including miR-133a/b and miR-326, were reported to regulate PKM2 expression in cancers[99,100]. Phosphofructokinase (PFK) catalyzes the conversion from fructose-6-phosphate to fructose-1, 6-bisphosphate and is over-expressed in cancers. A recent study showed that the miR-52 family mediated the regulation of Tat-activating regulatory DNA-binding protein (TARDBP) on PFK in HCC[101]. Some microRNAs were able to regulate multiple glycolytic enzymes. For instance, miR-34a was reported to regulate key enzymes including HK1, HK2, GPI, LDHA and PDK1[102,103]. Additionally, miR-199a-3p serves an important role in the aerobic glycolysis of testicular germ cell tumors by targeting MCT1 and PGK1[104].

Noncoding RNAs were able to regulate cancer metabolism by interactions with oncogenes (tumor suppressor genes) and oncogenic pathways. LncRNA-p21 was first discovered as a p53-inducible lncRNA that mediates p53-related apoptosis in mouse cells[105]. In cancer cells, the hypoxia-induced LncRNA-p21 was shown to be a direct transcriptional target of HIF-1α and in turn promoted the stability of HIF-1α by interfering with the VHL-HIF-1α association. The hypoxic microenvironment and the reciprocal regulation of p21 and HIF-1α constructs a positive-feedback loop leading to continual activation of GLUT1 and LDHA expression thus accelerating glycolysis in cancer cells[106]. In another study published in 2011, [Bruning](http://www.ncbi.nlm.nih.gov/pubmed/?term=Bruning%20U%5BAuthor%5D&cauthor=true&cauthor_uid=21807897) *et al*[107] evaluated the interaction between HIF-1α and miR-155 and proposed that miR-155 contributes to a negative-feedback loop for the degradation of HIF-1α-dependent transcription, under continuous hypoxic conditions. The tumor suppressor gene p53 is one the most frequent targets of microRNAs and LncRNAs. MicroRNAs including miR-125b, miR-504 and miR-1228 can regulate p53 expression by directly binding to sites in p53 3’-UTR[108,109]. It is worth noting that the over-expression of miR-1228 can negatively regulate p53 expression, and the down-regulation of p53, in turn, increases miR-1228 expression. This positive-feedback loop contributes to the progression of HCC[110]. Studies also showed that oncogenic pathways are regulated by noncoding-RNAs. Down-regulation of miR-451 was originally linked with cancer glycolysis through its contributions to the adaptation to glucose deprivation and its effect on the LKB1/AMPK pathway in glioma cells[111]. A further study confirmed that the regulation of the LKB1/AMPK pathway by miR-451 is mediated by MO25 (an upstream modulator of AMPK)[112]. Another study discovered a novel reciprocal negative-feedback loop that consists of OCT1, AMPK and miR-451 in glioblastoma multiforme. Briefly, under the conditions of glucose deprivation, the activation of AMPK inactivated OCT1, which subsequently reduced the level of miR-451, and conversely, sufficient glucose supply significantly increased miR-451 expression, which in turn impaired the activity of the AMPK pathway[113]. Moreover, microRNAs can regulate the PI3K/Akt/mTOR pathway in HCC. Tang *et al*[114] reported that miR-125a suppress HCC progression by inhibiting the PI3K/Akt pathway. Fang *et al*[115] investigated the molecular mechanism of miR-7 in HCC growth and metastasis and revealed the regulatory role of miR-1 in the PI3K/Akt pathway via targeting PIK3CD, mTOR and p70S6K.

**Advances in HCC therapy by targeting glucose metabolism**

# The metabolic shift from oxidative phosphorylation to aerobic glycolysis in HCC not only provides abundant ATP for sustaining tumor survival but also offers a favorable microenvironment for tumor progression. As one of the “hallmarks” of cancer, metabolic reprogramming relies on metabolic enzymes, thus providing many potential targets that could be exploited in HCC therapy.

# *Flavonoids (phloretin, silybin and quercetin*) *targeting GLUT*

# Flavonoids are safe and reliable agents that are extracted from natural products, which show a broad spectrum of biological activities with fewer side effects[116]. Phloretin is a natural phenol which could be extracted from manchurian apricot and apple tree leaves. Studies showed the ability of phloretin to suppress cell proliferation and induce apoptosis by inhibiting glucose uptake in cancers[117,118]. Wu *et al*[118] showed that the inhibition of GLUT2 by phloretin leads to apoptosis in HCC cells. Another study demonstrated that phloretin strengthens the anticancer effects of paclitaxel in HCC[119]. Another natural compound, silybin, was identified as a GLUT inhibitor and showed a significant inhibitory effect on HCC growth *in vivo*[120,121]. Moreover, a phase I clinical study of silybin-phosphatidylcholine has been conducted in advanced HCC[122]. Quercetin is another bioactive flavonoid which has been proposed as a promising anticancer agent[123]. The latest study showed that quercetin might be a potential agent in HCC therapy that induced apoptosis and metabolic inhibition by competitively inhibiting GLUT1[124].

# *2-Deoxy-D-glucose and* *3-bromopyruvate targeting of HK*

2-deoxy-D-glucose (2-DG) is a glucose analog that is frequently used in inhibiting glycolysis. The phosphorylation of 2-DG catalyzed by HK2 in turn noncompetitively inhibits the activity of HK2 and leads to the reduction of the glycolytic rate. Several studies showed increased apoptosis induced by 2-DG in cancer, including HCC[125,126]. However, normal cells are only arrested in G1 phase of mitosis when treated with 2-DG[127]. 3-bromopyruvate (3-BP) is a halogenated analog that suppresses the glycolytic pathway by directly inhibiting HK2 activity. A study performed on a rabbit VX2 tumor model of liver cancer showed that 3-BP induced more efficient damage to hepatoma cells compared with 2-DG. Apart from the inhibition of HK, this study also revealed that 3-BP inhibits HCC glycolysis by suppressing mitochondrial ATP synthesis[128]. Based on these promising research achievements in vitro and in vivo, the orphan drug, 3-BP, has been designated for HCC by the FDA[13] and was reported to prolong the lifetime and improved the quality of life of a patient with HCC[14].

***Metformin targeting AMPK pathway***

Metformin, a first-line anti-diabetic drug, was linked to cancer prevalence and therapy because diabetes mellitus is a risk factor for cancer death in some cancer types. The association between diabetes and HCC was evaluated in large populations in the 1990s[129,130]. Recent studies demonstrated that diabetes mellitus is an independent risk factor for HCC[131,132]. The preventive effect of metformin in HCC has been established. Studies showed a decreased incidence of HCC in the type 2 diabetic patients who received metformin therapy[133-135]. The results of a systematic review showed a direct anti-HCC effect of metformin in animal models[136]. The mechanism of metformin in HCC prevention and therapy in type 2 diabetic patients is closely linked with the AMPK pathway. Metformin activates the expression of LKB1 and AMPK by increasing the energy stress levels inside cells. The activated AMPK pathway reduced IRS-1 and caused the inhibition of insulin/IGF-1 signaling, which is involved in carcinogenesis and cancer glycolysis regulation[137]. Additionally, AMPK inactivated the downstream modulator, mTOR, which indirectly regulates glycolysis by targeting HIF-1α, as previously described.

**CONCLUSION**

The reprogramming of glucose metabolism in cancer is a multi-factor and multi-step process, which can be regulated by oncogenes, oncogenic signaling pathways, and even noncoding RNAs. The developments in the study of cancer metabolism greatly enriched the understanding of carcinogenesis and afforded numerous potential targets to hit the Achilles` heel of cancer[138]. The agents that target glycolytic enzymes directly and glycolysis-related pathways indirectly showed some promising effects in HCC prevention and therapy in the laboratory. However, the limitation of glycolysis targeted anti-cancer therapy should be noted. As multiple enzymes catalyze multiple steps in the process, there is a complex compensatory mechanism in cancer metabolism. Therefore, the inhibitors that specifically target a single modulator of glycolysis may not have a prominent or persistent effect on cancer metabolism in the human body. In the future, the effects of combination drug therapy should be evaluated. Moreover, noncoding-RNAs, which target multiple glycolysis-related enzymes and pathways, are also needed to be carefully considered in future studies.

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**Table 1 Oncogenes and tumor suppressor genes involved in glucose metabolic reprogramming during carcinogenesis**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Genes** | **Targets** | **Ref.** |
| Oncogenes | *HIF-1* | HK1 | [55] |
|  |  | HK2 | [55] |
|  |  | GAPDH | [55] |
|  |  | PKM | [55] |
|  | *Myc* | LDHA | [58] |
|  |  | GLUT1HK2 | [59][60] |
|  | *CD147* | MCT1 | [62] |
|  |  | GLUT1 | [62] |
|  | *PIM1* | GLUT1 | [65] |
|  |  | PKM2 | [65] |
| Tumor suppressor  | *P53* | GLUTs | [66] |
| genes | *RRAD* | GLUT1HK2 | [67,68][67] |

GLUT: glucose transporter; HK: hexokinase; PKM: pyruvate kinase isoform M; LDHA: lactate dehydrogenase A; MCT1: monocarboxylate transporter 1; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; RRAD: ras-related associated with diabetes.

**Table 2 noncoding RNAs regulate glucose metabolism by directly targeting enzymes and indirectly targeting glycolysis-related pathways**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Targets** | **noncoding RNAs** | **Ref.** |
| Enzymes | GLUT1 | miR-340 | [85] |
|  |  | miR-1291 | [86] |
|  |  | miR-22 | [87] |
|  |  | miR-144 | [88,89] |
|  | GLUT3 | miR-195-5p | [90] |
|  | GLUT4 | miR-133 | [91] |
|  |  | miR-223 | [92] |
|  | HK2 | miR-143 | [93-95] |
|  |  | miR-155/ miR-143 | [96] |
|  |  | miR-34a | [102,103] |
|  | PKM2 | miR-122 | [98] |
|  |  | miR-133-a/b | [99] |
|  |  | miR-326 | [100] |
|  | PFK | miR-52s | [101] |
|  | LDHA | miR-34a | [102,103] |
|  | MCT1 | miR-199a-3p | [104] |
| Pathways | AMPK | miR-451 | [111-113] |
|  |  | miR-195 | [112] |
|  | PI3K/Akt/mTOR | miR-125a | [114] |
|  |  | miR-7 | [115] |

GLUT: glucose transporter; HK2: hexokinase 2; PKM2: pyruvate kinase isoform M2; PFK: phosphate fructose kinase; LDHA: lactate dehydrogenase A; MCT1: monocarboxylate transporter 1; AMPK: AMP-activated protein kinase.



**Figure 1 Reprogramming of glucose metabolism in hepatocellular carcinoma.** Reprogramming of glucose metabolism-related enzymes and transporting proteins in HCC. The expression of GLUT1, GLUT2, HK2, HKDC1, GAPDH, PKM2, LDHA and MCT4 are up-regulated in HCC glycolysis pathway. GLUT: glucose transporter; HK: hexokinase; G6P: Glucose-6-phosphate; GPI1: Glucose-6-phosphate isomerase 1; F6P: fructose-6-phosphate; PFK: phosphofructokinase; FBP: fructose-1,6-bisphosphatase; ALDA: aldolase A, DHAP: dihydroxyacetone phosphate; TIM: triosephosphate isomerase; G3P: glyceraldehyde-3-phosphate; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; PG: phosphoglycerate; PGAM: phosphoglycerate mutase; ENO: enolase; PEP: phosphoenolpyruvate; PKM2: pyruvate kinase isoform M2; PFK: phosphate fructose kinase; LDHA: lactate dehydrogenase A; MCT4: monocarboxylate transporter 4.