Research progress in the metabolic reprogramming of hepatocellular carcinoma (Review)

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Abstract. Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and its morbidity is increasing worldwide due to increasing prevalence. Metabolic reprogramming has been recognized as a hallmark of cancer and serves a role in cancer progression. Glucose, lipids and amino acids are three major components whose altered metabolism can directly affect the energy production of cells, including liver cancer cells. Nutrients and energy are indispensable for the growth and proliferation of cancer cells, thus altering the metabolism of hepatoma cells can inhibit the progression of HCC. The present review summarizes recent studies on tumour regulatory molecules, including numerous noncoding RNAs, oncogenes and tumour suppressors, which regulate the metabolic activities of glucose, lipids and amino acids by targeting key enzymes, signalling pathways or interactions between the two. These regulatory molecules can regulate the rapid proliferation of cancer cells, tumour progression and treatment resistance. It is thought that these tumour regulatory factors may serve as therapeutic targets or valuable biomarkers for HCC, with the potential to mitigate HCC drug resistance. Furthermore, the advantages and disadvantages of metabolic inhibitors as a treatment approach for HCC, as well as possible solutions are discussed, providing insights for developing more effective treatment strategies for HCC.

Contents

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1. Introduction

Hepatocellular carcinoma (HCC) is a common type of cancer worldwide and the incidence is expected to exceed 1 million cases by 2025, posing a threat to human health (1). Tumour cells, stromal cells, and stroma constitute the tumor microenvironment (TME), which can be depleted of certain nutrients (2,3). Metabolic reprogramming refers to the process by which tumour cells undergo specific metabolic changes to adapt to the hypoxic and nutrient-deficient microenvironment, thereby enabling tumour cells to proliferate rapidly (4). Glucose metabolic reprogramming mainly includes changes in glycolysis and the pentose phosphate pathway (PPP). Compared with normal cells, which use mitochondrial oxidative phosphorylation (OXPHOS) to produce energy, most cancer cells use glycolysis as the main way to produce energy for their growth even in an aerobic state. This process is known as aerobic glycolysis or the 'Warburg Effect' and is the most well-studied part of glucose metabolism (5,6). In addition to glycolysis, the PPP also provides biomacromolecules to meet material requirements of cancer cells for cell replication (7). Fatty acid (FA) metabolism is another energy source that supports tumour metastasis. Lipids and cholesterol regulate the construction of lipid rafts and invadopodia on the cell membrane, which in turn affect tumor cell invasion and metastasis (8). Through deamination, amino acids can not only be oxidized and decomposed to produce energy but also provide carbon and nitrogen sources for the synthesis of sugars, lipids and nucleic acids (9). Therefore, the energy production of cancer cells can be affected by the reprogramming of these three major metabolic pathways to inhibit the growth and proliferation of cancer cells. The present review considers current research progress on noncoding RNAs (ncRNAs), oncogenes, tumour suppressors and other tumour regulatory factors affecting HCC through metabolic reprogramming. This review focuses on glucose, lipid and amino acid metabolism, aiming to report potential therapeutic targets and mechanisms for HCC treatment.

2. Glucose metabolic reprogramming affects HCC

In HCC cells, the glucose metabolism pathway is reprogrammed according to the requirements of the cancer cells. In normal cells, most glucose is converted to pyruvate by glycolysis, which is then subjected to OXPHOS under aerobic conditions or anaerobic oxidation to lactate under anaerobic conditions (10). However, cancer cells rely on glycolysis to provide energy even in the presence of oxygen. This is because although only 2 adenosine triphosphates (ATPs) are produced per molecule of glucose through the glycolytic pathway, the rate of glycolysis is faster than OXPHOS and thus is more suitable for the rapid proliferation of tumour cells (11). The metabolic intermediates produced during aerobic glycolysis are used to synthesize biological macromolecules, while the accumulation of lactic acid can create an acidic microenvironment which can drive tumour progression (12).

A previous study have reported that the levels of both glycolysis and the PPP are significantly increased in HCC (13) and that tumor regulators, such as ncRNAs, oncogenic factors, and tumor suppressors can mediate this change to reprogram glycolysis (Table I) and the PPP, resulting in an impact on HCC progression (14,15).

Alterations in metabolic enzymes and signalling pathways in the glycolytic pathway affect HCC. Glucose transporter 1 (GLUT1), the major glucose transporter, promotes glucose uptake in numerous tissues. GLUT1 is highly expressed in HCC tissues and the knockdown of GLUT1 expression by siRNA significantly inhibits the proliferation of HCC cells (16). A recent study reported that cyclin-dependent kinase 6 (CDK6) deficiency inhibited GLUT1 expression by inhibiting the H3K27ac, H4K8ac and H3K4me1 levels on the GLUT1 enhancer, resulting in the autophagy of HCC cells (17). Forkhead box transcription factor M1 (FOXM1) is a key transcriptional activator of GLUT1 (18). Basic transcription factor 3 (BTF3) can transactivate FOXM1 to regulate the expression of GLUT1. Furthermore, BTF3 knockdown inhibits the proliferation of HCC cells and the glycolysis in HCC cells through the FOXM1/GLUT1 axis (19). Similarly, the antisense lncRNA SLC2A1-AS1 can regulate HCC cell proliferation and metastasis by competitively binding to the transcription factor STAT3, which inhibits the transcriptional activation of FOXM1 (20). The GLUT1 inhibitor BAY-876 has been previously reported to demonstrate antitumour activity in HCC models, but its clinical application faces challenges due to the systemic distribution of the drug at the time of administration, which leads to insufficient drug dose at the tumor site (21). Based on these previous reports, CDK6, BTF3 and the lncRNA SLC2A1-AS1 are suggested as possible novel targets for targeting GLUT1 in the treatment of HCC. Moreover, given the effect of the lncRNA SLC2A1-AS1 on HCC cell proliferation and metastasis, it should be considered as a potential biomarker for predicting HCC recurrence (20).

Hexokinase (HK), the first rate-limiting enzyme in aerobic glycolysis, has four isoforms (HK1, HK2, HK3 and HK4). Most normal tissues express only HK1, but HK2 is highly expressed in HCC tissue and is directly related to patient prognosis (22). In animal models, HK2 depletion has been shown to reduce cancer cell proliferation without obvious side effects, indicating its potential as a therapeutic target (23). Ubiquitin Protein Ligase E3 Component N-Recognin 7 (UBR7) is an E3 ubiquitin ligase, Zhao *et al* (24) reported that the UBR7-mediated mono-ubiquitination of histone H2B promoted the transcriptional activation of Keap1 and indirectly inhibited the expression of HK2, thereby inhibiting aerobic glycolysis and HCC tumorigenesis. Furthermore, numerous studies have reported that HK2 is a direct target of miR-188-5p, miR-202, circCCT3 and HuaChanSu in HCC cells, which affect the proliferation, invasion and migration of HCC cells by regulating the expression of HK2 (25-29). Known direct HK2 inhibitors include 2-deoxyglucose (2-DG) and 3-bromopyruvate (3-BP); however these are not cell specific and can affect normal tissues causing drug-related hepatotoxicity (30). Therefore, miR-3662, miR-188-5p and miR-202 have been suggested as potential targets for HCC treatment. It is also reported a novel molecular mechanism by which the traditional Chinese medicine (TCM) extract HuaChanSu delays HCC progression, supporting the use of Huashansu in HCC treatment (28).

Pyruvate kinase muscle type (PKM) is a member of the phosphokinase family that regulates the final rate-limiting step of glycolysis. PKM has two isoforms PKM1 and PKM2, which are produced by alternative splicing of PKM precursor mRNA. PKM1 has tumor-suppressor activity (31). Whereas PKM2 is upregulated in most tumour tissues and serves a role in the energy metabolism of HCC by enhancing the Warburg Effect and supporting anabolism (32). ZFP91 has been proposed as a novel E3 ubiquitin ligase, which inhibits PKM2 isoform formation and HCC metabolic reprogramming (33). Moreover, transcription factor GATA6 epigenetically regulates PKM2 transcription, and the downregulation of GATA6 expression induces glycolysis and promotes tumorigenicity, self-renewal and metastasis in HCC cells (34). Circular (circ)RNAs acts as a sponge for miRNAs to regulate gene expression by affecting the transcription, the mRNA turnover and translation (35). Under hypoxic conditions, circMAT2B promotes glycolysis and HCC progression by acting as a sponge for miR-338-3p upregulating PKM2 expression (36). By contrast, miR-374b antagonizes the Warburg Effect by inhibiting PKM2 and resensitizing HCC cells to sorafenib (37). Sorafenib is an effective first-line therapy for patients with advanced HCC, but sorafenib resistance is becoming increasingly common, which is affected by the TME (38). Targeting PKM2 can also regulate the metabolism of immune cells, enhance the anticancer immune response and inhibit cancer growth and metastasis (39). Therefore ZFP91, GATA6, circMAT2B, miR-338-3p and miR-374b may serve as useful targets for the treatment of and prevention of drug resistance in HCC as they modulate PKM2 expression.

Lactate dehydrogenase A (LDHA) is a key enzyme in the glycolytic conversion of pyruvate to lactate. Abnormally high LDHA expression is closely related to the malignant progression of numerous types of cancer (40). Several specific inhibitors of LDHA are currently being assessed as potential anticancer treatments (41). A recent study reported that acyl phosphatase 1 (ACYP1) serves a tumour promoting role by activating the c-MYC/LDHA axis to promote glycolysis. Furthermore, ACYP1 expression is associated with lenvatinib resistance; lenvatinib is the first-line therapy for advanced

Table I. Roles of regulatory factors involved in metabolic reprogramming of the glycolytic pathway and the corresponding targets in HCC.

Targets	Regulatory factors	Impact on HCC	(Refs.)
GLUT1	CDK6, BTF3, miR-873	Promote	(17,19,57)
	lncRNA SLC2A1-AS1, miR-3662	Inhibit	(20,55)
HK1/2	miR-188-5p, miR-873	Promote	(25,57)
	UBR7, miR-202, circCCT3, HuaChanSu, miR-3662, miR-199a-5p	Inhibit	(24,26-28,54,55)
PKM1/2	circMAT2B	Promote	(36)
	ZFP91, GATA6, LINC01554, miR-3662	Inhibit	(33,34,49,55)
LDHA	ACYP1	Promote	(42)
	miR-122-5p, miR-34a, miR-142-3p, miR-3662	Inhibit	(43-45,55)
PI3K/AKT/mTOR	circRHBDD1, miR-873	Promote	(46,57)
pathway	CD36, PTEN, LINC01554, circRPN2	Inhibit	(47-50)
HIF-1α	miR-873	Promote	(57)
	miR-3662, miR-199a-5p	Inhibit	(54,55)
c-Myc	ACYP1	Promote	(42)
	miR-122-5p	Inhibit	(43)

HCC, hepatocellular carcinoma; GLUT1, Glucose transporter 1; HK, hexokinase; PKM, pyruvate kinase muscle type; LDHA, lactate dehydrogenase A; HIF-1α, hypoxia-inducible factor-1α; miR, microRNA; lncRNA, long noncoding RNA; circRNA, circular RNA; CDK6, cyclin-dependent kinase 6; BTF3, basic transcription factor 3; ACYP1, acyl phosphatase 1.

HCC, however, drug resistance limits the efficiency of lenvatinib. The targeting of ACYP1 can exert a synergistic effect with lenvatinib to more effectively treat HCC (42). Moreover, LDHA has been reported to be a direct target of miR-122-5p, miR-34a and miR-142-3p, which exhibit potential tumour suppressive effects in HCC, providing targets for future therapeutic strategies (43-45).

The PI3K/AKT/mTOR signalling pathway is involved in the regulation of glucose metabolism in HCC. Numerous components have been reported to impact this pathway. Firstly, tumor regulators can modulate the glycolytic pathway by directly targeting this signalling pathway, thereby affecting the development of HCC (46-48). circRHBDD1 and FA receptor CD36 directly activate the PI3K/AKT/mTOR pathway, thereby enhancing glycolysis and ultimately promoting HCC growth and metastasis (46,47). However, the tumour suppressor PTEN inhibits the activation of the PI3K/AKT pathway, thus inducing apoptosis and fighting against the development of HCC (48). Furthermore, the high expression of circRHBDD1 in patients with HCC has been reported to limit the efficacy of immunotherapy (46). Secondly, the activity of the PI3K/AKT/mTOR signalling pathway can be indirectly regulated by glycolytic metabolic enzymes, thereby affecting the Warburg Effect. For example, LINC01554 and circRPN2 promote the ubiquitin-mediated proteasomal degradation of PKM2 and enolase 1 (ENO1), respectively. This inhibits the Akt/mTOR signalling pathway to decrease aerobic glycolysis and the proliferation of HCC cells (49,50). Lastly, the activation of the PI3K/AKT/mTOR signalling pathway can lead to increased GLUT1 expression in HCC tumour tissue, which accelerates glucose uptake, thereby promoting glucose metabolism and contributing to impaired immune cell function in HCC (51).

Hypoxia-inducible factor-1α (HIF-1α) is involved in multiple aspects of tumorigenesis and cancer progression (52). HIF-1α can activate the expression of numerous glycolysis-related enzymes, including GLUT1, HK2, PKM2, LDHA and ENO2, and promotes glycolysis (53), whereas miR-199a-5p can interfere with the expression of HK2, abrogating HIF-1α-enhanced Warburg effect in HCC (54). Moreover, miR-3662 regulates the GLUT1, HK2, PKM2, and LDHA expression via directly targeting HIF-1α, thereby exerts its suppressive effect on HCC glycolysis and proliferation (55). Furthermore, PKM2 is also a coactivator of HIF-1α, which increases the levels of HIF-1α creating a positive feedback loop for this pathway (56). Moreover, HIF-1α can also affect the AKT/mTOR signalling pathway. HIF-1α enhances the process that miR-873 promotes the expression of GLUT1 and HK2 in HCC cells by activating the AKT/mTOR pathway and promotes glycolysis, proliferation, invasion and metastasis in HCC (57). Therefore, targeting HIF-1α may be an effective strategy for the treatment of HCC.

Alterations in metabolic enzymes in the PPP affect HCC. The PPP is the main pathway of glucose catabolism. Glucose outside HCC cells is transported into the cells through GLUT1 and then phosphorylated by HK to form glucose-6-phosphate (G6P), which can be further metabolized through the glycolytic pathway or the PPP. The PPP is made up of an oxidative and non-oxidative pathway. In the oxidative pathway, G6P is dehydrogenated by the rate-limiting enzyme glucose-6-phosphate dehydrogenase (G6PD) to produce ribose-5 phosphate and NAPDH, which is critical to maintain redox balance of cancer cells (58). The non-oxidative pathway metabolizes the glycolytic intermediate to supply cancer cells with ribose 5-phosphate for nucleic acid synthesis and precursors

for amino acid synthesis (59). G6PD has been reported to induce epithelial-mesenchymal transition by activating the STAT3 signalling pathway, thereby promoting the migration and invasion of HCC cells (60). miR-122 can inhibit HCC cells proliferation by reducing G6PD activity, inhibiting the PPP (61). The knockdown of glucose-6-phosphate lactonase (PGLS), a cytosolic enzyme involved in the oxidation stage of the PPP, has been shown to inhibit the PPP and HCC progression (7). Similarly, transketolase (TKT), a key enzyme in the non-oxidative branch of the PPP, promotes HCC progression through significantly increasing the level of glucose flux and NADPH, which maintaining redox homeostasis of HCC cells (62). Oroxylin A, a small molecule inhibitor of TKT, directly targets TKT and leads to accumulation of glycolytic intermediates in the non-oxidative PPP, which inhibits HCC proliferation by inducing apoptosis and cell cycle arrest, providing a novel approach for the treatment of HCC (63). Therefore, in addition to the rate-limiting enzymes G6PD and TKT, miR-122 and PGLS could also be used as novel potential therapeutic targets to inhibit HCC progression by regulating HCC cell metabolism.

3. Lipid metabolic reprogramming affects HCC

In addition to glucose metabolism, alterations in lipid metabolism are also thought to contribute to HCC progression. Accelerated *de novo* FA synthesis and cholesterol biosynthesis, as well as altered FA oxidation (FAO), contribute to the development and progression of HCC (64). Some tumor regulators serve roles in lipid metabolism by regulating the expression of lipid metabolism enzymes such as lipid synthetase and FA oxidase, thereby affecting the progression of HCC.

Sterol-regulatory element binding proteins (SREBPs) are key transcription factors for lipid synthesis. There are three SREBP isoforms, SREBP1a, SREBP1c and SREBP2 (65). SREBP1 transcriptionally activates acetyl-coenzyme A carboxylase 1 (ACC1), FA synthase (FASN), stearoyl-coenzyme A desaturase 1 (SCD1) and other lipid synthases. mSREBP-1, the mature form of SREBP-1, is transported to the nucleus to play a transcriptional regulatory role, where it promotes the expression of lipid synthetase (66). The oncoprotein c-Myc can interact with SREBP1 to further activate the expression of these lipid synthases, thereby increasing FA synthesis to promote cancer growth (67). Long-chain acyl-coenzyme A synthetase 4 (ACSL4) and stomatin-like protein 2 (SLP2) increase *de novo* FA synthesis and HCC progression through the upregulation of SREBP1 and its downstream lipogenic enzymes by c-Myc (68,69). Mitochondria continuously change their morphology through fission and fusion processes that are tightly regulated to meet cellular metabolic demands. Abnormal increase of mitochondrial fission has been shown to be closely related to the progression of cancer (70). Wu *et al* (71) reported that the activation of mitochondrial fission not only increased the expression of ACC1 and FASN in HCC cells by upregulating SREBP1 expression, but also significantly promotes *de novo* FA synthesis. Furthermore, SREBP1 can also inhibit FAO by downregulating the FA oxidase carnitine palmitoyltransferase 1 (CPT1), thereby promoting the proliferation and metastasis of HCC cells (71). Likewise, circPRKAA1 can increase *de novo* FA synthesis by increasing the stability of mSREBP-1 (72). Caspase-3 (CASP3) mediates SREBP2 cleavage from the endoplasmic reticulum, allowing SREBP2 to stimulate the transcription of genes involved in cholesterol biosynthesis (73). Conversely, miR-612 inhibits the expression of HMG-CoA reductase (HMGCR) by inhibiting SREBP2 transcriptional activity, thereby inhibiting cholesterol synthesis and the formation of invadopodia, and further inhibiting HCC migration and invasion (8).

Inhibitors targeting ACC1, FASN and SCD1 have shown antitumour effects in xenograft models (74-76), and a new-generation FASN inhibitor, TVB-2640, has entered clinical trials for patients with solid tumours (77). The inhibition of SREBPs can also inhibit tumour growth and induce cancer cell death, but the direct inhibition of transcription factors is a challenge, as transcription factors often make poor drug targets (78). Therefore, the aforementioned findings indicate that ACSL4, SLP2, circPRKAA1, CASP3 and miR-612, which can directly regulate lipid synthases and SREBPs, are potential therapeutic targets.

4. Regulation of amino acid metabolism affects HCC

HCC cells can also participate in redox homeostasis by reprogramming amino acid metabolism to provide intermediates for HCC biosynthesis and energy requirements. Amino acids can be divided into two groups: Non-essential amino acids, including glutamate, glutamine, serine, aspartic acid and proline; and essential amino acids, including threonine, leucine and methionine. It is shown that amino acids can act as metabolic regulators to support cancer cell growth, with glutamine and methionine being the most studied (9).

Glutamine is a non-essential amino acid, which is converted to glutamate by glutaminase (GLS), before being further converted to α-ketoglutaric acid (α-KG) and metabolized to ATP in the citric acid cycle (TCA). GLS exist as two isozymes in mammalian cells named GLS1 and GLS2. It was reported that GLS1 functions as a tumor promotor in many cancer types, while GLS2 seems to act as a tumor suppressor (79). Numerous tumour cells use glutamine as a carbon source for energy production and anabolism (80). The upregulation of glutamate dehydrogenase 1 (GDH1) expression and the silencing of oxoglutarate dehydrogenase-like (OGDHL) expression both promote glutamine metabolism and drive α-KG synthesis, thereby promoting TCA cycle, providing energy and biosynthetic substrates for HCC cell growth and proliferation (81,82). Moreover, OGDHL can activate the mTORC1 signalling pathway, which upregulates SREBP1 expression and induces the expression of key enzymes involved in lipogenesis, which increases lipogenesis and HCC progression (82). c-Myc also serves a role in glutamine metabolism in HCC cells. SMYD2 is a protein lysine methyltransferase that stabilizes c-Myc, increases its expression through the ubiquitin-proteasome system and further upregulates GLS1, thereby activating glutamine metabolism and promoting the development of HCC (83). In phase I clinical trials, the GLS inhibitor telaglenastat has been reported to exhibits modest single-agent activity for renal cell carcinoma, but whether it is also effective for HCC treatment is unknown (84). Furthermore, SMYD2 targets GLS1 in HCC,

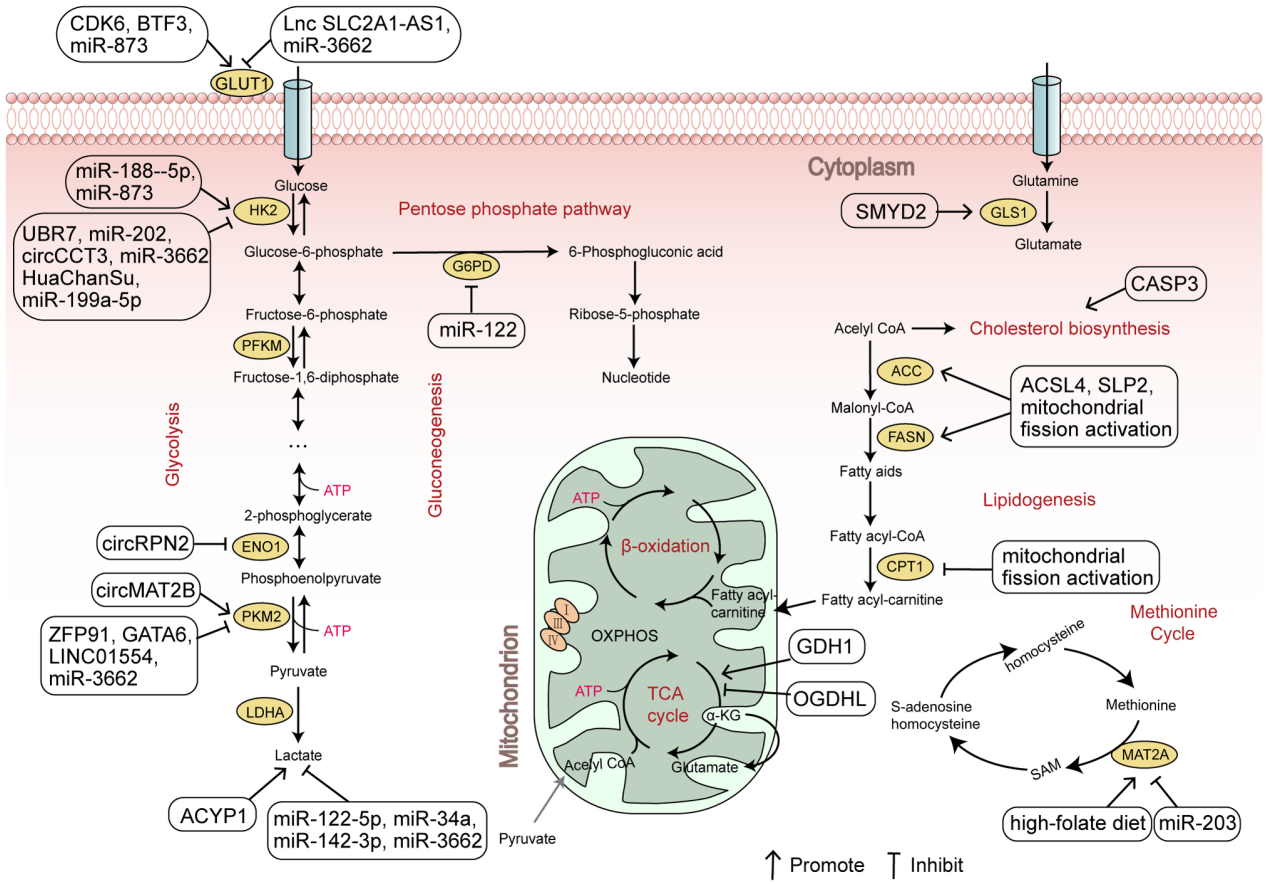

Figure 1. Effect of treatments on the metabolic pathways in HCC. Metabolic reprogramming serves a role in HCC, including glucose, lipid and amino acid metabolism. Novel treatments have been reported to be able to influence the onset and progression of HCC by affecting the metabolism of HCC. GDH1, glutamate dehydrogenase 1; OGDHL, oxoglutarate dehydrogenase-like; HCC, hepatocellular carcinoma; TCA, the citric acid cycle; OXPHOS, oxidative phosphorylation; CoA, coenzyme A; GLUT1, Glucose transporter 1; α-KG, α-ketoglutaric acid; GLS, glutaminase; HK, hexokinase; PKM, pyruvate kinase muscle type; MAT2A, methionine adenosyltransferase 2A; ATP, adenosine triphosphate; LDHA, lactate dehydrogenase A; ENO1, enolase 1; HIF-1α, hypoxia-inducible factor-1α; G6PD, glucose-6-phosphate dehydrogenase; CPT1, carnitine palmitoyltransferase 1; CASP3, Caspase-3; miR, microRNA; lncRNA, long noncoding RNA; circRNA, circular RNA; ACSL4, acyl-coenzyme A synthetase 4; SLP2, stomatin-like protein 2; CDK6, cyclin-dependent kinase 6; BTF3, basic transcription factor 3; ACYP1, acyl phosphatase 1; PFKM, 6-phosphofructokinase; SAM, S-adenosylmethionine.

which may provide a novel direction for inhibiting glutamine metabolism and thus inhibiting HCC progression.

The essential amino acid methionine is metabolized to S-adenosylmethionine (SAM) through the methionine cycle by methionine adenosyltransferase 2A (MAT2A) (85). Hung *et al* (86) reported that the loss of MAT2A can lead to the inhibition of HCC growth by inducing T cell dysfunction. Moreover, miR-203 can directly inhibit MAT2A expression and increase SAM expression in HCC, producing a tumour suppressor effect (87). Tetrahydrofolate is one of the products of the methionine cycle, and a high folate diet can promote HCC development by increasing the expression of MAT2A to accelerate the methionine cycle (88). Methionine restriction has been reported to be a promising therapeutic avenue for the treatment of numerous cancers, such as metastatic melanoma and gastric cancer, and colorectal cancer (CRC) (89). Such restriction can be achieved in three ways: By restricting methionine in the diet; using methionine-depleting enzymes; and inhibiting methionine metabolism. At present, clinical studies on methionine-restricted diet are limited and a more promising treatment method may be the use of methionine-depleting enzymes, such as recombinant methioninases, which reduce serum methionine levels, resulting in insufficient methionine supply to tumours and resulting in reduced tumour volume (89,90). Moreover, metabolic inhibitors including MAT2A inhibitors, can prevent tumours from using exogenous methionine for energy, thereby inhibiting tumour growth (91). At present, MAT2A inhibitors are in phase I clinical trials. However, drug resistance and off-target effects have been reported for these inhibitors (85). Therefore, it can be hypothesised that targeting miR-203 and individualized folic acid diets may serve as novel strategies for HCC treatment.

5. Discussion

HCC poses a serious threat to human health and is the fourth leading cause of cancer-related mortality worldwide (1). Emerging targeted therapies have been reported to only achieve lasting clinical benefits for a small proportion of patients; therefore, there are still major challenges regarding the treatment of HCC, and the development of novel effective therapeutic targets is needed (92). Metabolic reprogramming is a characteristic of cancer cells, which ensures they can meet the increased energy demand and maintain redox

balance (93). In HCC, this reprogramming is mainly caused by the activation of metabolic enzymes: Including glucose metabolism-related proteins GLUT1, HK2, PKM2 and LDHA; lipid metabolism-related enzymes ACC1 and FASN; and amino acid metabolism-related enzymes GLS and MAT2A. The metabolism of proteins, lipids and amino acids produces biological macromolecules and releases energy. The expression of GLUT1, HK2, PKM2, LDHA, ACC1, FASN, GLS and MAT2A is upregulated in HCC to promote the metabolic process, thereby ensuring the rapid growth and proliferation of liver cancer cells. In addition, dysregulation of transcription factors and signalling pathways, such as the PI3K/AKT/mTOR pathway, HIF-1α, c-Myc and SREBPs involved in lipid metabolism, also serve a role in HCC metabolic reprogramming.

Multiple studies have reported that metabolic inhibitors, such as the GLS inhibitor CB-839 and FASN inhibitor TVB3664, which exert therapeutic effects in HCC by inhibiting the metabolic reprogramming of HCC cells, are currently in clinical studies of multiple solid tumours, including CRC and breast cancer (94,95). In the present review, numerous ncRNAs, oncogenes, and tumour suppressors that target glucose, lipid, and amino acid metabolic reprogramming were summarized. These impact the expression of key metabolism-related enzymes in HCC cells directly or by altering the activity of transcription factors and signalling pathways, which affect the energy and nutrient production of HCC cells, subsequently affecting their growth and proliferation (Fig. 1). These tumour regulators can be used as promising therapeutic targets or potential prognostic biomarkers for HCC. The oncogenes CDK6, CD36, ACSL4 and CASP3 and the tumour suppressors GATA6, PTEN, miR-34a, miR-122 and miR-203 are considered to have significant effects on HCC progression. These regulators are suggested as future targets in the treatment of HCC. Certain molecules can also affect the sensitivity of cells to existing drugs. For example, ACYP1 and CASP3 impact the chemoresistance of HCC cells to lenvatinib by re-regulating the glycolytic pathway and lipid synthesis, respectively (42,73).

Although the targeting of metabolic reprogramming in cancer cells has therapeutic potential, its application remains problematic. First, there are multiple isoforms of many of the enzymes involved in metabolism, and small-molecule inhibitors may not be able to precisely target the predominant isoform expressed by cancer cells (96). Second, some inhibitors are not highly specific and may target normal tissues and cause drug-related hepatotoxicity (96). For example, a small clinical trial reported that nearly all patients with breast, thyroid, or non-small-cell lung cancer (NSCLC) treated with the HK2 inhibitor 2-DG had hypoglycaemic symptoms, including fatigue, sweating, dizziness, nausea; asymptomatic QTc prolongation occurred in 72% of patients; upper gastrointestinal bleeding occurred in 6% of patients (97). Moreover, cancer cells may develop resistance to metabolic pathway inhibitors (96). To overcome these problems, metabolic inhibitors can be combined with other targeted drugs to improve treatment efficacy. Studies have reported that the combination of the FASN inhibitor TVB3664 and sorafenib can improve therapeutic efficacy in a mouse model of HCC and that the combination of the glycolysis inhibitor 2-DG and sorafenib can significantly decrease the viability of sorafenib-sensitive and resistant cells (94,98). Furthermore, the combination of two metabolic inhibitors has been shown to have a stronger anticancer effect than the equivalent monotherapies. The combination of the GLS inhibitor CB-839 and the ASCT2 glutamine transporter inhibitor V-9302 can inhibit Gln metabolism and reduce extracellular glutamine uptake, respectively, leading to a shortage of Gln supply and GSH synthesis, thereby inhibiting HCC xenograft growth and inducing apoptosis *in vivo* (95). Therefore, studies should develop more effective metabolic inhibitors with fewer side effects. Most of the side effects of current metabolic inhibitors are caused by the failure to precisely target the metabolic enzyme isoform expressed by cancer cells. Therefore, we can indirectly target the isoform expressed by cancer cells by trying to develop inhibitors and/or activators of the tumour regulators mentioned in this review, especially those that have significant effects on HCC progression, to reduce side effects. Further research is required to assess the therapeutic potential of combination therapies which use metabolic inhibitors with other targeted agents.

In conclusion, despite certain limitations and difficulties, in-depth exploration of regulatory factors related to HCC metabolic reprogramming continues to reveal options for the development of novel and effective HCC treatment strategies, especially the combination of metabolic inhibitors with other targeted agents, which may help to improve the anticancer efficacy of existing treatments.

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Authors' contributions

WG and JW performed the literature review and wrote the manuscript. YX, HY, SY, CB and QC revised the manuscript and provide critical review of the scientific content. YZ conceived the work and approved the final version. All authors approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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