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REVIEW

Research Progress of Liver Cancer Recurrence Based on Energy Metabolism of Liver Cancer Stem Cells

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Objective: The aim of this study is to investigate the recurrence and progression of liver cancer by focusing on the energy metabolism of liver cancer stem cells.

Methods: A comprehensive literature search was conducted using databases including CNKI, PubMed, Wanfang, and Citexs to analyze the etiology and treatment of hepatocellular carcinoma (HCC), the factors and mechanisms contributing to HCC recurrence, and the impact of energy metabolism in HCC stem cells on the development of HCC. Furthermore, the association between HCC recurrence and the energy metabolism of HCC stem cells was examined.

Results: The primary targets associated with the glycolytic metabolism of HCC stem cells included HK2, PFK, PK, LDH, among others. Glutamine metabolism primarily involves the tricarboxylic acid (TCA) cycle, with main targets such as mTORC1 and reactive oxygen species (ROS). The principal pathway in lipid metabolism is fatty acid (FA) biosynthesis, with key targets being fatty acid synthase (FASN), acetyl-coenzyme A carboxylase (ACC), stearoyl-coenzyme A desaturase-1 (SCD1), and adenosine monophosphate-activated protein kinase (AMPK). Targets in the oxidative phosphorylation pathway include PGC1a. Finally, key targets in iron metabolism encompass System Xc, glutathione peroxidase 4 (GPX4), and DMT1.

Conclusion: The glycolytic metabolism of HCC stem cells represents a primary metabolic pathway in HCC stem cells, with key targets including HK2, PFK, PK, and LDH warranting closer attention. Glutamine metabolism should focus on the TCA cycle and targets such as mTORC1 and ROS. Lipid metabolism pathway involves FA biosynthesis, with significant targets being FASN, ACC, SCD1, and AMPK. Iron metabolism, specifically System Xc, GPX4, and DMT1 targets, should be carefully considered. Therefore, interventions for the prevention and treatment of liver cancer recurrence should be directed towards these aspects of liver cancer stem cells.

Keywords: liver cancer recurrence, liver cancer stem cells, energy metabolism

Introduction

Liver cancer is a leading global health concern, with significant disease burden worldwide. According to the World Health Organization's 2020 Global Cancer Statistics report, liver cancer is ranked sixth in terms of global incidence, with 910,000 new cases reported in 2020. Additionally, liver cancer is noted for having the third-highest mortality rate among tumors.[1] Primary liver cancer (PLC) consists mainly of hepatocellular carcinoma (HCC) and intrahepatic cholangiocellular carcinoma, with HCC representing approximately 90% of PLC.[2] The development of HCC is attributed to a combination of various external environmental exposures and intrinsic factors within the body. The principal high-risk factors for the development of HCC include chronic infection with the hepatitis B virus (HBV) and the hepatitis C virus (HCV), and hepatitis A virus. Additionally, the influence of environmental factors such as aflatoxin B1 (AFB1) and the increased risk of HCC can be attributed to

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a combination of factors, including excessive alcohol consumption, non-alcoholic fatty liver disease (NAFLD), and other environmental factors. Factors such as NAFLD, metabolic syndrome induced by diabetes, Additionally, other endogenous factors have been demonstrated to exert a considerable influence on the pathogenesis of HCC.[3] The evolution of HCC is a multifaceted and intricate process influenced by a myriad of factors, including genetics, epigenetic inheritance, activation of oncogenic pathways, and the interplay within the immune microenvironment.In addition, an increasing number of studies have shown that the development of liver fibrosis, cirrhosis, hepatocellular carcinoma and changes in the mechanical microenvironment of liver tissue are closely related to the development of hepatocellular carcinoma tissue.[4]

The recurrence of HCC represents a significant hurdle in therapeutic outcomes, with cancer stem cells (CSCs) have been identified as a key factor in the recurrence and metastasis of HCC. CSCs, A minor proportion of cells within tumour tissues that possess the capacity for self-renewal, proliferation and differentiation are designated as liver cancer stem cells (LCSCs) in the context of HCC. LCSCs They are of great consequence in driving the initiation, migration, recurrence, and drug resistance of HCC. Understanding the intricate interplay between the immune microenvironment of HCC tumors and LCSCs can offer a novel theoretical framework for enhancing HCC prevention and prognosis.[3] Despite the abundant research on liver cancer stem cells, a comprehensive synthesis and organization of studies on the energy metabolism of LCSCs and its association with liver cancer recurrence is lacking. The objective of this study was to investigate the underlying causes and mechanisms of liver cancer recurrence, as well as the molecular pathways and relevant targets involved in the energy metabolism of HCC stem cells. Through a comprehensive search of databases such as Zhi.com, PubMed, Wanfang, and others, along with utilization of the Citexs comprehensive literature database, we aimed to elucidate the factors contributing to HCC recurrence and offer insights to guide the exploration of therapeutic strategies for managing HCC recurrence.

Causes of Liver Cancer Recurrence

The process of tumor recurrence and metastasis is intricate and multifaceted, involving various factors such as the energy metabolism of liver CSCs, gene mutations, tumor immunity, and metabolic dysregulation. While recent research has predominantly focused on the energy metabolism of liver CSCs, Gene mutations are a critical factor in the development of tumours and are strongly linked to the recurrence and metastasis of malignant growths. Over the past two decades, the advancement of second-generation sequencing technology has significantly progressed, This has resulted in the identification of numerous mutated genes that are associated with the development of tumours, including TERT, CTNNB1, TP53, among others.[5] Exome sequencing of primary and recurrent tumor tissues has revealed that gene mutations serve as not only the initiating events in tumor dissemination but also persist throughout the entire process of tumor recurrence.[6] Furthermore, the functional roles of mutant gene types, commonly identified in other tumor types, within liver tumors have been further elucidated, exemplified by the study of KRAS.[7] In the latest study, researchers used whole genome sequencing (WGS) to identify two patterns of hepatocellular carcinoma recurrence, de novo recurrence and ancestral recurrence. As the name suggests, de novo recurrence is genetically independent of the primary tumour, while ancestral recurrence is clonally related to the primary tumour. This gives us a clearer understanding of the development of early recurrence in HCC.[8] The liver, as a crucial immune organ in the human body, possesses a unique blood supply anatomy that contributes to a complex composition of immune cells. The interaction between tumour cells, immune cells and stromal cells gives rise to the formation of a distinctive immunosuppressive tumour immune microenvironment. This immunosuppressive milieu shields tumor cells from immune surveillance, thereby fostering tumor recurrence and metastasis. While normal cells primarily rely on the glycolysis-TCA cycle-oxidative phosphorylation pathway for energy production, tumor cells predominantly utilize glycolysis as their main energy generation pathway, even under aerobic conditions. This phenomenon, known as the Warburg effect, has been observed. A number of glycolytic enzymes have been identified as playing a role in tumour cell progression, and their presence is associated with a poor prognosis in patients with HCC.[9] Beyond glycolysis, amino acid metabolism, lipid metabolism, Furthermore, additional factors may also exert an influence on the malignant potential of tumours.[10] The energy metabolism of HCC stem cells is a primary driver of their recurrence. Consequently, the recurrence and metastasis of HCC typically involve a multifactorial and complex process. In-depth mechanistic investigations can offer valuable insights for clinical diagnosis and treatment strategies, facilitating the shift from traditional monotherapy to multi-drug combination therapies. This transition holds promise for enhancing patient survival rates.

The Main Mechanism of Energy Metabolism of HCC Stem Cells Mediating the Recurrence of HCC

Recent research has highlighted variances in the features of CSC across different HCC subtypes. LCSCs, also referred to as hepatic tumor-initiating cells, are believed to instigate tumor onset and metastasis. The modulation of cancer stemness in HCC is a complex process that involves a multitude of mechanisms and factors, this encompasses mitochondrial autophagy, mitochondrial dynamics, epigenetic alterations, the tumour microenvironment and tumour plasticity.

Following the recognition and characterization of CSCs in hematologic malignancies, the existence of CSCs has been confirmed in a variety of solid tumours, including breast, colorectal, brain, and liver cancers. Subsequent investigations have increasingly indicated that CSCs play a central role in tumour formation, drug resistance, metastasis and recurrence, as research in this field progresses.[11] It is postulated that, analogous to the microenvironment of normal stem cells, CSCs are situated in a discrete CSC niche comprising a plethora of immune cells and mesenchymal cells. Recent studies have demonstrated the pivotal function of non-CSC cytokines within the CSC niche in regulating CSC behaviour. The CSC niche not only fosters cancer stemness but also modulates CSC metabolism, immune evasion, and drug resistance.[12]

HCC Stem Cell Energy Metabolism

Glycolytic Pathway of Liver Cancer Stem Cells

The liver serves as a pivotal hub for human metabolism, particularly in sugar metabolism. Glycolysis stands as a fundamental pathway in sustaining energy metabolism within tumor cells. Increased glucose consumption, decreased ATP production and increased lactate production characterise the Warburg effect.[12] CSCs exhibit a greater dependence on glycolysis compared to non-tumor stem cells, and the glucose levels directly impact the microenvironment and energy metabolism of CSCs.[13] It has been noted that LCSCs exhibit elevated expression levels of key glycolytic enzymes compared to non-tumor stem cells, and their stemness characteristics are associated with the activation of the glycolytic pathway.[13] Four pivotal rate-limiting enzymes, namely hexokinase 2 (HK2), phosphofructokinase (PFK), pyruvate kinase (PK), and lactate dehydrogenase (LDH), are involved in the glycolytic process of cancer stem cells. These enzymes play a metabolic role in promoting glycolysis in LCSCs, thereby directly or indirectly reinforcing the stemness phenotype of LCSCs and contributing to increased heterogeneity within the LCSC population.

HK2, A great member of the hexokinase enzyme family serves as the initial rate-limiting enzyme in glycolysis, facilitating the conversion of glucose to glucose-6-phosphate(G-6-P). During hepatocarcinogenesis, HK2 expression is upregulated in vivo, with studies indicating relatively high expression levels in CSCs.[14] In a recent study, Li et al[15] employed a genome-wide CRISPR/Cas9 screen in vivo to identify 67 hCC oncogenic metabolism-associated genes. Their findings demonstrated that HK2 is involved in the promotion of the maintenance and self-renewal of LCSCs. FoxA2, a transcriptional regulator critical in early embryonic development, binds to chromosomal proteins and DNA, participating in early gene activation and maintaining liver homeostasis. The inhibition of FoxA2 expression has been demonstrated to facilitate the transcription of genes associated with the phosphatidylinositol-3-kinase (PI3K) pathway, leading to downstream Akt phosphorylation, reduced HK2 expression, and diminished aerobic glycolysis in LCSCs. This inhibition suppresses the proliferation of LCSCs and tumor growth.[16]

PFK plays a crucial role in glycolysis, functioning as the second rate-limiting enzyme that facilitates the conversion of fructose-6-phosphate (F-6-P) to fructose-1,6-bisphosphate. Xin et al[17] demonstrated that platelet-type phosphofructo-kinase-platelet (PFKP) is involved in the accelerated proliferation and accumulation of liver cancer cells. The inhibition of PFKP has been shown to reduce HCC cell proliferation, colony-forming capacity, and clone formation. In vitro studies have shown that PFKP inhibition results in decreased expression of surface markers (ALDH1, CD44, CD133, Sox-2) in LCSCs. PK catalyzes the conversion of phosphoenolpyruvate to pyruvic acid and consists of four isoforms: PKR, PKL, PKM1, and PKM2. These are encoded by the PKM and PKL genes. It is noteworthy that PKM1 is expressed in normal hepatocytes, whereas PKM2 is markedly expressed in HCC The overexpression of PKM2 in HCC is linked to pathological grading, clinical stage, tumor size, and prognosis of recurrence in patients.[18]

LDH functions as the final rate-limiting enzyme in the glycolytic pathway, facilitating the conversion of pyruvate to lactate through a catalytic process, which is essential for sustaining energy metabolism in tumors. The accumulation of

lactate contributes to the creation of an acidic microenvironment that is conducive to tumour cell proliferation. LDH exists in three isoforms - LDHA, LDHB, and LDHC. LDHA is the primary enzyme involved in the conversion of pyruvate to lactate, while LDHB plays a pivotal role in the reverse reaction, facilitating the conversion of lactate back to pyruvate. This process is essential for maintaining cellular microenvironment homeostasis.[19]

Key proteins involved in glycolysis in tumor cells encompass glucose transporter (GLUT) and monocarboxylate transporter proteins (MCTs). GLUT, situated on the cell membrane, plays a pivotal role as a transporter protein facilitating glucose entry into the cell from the extracellular environment, thereby meeting the heightened glucose demands characteristic of tumor cells. Lactate, a crucial byproduct of cellular glycolysis for energy generation, is efficiently transported out of the cell by MCTs to prevent intracellular acidosis and maintain the tumor microenvironment (TME) pH balance.[20] The specific mechanism of action is shown in Figure 1.

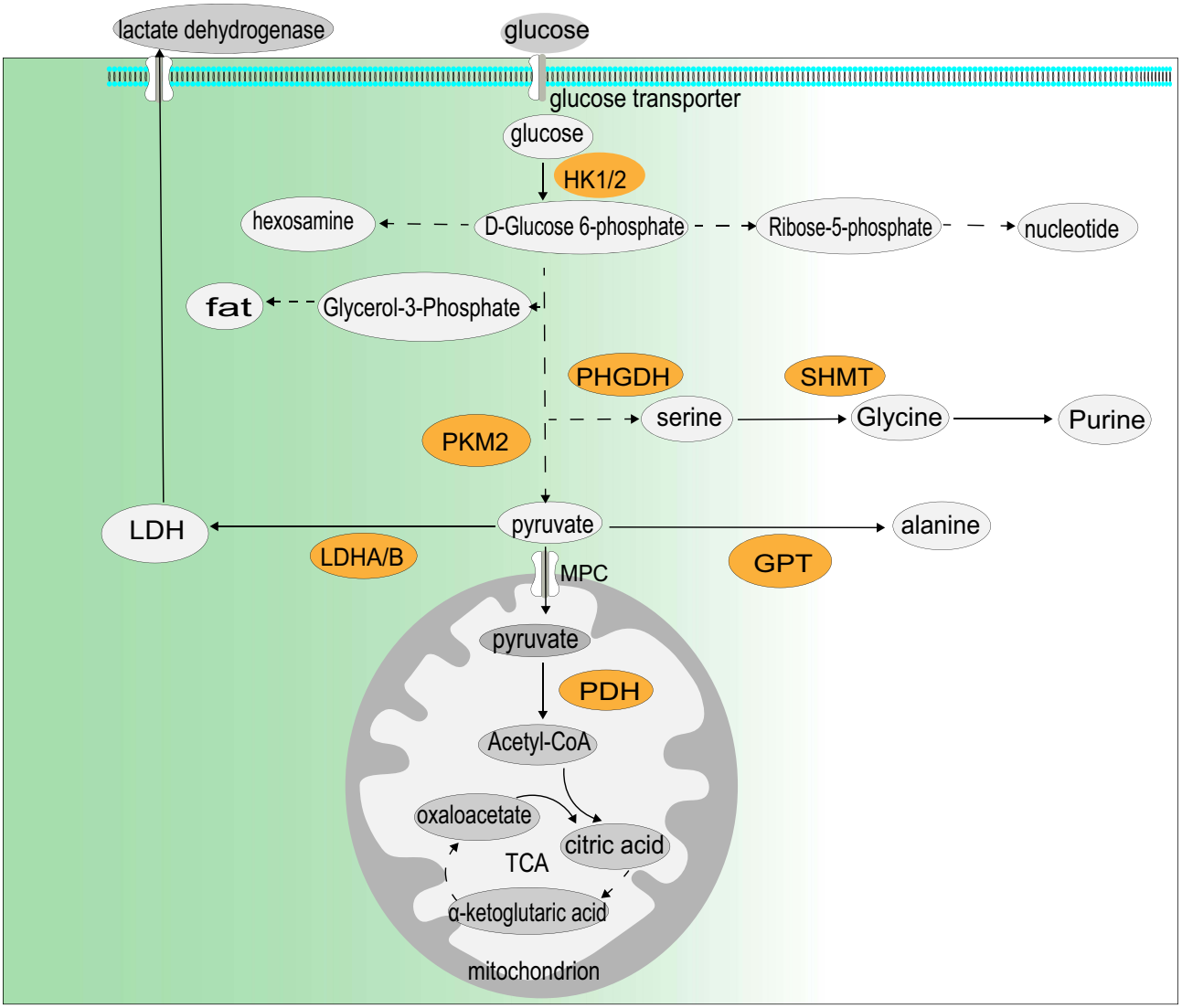

Figure 1 Glycolytic pathway of liver cancer stem cells. Glycolysis stands as a fundamental pathway in sustaining energy metabolism within tumor cells. Four pivotal rate-limiting enzymes, namely hexokinase 2 (HK2), phosphofructokinase (PFK), pyruvate kinase (PK), and lactate dehydrogenase (LDH), are involved in the glycolytic process of cancer stem cells.

Abbreviations: PHGDH, Phosphoglycerate dehydrogenase; SHMT, Serine hydroxymethyltransferse; GPT, glutamic-pyruvic transaminase; PDH, pyruvate dehydrogenase; TCA, tricarboxylic acid cycle.

Glutamine Pathway in Liver Cancer Stem Cells

Glutamine, in addition to glucose, is a extensively researched nutrient in the realm of cancer cell metabolism due to its significance as a vital carbon and nitrogen supplier that supports the metabolic requirements for rapid cancer cell proliferation.[21] Glutamine contributes to processes such as cellular FA synthesis, nucleotide synthesis, amino acid generation, and the production of ATP and NADPH.[22] By promoting the TCA cycle, glutamine generates metabolic intermediates crucial for lipid, protein, and nucleic acid synthesis, this consequently enables anabolic growth and proliferation.

Glutamine also functions as a significant carbon source for biosynthesis by entering the TCA cycle.[23] While cancer cells heavily uptake glucose, a substantial portion of the carbon is converted into lactic acid. Glutamine metabolism offers an alternative carbon reservoir to fuel the TCA cycle, leading to the production of citrate for FA synthesis through reductive carboxylation.[24] Glutamine catabolism can replenish oxaloacetate, serving as a carbon source that can be converted to aspartate and asparagine to support nucleotide production.[22] In conclusion, glutamine plays a pivotal role in the biosynthesis of tumour cells, serving as a critical carbon source that facilitates the production of essential molecules, including nucleotides, pyruvate, and FAs, via the TCA cycle. additionally, glutamine serves as a nitrogen source and is used directly for nucleotide synthesis or indirectly for the production of other amino acids via aminotransferases. Beyond its roles in providing carbon and nitrogen for various biological precursors, glutamine also drives ATP generation through oxidative phosphorylation within the TCA cycle.[21]

Glutamine metabolism is of great importance in maintaining cellular redox homeostasis, primarily through its involvement in glutathione synthesis.[24] Glutamine contributes to glutathione generation directly and aids in maintaining glutathione in its reduced state by supplying NADPH. During antioxidant activities, glutathione donates electrons for oxidation, necessitating NADPH for its restoration to the reduced state. Glutamine furnishes reducing equivalents for glutathione synthesis through the TCA cycle, with subsequent export to the cytoplasm for the conversion of aspartic acid or malic acid to pyruvic acid. This process involves malic enzyme to generate NADPH, a critical component for the reduction of glutathione.[25]

In addition to its direct metabolic impacts, glutamine modulates cellular signaling pathways to enhance growth. Glutamine promotes mammalian target of rapamycin complex 1 (mTORC1) activation and suppresses autophagy by a dual mechanism. Firstly, glutamine uptake into the cell via the high-affinity transporter protein SLC1A5 directly influences mTORC1 activity,[26] thereby impeding autophagy. Secondly, intracellular glutamine uptake leads to the exchange of essential amino acids through the SLC1A5 transporter protein, activating mTORC1 in an essential amino acid-dependent manner.[27] Glutamine metabolism regulates mTORC1 activity by fostering the accumulation of an amino acid pool within the cell, subsequently stimulating anabolic pathways. Apart from its role in signaling pathways via mTORC1, glutamine influences signaling during mitochondrial oxidative metabolism by modulating mitochondrial reactive oxygen species (ROS) production.[28] The specific mechanism of action is illustrated in Figure 2.

Lipid Metabolism Pathway in Liver Cancer Stem Cells

Dysregulation of fatty acid (FA) synthesis has emerged as a prominent area of research, with several studies suggesting that altered lipid metabolism may play a central role in cancer development.[29] While a comprehensive assessment of the mechanism of fatty acid biosynthesis in HCC remains to be conducted, numerous studies have highlighted the abnormal up-regulation of key enzymes such as fatty acid synthase (FASN), acetyl-coenzyme A carboxylase (ACC), and stearoyl-coenzyme A desaturase-1 (SCD1) in this process across various human solid tumors, including HCC. Inhibiting the FA biosynthetic pathway has demonstrated efficacy in impeding cancer cell proliferation, with several potential targets within this pathway presenting as promising candidates for drug intervention in the therapeutic management of HCC.

ATP citrate lyase (ACLY) is a cytoplasmic enzyme responsible for catalyzing the ATP-dependent conversion of citrate and coenzyme A into oxaloacetate and acetyl-coenzyme A (acetyl-CoA).[30] Acetyl-CoA is a pivotal precursor for FASN and is essential for generating acetyl-coenzyme A in the mevalonate pathway for cholesterol synthesis. In addition, acetyl-CoA is crucial for protein modifications through acetylation reactions, such as histone acetylation.[31] Positioned at the intersection of glycolysis and lipid metabolism, ACLY plays a pivotal role in coordinating these two fundamental

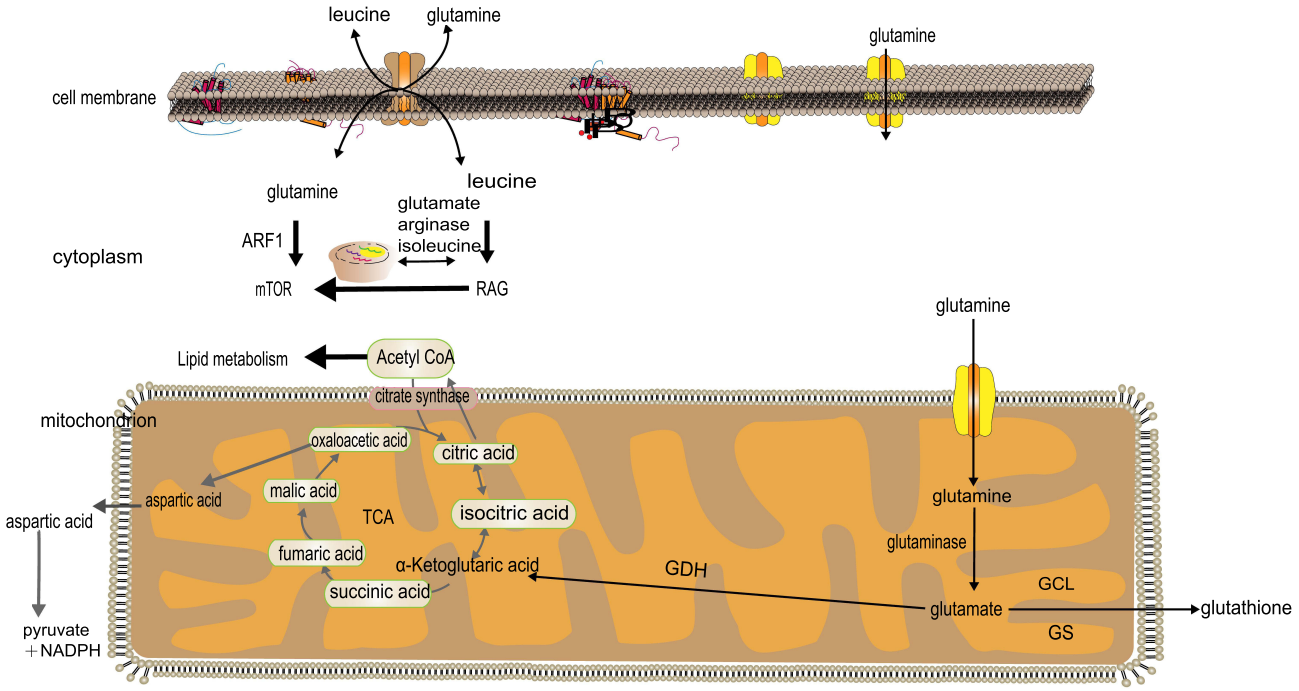

Figure 2 Glutamine pathway in liver cancer stem cells. Glutamine is a extensively researched nutrient in the realm of cancer cell metabolism due to its significance as a vital carbon and nitrogen supplier that supports the metabolic requirements for rapid cancer cell proliferation. Glutamine contributes to processes such as cellular FA synthesis, nucleotide synthesis, amino acid generation, and the production of ATP and NADPH.

Abbreviations: ARF1, ADP-ribosylation factor 1; mTOR, mammalian target of rapamycin; GDH, Glutamate Dehydrogenase; GCL, Glutamate cysteine ligase; GS, Glucose Solution.

metabolic processes, making it a critical enzyme in tumorigenesis. Therefore, ACLY represents a promising therapeutic target for cancer treatment.[32]

SCD is an endoplasmic reticulum enzyme that catalyses the conversion of palmitoyl coenzyme A to palmitoyl coenzyme A and stearoyl coenzyme A to oleoyl coenzyme A.[33] Within this enzymatic cascade, SCD functions downstream of FASN and is the rate-limiting enzyme. Of the five SCD isozymes identified, two are expressed in humans, SCD1 and SCD5. While these isoforms exhibit distinct tissue distributions and expression profiles, they maintain enzymatic activities.[34] Notably, upregulation of SCD1 expression has been observed in several cancers, including HCC. Analysis of numerous clinically accessible HCC tissue samples has revealed elevated levels of SCD1. It is postulated that overexpression of SCD1 may facilitate augmented cell proliferation and resistance to apoptosis.

The precise involvement of FASN in liver tumorigenesis and HCC metabolism remains incompletely understood by the scientific community. Analogous to SCD1, FASN has emerged as a promising candidate for the treatment HCC owing to its central function in mediating intracellular FASN.[35]

ACC is recognised as a pivotal enzyme in conventional lipid metabolism in both animals and humans.[36] In the process of normal de novo FASN, ACC serves as the rate-limiting enzyme responsible for converting acetyl coenzyme A to malonyl coenzyme A. Mammals express two isoforms of ACC, namely ACC1 and ACC2. Due to its critical role as the rate-limiting enzyme in de novo FASN, ACC has garnered significant interest as a potential therapeutic target for various cancers, including HCC.[37]

Adenosine monophosphate-activated protein kinase (AMPK) exerts a wide range of effects on cellular metabolism, primarily through its central role in lipid metabolism. AMPK exerts inhibitory control over FASN by promoting the inhibitory phosphorylation of two crucial molecules, ACC and sterol regulatory element binding protein 1 (SREBP1).[38] Reduced expression of phosphorylated AMPK was observed in samples from patients with HCC in comparison to those from individuals with precancerous liver tissue. The finding indicates that AMPK may inhibits the progression of HCC.[39] The specific mechanism of action is depicted in Figure 3.

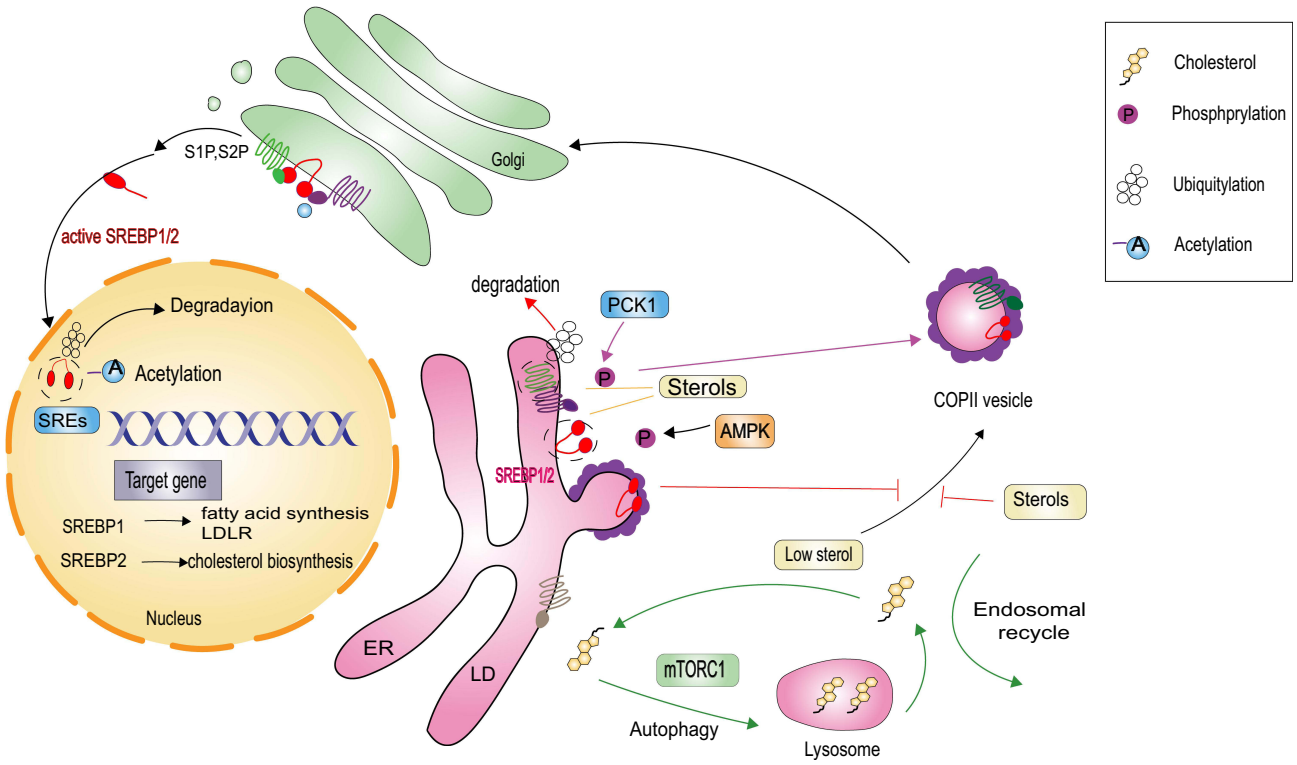

Figure 3 Lipid metabolism pathway in liver cancer stem cells. Study suggests altered lipid metabolism may play a central role in cancer development.AMPK exerts a wide range of effects on cellular metabolism, primarily through its central role in lipid metabolism. AMPK exerts inhibitory control over FASN by promoting the inhibitory phosphorylation of two crucial molecules, ACC and SREBP1.

Abbreviations: AMPK, Adenosine monophosphate-activated protein kinase; PCK1, phosphoenolpyruvate carboxykinase 1; mTORC1, mammalian target of rapamycin complex 1; LD, lactate dehydrogenase; ER, estrogen receptor; SREBP, Sterol-regulatory element binding protein; LDLR, low density lipoprotein receptor.

Oxidative Phosphorylation Pathway in Liver Cancer Stem Cells

The mitochondrial oxidative phosphorylation (OXPHOS) pathway is of critical importance in the context of tumour cell proliferation and the regulation of the tumour microenvironment. It fulfils a number of functions, including the provision of bioenergy and the coordination of macromolecular synthesis.[40] Recent studies have shown that certain tumour subtypes rely predominantly on OXPHOS rather than glycolysis for their proliferation and survival.[41,42] In Liu et al, the transition of HCC metabolic phenotype from glycolysis to OXPHOS inhibited HCC cell proliferation and tumor growth.[43] The liver stands out as one of the organs with high mitochondrial density and number, reflecting variations in mitochondrial density across different tissues based on their OXPHOS demand. The accumulation of dysfunctional mitochondria is a key contributor to chronic liver diseases,[44] with mitochondrial dysfunction commonly observed in PLC.[45] Mitochondrial dysfunction has been linked to reduced ROS production, compromised apoptosis, increased anabolic processes, decreased proliferative capacity, and impaired autophagic degradation.[46]

Mitochondrial biogenesis is a tightly regulated process that involves the coordinated transcription and translation of mitochondrial and nuclear transcripts.[47] In PLC, cancer cells may enhance glycolysis by suppressing gluconeogenesis, thereby promoting cell survival in the hypoxic and nutrient-poor tumour microenvironment characteristic of early stages of tumourigenesis.[48] The specific mechanism of action is illustrated in Figure 4.

Iron Metabolism Pathway in Liver Cancer Stem Cells

Recent studies have highlighted elevated iron levels in CSCs across various tumor types, implicating disrupted iron transport in the tumorigenic potential of CSCs. The aberrant iron levels in CSCs are orchestrated through precise modulation of iron metabolism gene expression. Elevated iron content in CSCs is frequently associated with heightened expression of the iron storage protein ferritin in most investigations.[49,50] The observation that iron chelation impedes the

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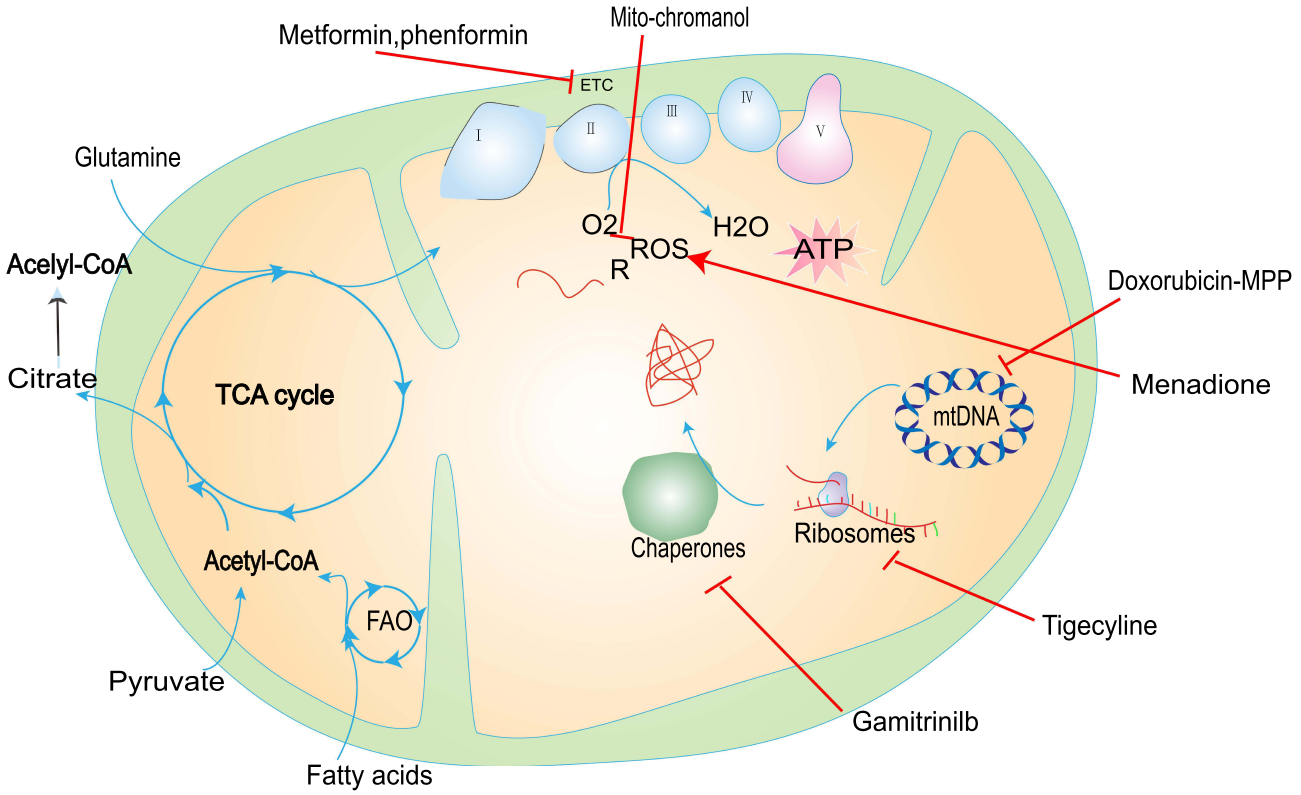

Figure 4 Oxidative phosphorylation pathway in liver cancer stem cells. The mitochondrial oxidative phosphorylation (OXPHOS) pathway is of critical importance in the context of tumour cell proliferation and the regulation of the tumour microenvironment.The transition of HCC metabolic phenotype from glycolysis to OXPHOS inhibited HCC cell proliferation and tumor growth.
Abbreviations: FAO, fatty acid oxidation; ROS, reactive oxygen species.

development of tumorspheres, serving as a proxy for CSCs, in various cancers provides strong evidence for a functional role of elevated iron levels in CSC formation and stemness maintenance. Moreover, the manipulation of iron levels has been shown to influence the expression of canonical stemness markers.[49]

Iron death is a distinctive form of regulated cell death characterised by intracellular iron accumulation, lipid peroxidation, heightened intracellular ROS levels, altered mitochondrial morphology, increased membrane density, and diminished mitochondrial cristae, while preserving nuclear integrity. Maintaining redox homeostasis and mitigating ROS levels are pivotal functions regulated by reduced glutathione (GSH) within cells. Glutathione synthesis relies on the transport of glutamate and cystine facilitated by the cystine/glutamate antiporter system (System Xc). Inhibition of System Xc impedes intracellular glutathione production, diminishing the cell's capacity to scavenge ROS. This disruption results in excessive ROS accumulation and an antioxidant imbalance, culminating in iron death. System Xc inhibition serves as a principal mechanism underlying iron death, and targeted inhibitors of System Xc, such as erastin and sorafenib (Sora), have demonstrated efficacy as inducers of iron death. A significant mechanism contributing to iron death involves the suppression of glutathione peroxidase 4 (GPX4) activity. GPX4 plays a pivotal role in mediating the antioxidant functions of reduced GSH. In instances where GPX4 activity is inhibited or reduced, an imbalance in antioxidant defense mechanisms ensues, leading to excessive accumulation of ROS and lipid peroxidation, ultimately culminating in iron death.[51]

The disruption of intracellular iron metabolism is a pivotal factor in the process of iron death. Maintenance of intracellular iron homeostasis is governed by mechanisms involving iron transport, storage, and ferritin autophagy. Extracellular trivalent ferric ions (Fe^{3+}) enter the cell facilitated by transferrin (TF). Within lysosomes, Fe^{3+} is converted to ferrous ions by the activity of six-transmembrane epithelial antigen of prostate 3 (STEAP3) and subsequently translocated into the cytoplasm via divalent metal ion transporter 1 (DMT1), contributing to the formation of the cytoplasmic labile iron pool. In the intracellular labile iron pool, ferrous ions (Fe^{2+}) can undergo conversion to Fe^{3+} through the Fenton reaction catalyzed by intracellular ROS, generating highly reactive hydroxyl radicals (•OH) with potent oxidizing properties. Disruption of cellular iron

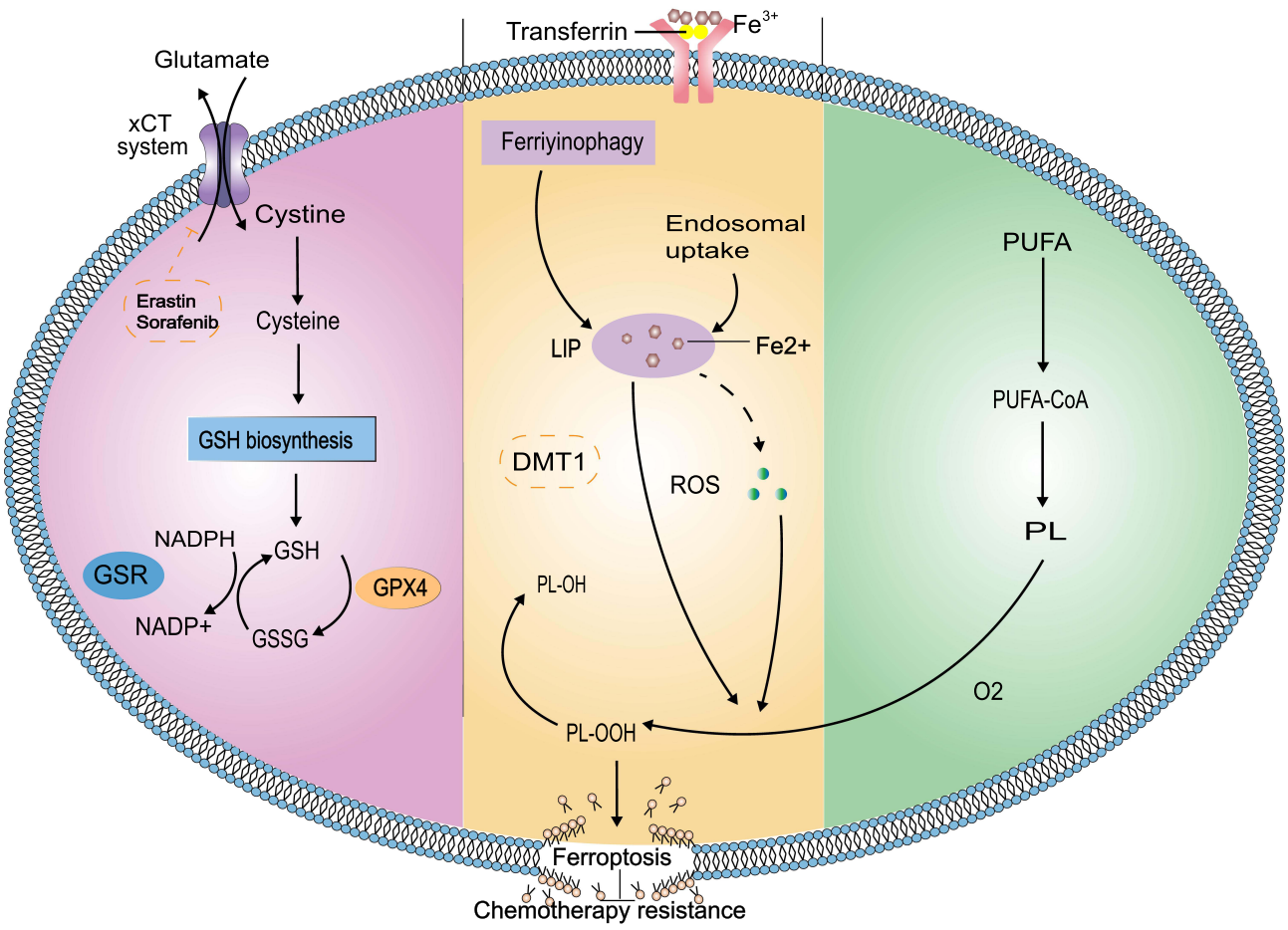

Figure 5 Iron metabolism pathway in liver cancer stem cells. Recent studies have highlighted elevated iron levels in CSCs across various tumor types, implicating disrupted iron transport in the tumorigenic potential of CSCs.A significant mechanism contributing to iron death involves the suppression of GPX4 activity. GPX4 plays a pivotal role in mediating the antioxidant functions of reduced GSH. Disruption of cellular iron metabolism, such as DMT1 function inhibition, can impede proper lysosomal iron transport, resulting in lysosomal damage and rupture, thereby promoting cellular iron death.

Abbreviations: GSR, Glutathione disulfide reductase; GPX4, glutathione peroxidase 4; GSH, glutathione; GSSG, Oxidized glutathione; DMT1, divalent metal transporter 1; PUFA, polyunsaturated fatty acid; PL, Plasmin.

metabolism, such as DMT1 function inhibition, can impede proper lysosomal iron transport, resulting in lysosomal damage and rupture. Hydroxyl radicals can induce membrane lipid peroxidation, thereby promoting cellular iron death.[3] The specific mechanisms underlying these processes are depicted in Figure 5.

Drug Development Based on HCC Stem Cell Metabolism

HCC is an extremely aggressive associated with a dismal prognosis. Current conventional anticancer modalities, such as chemotherapy, radiotherapy, and immunotherapy, have shown limited efficacy in enhancing the outcomes of patients with HCC. Emerging evidence suggests that hepatic CSCs make a significant contribution to the unfavorable prognosis of HCC patients, as they possess inherent drug resistance and exhibit stem cell-like properties, including differentiation capabilities and self-renewal. Consequently, the survival of hepatic CSCs post-treatment contributes to disease recurrence and progression. Given the pivotal role of CSCs in HCC pathogenesis and therapeutic resistance, targeting and eradicating CSC populations have been identified as promising strategies to ameliorate patient prognosis. Approaches aimed at targeting CSC surface markers utilizing antibodies, inhibitors, or combination therapies have demonstrated efficacy in reducing hepatic CSC populations and hold promise for improving clinical outcomes in patients with HCC. In addition, a team of researchers recently collected data from a subset of HCC patients at high risk of recurrence after liver resection, and through in-depth analyses concluded that adjuvant therapy with anti-programmed cell death 1 antibody (PA-PD-1) had a significant improvement in the survival prognosis of HCC patients at high risk of recurrence after liver resection.[52]

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Increasing evidence suggests that hepatic CSCs predominantly rely on glycolytic pathways while exhibiting diminished OXPHOS rates. In light of the distinctive metabolic phenotype exhibited by CSCs, there has been a focus on exploring glycolysis-inhibiting agents as potential anti-cancer therapeutics. For instance, 2-deoxy-D-glucose (2-DG), a glucose analogue that competitively hinders glucose uptake, has been investigated for its ability to induce apoptosis in hepatic CSCs when used in conjunction with sorafenib.[53] Another promising agent, ADI-PEG20, has been shown to counteract the Warburg effect by dampening OXPHOS elevation and targeting glutamine and glycolytic metabolism pathways in CSCs.[54] The efficacy of ADI-PEG20 in stabilising disease progression in pre-treated advanced HCC in the Asian population has been demonstrated in clinical trials.[55] Conversely, metformin, an agent that disrupts OXPHOS by inhibiting NADH coenzyme Q oxidoreductase (complex I), has been associated with increased tumor invasiveness and resistance to sorafenib treatment in diabetic patients with advanced HCC. Therefore, future strategies for PLC treatment may involve the combination of glycolysis inhibitors or agents that modulate OXPHOS with chemotherapy to potentially enhance treatment efficacy. This approach could prove more effective in targeting hepatic CSCs and overcoming therapeutic resistance in PLC. Some findings suggest that glycolytic metabolism contributes to the antitumour effect of demethylmalonic acid (DML), and that DML inhibits the tumourigenesis of LCSCs through inhibition of H3 histone lactonisation, which can be considered as a potential drug for the treatment of hepatocellular carcinoma.[56]

Studies on mitochondria in HCC have primarily investigated the inhibition of aerobic glycolysis, ROS production via OXPHOS, and receptor tyrosine kinase-mediated signaling pathways. Recently, there has been a growing interest in the regulation of mitochondrial protease activity, which holds promise for identifying novel druggable targets aimed at enhancing the prognosis of HCC patients.[57] In addition, Liu et al have proposed that mitochondrial autophagy may exert a positive regulatory effect on hepatic CSCs by inhibiting the tumour suppressor p53.[58] The PTEN-induced putative kinase 1 (PINK1) has been demonstrated to play a role in the process of mitochondrial autophagy and phosphorylates p53 at site S392. The collective findings indicate that mitophagy plays a pivotal role in the regulation of the hepatic CSC population, exerting its influence through the modulation of p53 activity. Therefore, the development of novel inhibitors targeting mitochondrial autophagy holds promise for eliminating liver CSCs and impeding the progression of HCC.

Given the close association between mitochondrial function and hepatic CSC characteristics, exploring drugs that modulate mitochondrial function may hold promise as novel therapeutic avenues. XIAP, a potent inhibitor of cysteine aspartic acid-specific protease, has been identified as a key suppressor of mitochondria-mediated apoptosis.[59] AEG35156, an antisense oligodeoxynucleotide targeting the anti-apoptotic protein XIAP, has been shown to enhance apoptosis. The results of a randomised Phase II trial demonstrated that the combination of AEG35156 and sorafenib resulted in an improved progression-free survival (PFS) rate in patients with advanced HCC compared to sorafenib monotherapy. The results of this study indicate that targeting mitochondrial function may offer a promising avenue for the treatment of HCC.[60]

In light of the tumour-specific upregulation of key lipid metabolism proteins in HCC and the precise regulation of this pathway in normal tissues, there is a rationale for anticipating specific therapeutic responses in HCC tumours through the use of targeted inhibitors. Thus far, advancements in therapies targeting adipogenesis in HCC have been limited, highlighting an area ripe for further exploration and development.[32] Significant research efforts are underway to explore SCD1 as a potential therapeutic target in various cancers, including HCC. The novel enzyme inhibitor SSI-4 has shown promising efficacy both in monotherapy and combination therapy with other agents. It is particularly noteworthy that this agent exerts synergistic effects when combined with sorafenib in HCC models and with immune checkpoint inhibitors in breast cancer.[61] In addition to SCD1, inhibitors targeting a range of enzymes involved in neoadipogenesis, and their potential anti-tumour efficacy is currently being further investigated.[62] Notably, recent in vitro studies utilizing the thienopyrimidine Fasnall, a FASN inhibitor, have revealed antiproliferative and apoptotic effects.[63] Furthermore, HMGCR, the target of statins known for their cholesterol-lowering effects, has shown potential as an anticancer target.[64] Additionally, statins have been observed to reverse resistance to sorafenib therapy, further highlighting their therapeutic potential in the treatment of HCC.[65]

Clinical strategies targeting iron overload are currently available, with a range of iron chelators either investigated in preclinical studies or already employed in clinical settings.[66] Notably, iron chelators like ICL670 (at a concentration of 25 μmol/L) and CP20 (at a concentration of 150 μmol/L) have demonstrated inhibitory effects on HUH7 cell proliferation (approximately 50% reduction) and DNA replication (approximately 90% reduction).[67] Moreover, the iron chelator deferoxamine (DFO) has been shown to enhance the antiproliferative impact of interferon γ on HCC cells.[68] The iron

Table 1 Drug Development Based on HCC Stem Cell Metabolism

Drug Name	Target	Mechanism	Development Status
PINK1	Tumor suppressor p53	Inhibits mitochondrial autophagy	Under development
AEG35156	Apoptosis protein XIAP	Promote mitochondria-mediated apoptosis	Under development
Fasnall	FANS	Promote apoptosis of cancer cells	Under development
2-DG		Inhibit glycolysis	Under development
ADI-PEG20		Inhibit glycolysis	Under development
Metformin		Upregulates OXPHOS	Marketed
SSI-4		Inhibition of lipase production	Under development
ICL670	Iron overload	Inhibits proliferation of hepatocellular Carcinoma cells	Under development
CP20	Iron overload	Inhibits proliferation of hepatocellular Carcinoma cells	Under development
TSC24	Iron overload	Inhibits proliferation of hepatocellular Carcinoma cells	Under development
KTp4-Me		Inhibits proliferation of hepatocellular Carcinoma cells	Under development

chelator thiosemicarbazone-24 (TSC24) has been demonstrated to induce cell cycle arrest, promote apoptosis, and impede the growth of HCC cell lines as well as human-derived transplanted liver tumors.[69] Furthermore, iron chelators such as potassium tris(4-methyl-1-pyrazolyl)borohydride (KTp4-Me),[70] and deferasirox (DFX)[71] have demonstrated the ability to hinder the progression of HCC by limiting the proliferation of liver cancer cells. Although iron chelators have demonstrated anti-tumour activity in vitro and in animal models, clinical trials involving patients with HCC have produced less promising results.[72] In vivo investigations have suggested that iron chelators may not be as effective in treating liver cancer and could potentially accelerate disease progression. Therefore, the utilization and wider adoption of iron chelation therapy in clinical practice necessitate further investigation to clarify its efficacy and safety profile in the management of liver cancer. Specific drug development is shown in Table 1.

Discussion

CSCs are of pivotal importance in the intricate composition of tumours and tumour recurrence, particularly in the context of HCC. The presence of HCC stem cells is a significant predictor of recurrence in patients with HCC. The latest experimental evidence indicates that the energy metabolism of HCC cells plays a crucial role in maintaining their stem cell characteristics. However, current research on the energy metabolism of HCC stem cells and its association with HCC recurrence lacks a comprehensive synthesis and organization. In this study, A systematic review of literature was conducted using a range of databases, including PubMed, Wanfang, and others, as well as the comprehensive Citexs database. Our findings indicate a close correlation between liver cancer recurrence and various metabolic pathways, including glycolysis, oxidative phosphorylation, lipid metabolism, glutamine metabolism, and iron metabolism in HCC stem cells. This emphasises the significance of metabolic pathways in the biology of HCC stem cells and recurrence, warranting further investigation in this area. In HCC stem cells, key targets of glycolysis metabolism include HK2, PFK, PK, and LDH. Glutamine metabolism primarily involves the TCA cycle with targets such as mTORC1 and ROS. In lipid metabolism pathways, the focus is on FA biosynthesis, with key targets including FASN, ACC, SCD1, and AMPK. The oxidative phosphorylation pathway's main target is PLC. Iron metabolism revolves around System Xc, GPX4, and DMT1 as key targets. Clinical drugs currently under development targeting HCC stem cell metabolism include PINK1 and AEG35156, which modulate mitochondrial energy metabolism. Additionally, drugs such as ADI-PEG20 and 2-DG aim to inhibit glycolysis, while ICL670, CP20, TSC24, and KTp4-Me target iron metabolism to inhibit HCC cell proliferation. These agents are all in various stages of research and development for potential clinical application. The development of therapeutics targeting energy metabolism in HCC stem cells currently lacks a comprehensive exploration of glutamine and lipid metabolism processes. Based on the insights derived from this study, investigations into liver cancer recurrence concerning the energy metabolism of liver cancer stem cells should prioritize the study of glutamine and lipid metabolism pathways. It is anticipated that future research efforts will focus on the development of drugs that target and inhibit cancer stem cells by modulating glutamine and lipid metabolism pathways in HCC. In recent years, there has been an increasing number of studies on the prediction of HCC recurrence after surgery. For example, in a recent study, L et al analysed 24 patients with recurrence after liver transplantation and found that age,

microvascular invasion, CTTR (time in therapeutic range calculated according to the Chinese guidelines) and mean trough concentration of tacrolimus were predictors of HCC recurrence after liver transplantation, and concluded that TTR (time in therapeutic range) predicted postoperative HCC recurrence.[73] In addition, some researchers have also introduced the tensor fusion method into the HCC surgical recurrence prediction model, which introduces the key information of HCC post-operative recurrence in addition to firstly considering the effect of liver background. This method has obvious advantages in data processing, and the model was subsequently validated and proved to be highly effective in predicting HCC postoperative recurrence.[74] These studies will bring confidence and hope for more accurate prediction of clinical outcomes in postoperative recurrence of hepatocellular carcinoma, thus contributing to the improvement of the treatment of HCC recurrence.

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Disclosure

The authors report no conflicts of interest in this work.

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