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Review Article

Duplexity of Lipids in Hepatocellular Carcinoma Cells

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Abstract

Hepatocellular carcinoma (HCC) is one of the most lethal malignancies. We aimed to identify lipid metabolism-related features associated with the HCC microenvironment to improve the prognosis prediction of HCC patients. The increased metabolic demands of cancer cells emphasize the importance of metabolic pathways in cancer cell survival. Lipid metabolism plays an important role in the development of HCC; aberrant overexpression of several key lipid-related enzymes can be seen in many solid human tumors.

Keywords: *lipids, hepatocellular carcinoma*

Sources and routes of lipids

Lipids, also known as fats, are composed of many different types of molecules, including phospholipids, fatty acids, triglycerides, sphingolipids, cholesterol and cholesteryl esters. Lipids are widely distributed in cellular organelles and are an important component of all cell membranes [1]. In addition, lipids in cell membranes have organelle functions that can act as second messengers in cells transmitting signals and acting as an important source of energy when nutrients are limited [2]. Mammalian cells acquire lipids through two mechanisms which is de novo synthesis and *in vitro* uptake. Glucose is the main substrate for the de novo synthesis of lipids, which is converted to pyruvate by glycolysis, enters the mitochondria to form citric acid and is released into the cytoplasm as a precursor for the synthesis of fatty acids and cholesterol [3]. A variety of glucose transporter proteins, as well as a range of enzymes that regulate glycolysis and lipid synthesis, are strongly upregulated in cancer cells [4]. For example, the glutamine transporter protein SLC1A5 (also known as ASCT2) is upregulated in various cancers [5]. In addition, glutamine can be converted to glutamate and α-ketoglutarate in mitochondria, and through oxidative phosphorylation to generate ATP and synthesise lipids [6]. Glutamine (Gln) is the most abundantly expressed amino acid in blood and tissues, and it is also the main nitrogen donor necessary for tumour growth [7]. Under conditions of hypoxia or mitochondrial defects, the reductive carboxylation of glutamine-derived α-ketoglutarate is converted to citric acid thereby contributing to the de novo synthesis of lipids [8].

Lipid metabolism promotes the growth and metastasis of tumor cells

Lipogenesis in normal tissues is mainly derived from hepatocytes and adipocytes. However, cancer cells activate lipogenesis in response to their high metabolic demand, using exogenous lipids to provide unsaturated fatty acids. This ability appears to depend on oxygen levels and the type of oncogene they express, and not all lipids are utilised equally [9]. Dysregulated lipid metabolism is one of the most significant metabolic alterations in cancer, and cancer cells use lipid metabolism for energy, biofilm components, and signalling molecules required for proliferation, survival,

invasion, and metastasis [10]. CD36 is also known as a fatty acid (FA) translocase, and high CD36 expression is associated with poor prognosis in patients with breast, ovarian, gastric, and prostate cancers [11]. In addition to ab initio synthesis, CD36 uptake of lipids from the exogenous environment is another important way for cells to acquire fatty acids. CD36 transports fatty acids into cells and plays a key role in cancer cell growth, metastasis and epithelial-mesenchymal transition. For example, omental adipocytes induce CD36 expression and associated lipid accumulation in ovarian cancer cells, and inhibition of CD36 attenuates adipocyte-induced accumulation of cholesterol and lipid droplets in ovarian cancer cells, peritumoral dissemination of tumour cells and tumour growth [12]. Similar to adipocytes, cancer-associated fibroblasts derived from pancreatic stellate cells remaining in pancreatic ductal adenocarcinoma (PDAC) tissue secrete lipids including lysophosphatidylcholine for uptake and synthesis of phosphatidylcholine by cancer cells [13]. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is a key enzyme that regulates the cellular senescence phenotype of A549 cells by modulating the AMPK network, a key pathway associated with lipid metabolism in cancer cells [14].Plakophilin 2 (PKP2) encodes the plakophilin (a member of the bridging granule proteins) protein, and studies have demonstrated the role of PKP2 in overexpressed in several human cancers, including lung cancer; it is an unfavourable prognostic biomarker for patients with lung adenocarcinoma (LUAD) and, in addition, PKP2 exerts oncogenic effects by activating the EGFR signalling pathway in LUAD cells [15]. Cancer cells acquire lipids and lipoproteins through two mechanisms: uptake of exogenous lipids from the local microenvironment and de novo synthesis of endogenous lipids. Lipid metabolism in cancer cells can be regulated not only by intracellular oncogenic signals but also by inputs from the tumour microenvironment consisting of various cell types, cytokines, growth factors, DNA, RNA, nutrients and including lipids. In turn, abnormal lipid metabolism can alter oncogenic signalling pathways in cancer cells and affect adjacent normal cell populations through secreted components including lipids [16].

Lipid metabolism promotes survival and proliferation of hepatocellular carcinoma cells

Sources of lipids in hepatocellular carcinoma cells

The two main sources of intracellular lipids are the ab initio synthesis of lipids and external uptake. Normal cells preferentially use circulating exogenous lipids, whereas cancer cells (including HCC cells) exhibit a higher rate of ab initio lipid synthesis thereby indicating that FA accumulates in tumour cells [17].

Lipids synthesized de novo in hepatocellular carcinoma cells are derived from glucose, acetic acid and glutamine. In hepatocellular carcinoma cells, pyruvate produced by glycolysis is oxidatively decarboxylated in the mitochondria to produce acetyl coenzyme A and condensed with oxaloacetate to form citric acid, which relies on SLC25-A1 for transport from the mitochondria to the cytoplasmic matrix. In the cytoplasm, citric acid is converted to acetyl coenzyme A by ATP citrate lyase. Cancer cells can rely on glutamine to enter the tricarboxylic acid cycle (TCA) through mitochondrial oxidative phosphorylation to meet the energy demand for proliferation. It plays an important role in cancer cell growth. Glutamine, as an energy substance commonly used by tumour cells, is an important carbon source in liver cancer cells and can also be converted to citric acid under hypoxic conditions through reduction Under hypoxic conditions. Glutamine can be converted to citric acid by reduction and then to acetyl coenzyme A to promote de novo lipid synthesis (DNL) [18]. In addition, hepatocellular carcinoma cells can also use exogenous acetic acid to produce acetyl coenzyme A for lipid synthesis. These exogenous acetic acids inhibit the decrease in histone acetylation, which is closely related to transcriptional activity, and acetic acid-induced histone acetylation drives the expression of fatty acid synthase and acetyl-CoA carboxylase α (ACCα) to promote lipid synthesis. Exogenous acetic acid can also act as a direct substrate for eventual conversion to lipids by the action of enzymes. The acetyl coenzyme A produced by the above pathway is

carboxylated by ACCα to produce malonyl-coenzyme A (malonyl-CoA), which is then passed through FASN to produce fatty acids, which are ultimately stored in the lipid droplets of the cells as TG.

Hepatocellular carcinoma cells obtain energy mainly through aerobic glycolysis, but the fact that they are often in an oxygen and glucose-deficient microenvironment makes lipid metabolism an important metabolic pathway for hepatocellular carcinoma cells and is essential for their survival and proliferation. At adequate nutrient levels, hepatocellular carcinoma cells produce ATP mainly through active glycolysis and oxidative phosphorylation in the mitochondria, but at low extracellular glucose concentrations, fatty acid oxidation (FAO) produces more ATP than glycolysis and the tricarboxylic acid cycle in the mitochondria, thus maintaining the survival and proliferation capacity of hepatocellular carcinoma cells. Fatty acids synthesized by hepatocellular carcinoma cells in the presence of high extracellular glucose concentrations can provide energy for hepatocellular carcinoma cells by producing NADPH and ATP through beta oxidation in the absence of glucose.

In addition to being an important component of the plasma membrane, lipids are also important signalling molecules and sources of energy, so reprogramming of lipid metabolism has become one of the new hallmarks of cancer. Fatty acid synthase (FAS) is particularly important for hepatocellular carcinoma cells as it is a major component of membrane structure that needs to be synthesized in large quantities for proliferation and is also a component of signalling molecules within hepatocellular carcinoma cells. Under normal culture conditions, FAS can provide hepatocellular carcinoma cells with large amounts of lipids to promote their proliferation. However, as hepatocellular carcinoma cells are often in a glucose- and oxygen-deprived tumour microenvironment, the substrate and oxygen required for aerobic glycolysis cannot be replenished in a timely manner, and hepatocellular carcinoma cells will regulate their own fatty acid synthesis according to the extracellular glucose concentration. When the extracellular glucose concentration is high, the ability of hepatocellular carcinoma cells to synthesize fatty acids is enhanced. Hepatocellular carcinoma cells produce a large amount of pyruvate through glycolysis, but these pyruvate cannot provide energy for hepatocellular carcinoma cells through the tricarboxylic acid cycle in time under the conditions of lack of oxygen, then hepatocellular carcinoma cells use the excess pyruvate in glycolysis to synthesize fatty acids under the catalytic action of a series of enzymes such as acetyl CoA carboxylase and These are stored in lipid droplets (LD) as triglyceride (TG). In contrast, at low extracellular glucose concentrations, as pyruvate produced by glycolysis is promptly oxidized and broken down, hepatocellular carcinoma cells have less raw material for de novo lipid synthesis (DNL), their ability to synthesize fatty acids is reduced, and fatty acid synthase (FAS) is inhibited to conserve ATP for hepatocellular carcinoma cell survival.

Aberrant role of genes for fatty acid metabolism-related enzymes in hepatocellular carcinoma and related research progress

Lipid metabolism, including the uptake, transport, synthesis and degradation of lipids, is a complex process. Key regulators of lipogenesis are SREBP, acetyl coenzyme A carboxylase (ACC), fatty acid synthase (FASN) and stearoyl coenzyme A desaturase 1 (SCD1) all of which are significantly upregulated in various human cancers [19].

SREBPs are a family of basic helix-loop-helix leucine zip transcription factors that regulate the ab initio synthesis of fatty acids and cholesterol as well as cholesterol uptake [20]. Mammalian cells express three SREBP proteins, SREBP-1a, -1c and -2, which are encoded by two genes, SREBF1 and SREBF2. SREBP-1a regulates fatty acid and cholesterol synthesis and cholesterol uptake, while SREBP-1c primarily controls fatty acid synthesis [21]. SREBF2 encodes the SREBP-2 protein and plays a major role in the SREBF2 encodes the SREBP-2 protein, which plays a major role in the regulation of cholesterol synthesis and uptake [22]. SREBP-1 has been found to be significantly upregulated in glioblastoma, one of the most common primary brain tumours and one of the most lethal cancers [23]. The use of

SREBPs inhibitory drugs at the genetic level significantly inhibited tumour growth and induced cancer cell death, making SREBPs a promising new therapeutic target [24]. Solute carrier family 25 member 1 (SLC25A1), also known as citrate carrier (CIC), provides a key precursor for fatty acid and cholesterol synthesis as a key transporter protein for the export of citrate from the mitochondria to the cytoplasm [25]. SLC25A1 is regulated by SREBP-1 and plays an important role in inflammation and tumour growth. In lung cancer cells, SLC25A1 is upregulated by mutant p53 [26,27]. SREBP1 is overexpressed in hepatocellular carcinoma as an important transcription factor regulating fatty acid synthesis and is strongly associated with worse clinical outcome in hepatocellular carcinoma, where SREBP1 promotes growth and metastasis.

ACC is upregulated in several human cancers, including glioblastoma and head and neck squamous cell carcinoma [28,29]. Inhibition of ACC significantly reduces fatty acid synthesis and inhibits tumour growth in various xenograft models. the ACC inhibitors TOFA, soraphenA and ND646 show significant antitumour effects in xenograft tumour models [30,31].

Fatty acid synthase (FASN) is the key enzyme that catalyses the final step in the ab initio synthesis of fatty acids. FASN is a large multi-enzyme complex with a monomeric protein size of approximately 270 kDa containing six separate enzyme grooves, and FASN acts synergistically with NADPH to produce 16-carbon chain saturated fatty acids (FA) and palmitate from acetyl coenzyme A (CoA) and malonyl coenzyme A [32]. A new generation of FASN inhibitor, TVB-2640, has entered clinical trials in patients with solid tumours [33]. Recent studies have found that expression of fatty acid synthase (FASN) is necessary for lipid synthesis and maintenance of palmitate levels, particularly in an environment without exogenous lipids. Fatty acid synthesis is required for liver tumour growth and FASN could be a potential therapeutic target for brain metastases from hepatocellular carcinoma.

Stearoyl-CoA desaturase (SCD) is overexpressed in cancer cells and SCD controls the proliferation of hepatocellular carcinoma cells by inducing apoptosis, arresting the cell cycle and preventing migration, but the antitumor effects of SCD inhibitors can be reversed by exogenous oleic acid.SCD1 stearoyl-CoA desaturase (SCD) is an endoplasmic reticulum-resident integral membrane protein catalyzes the formation of stearoyl, palmitoleic or palmitoleic acid. the SCD1 inhibitors BZ36, A939572 and MF-438 have shown antitumour effects in preclinical xenograft models [34-36].

ATP citrate lyase (ACLY) converts cytoplasmic citrate to acetyl coenzyme A, a precursor for lipid synthesis and a substrate for protein acetylation. ACLY is a downstream target of SREBP [37] and is upregulated in many cancers, including glioblastoma, colorectal cancer, breast cancer, non-small cell lung cancer and hepatocellular carcinoma [38, 39]. The ACLY inhibitor SB -204990 strongly inhibited tumour growth in mice with xenografts of lung, prostate or ovarian cancers [40], suggesting that ACLY could be an attractive anti-cancer target [41]. Overexpression or enhanced activity of ATP citrate lyase (ACLY), an enzyme involved in fatty acid synthesis in hepatocellular carcinoma, was associated with tumour progression. Expression of ACLY reduced tumour cell viability and inhibited tumour cell proliferation, invasion and metastasis. The fatty acid rate-limiting enzyme acetyl-CoA carboxylase alpha (ACACA) is highly expressed in hepatocellular carcinoma. ACACA depletion reduces FA synthesis and induces apoptosis in liver tumour cells but not in non-malignant cells.

Dysregulated lipid metabolism can lead to the progression of various metabolic diseases, including cardiovascular disease, obesity, hepatic steatosis and diabetes mellitus.

Uptake and transport of exogenous fatty acids by hepatocellular carcinoma cells66

The uptake of exogenous fatty acids by hepatocellular carcinoma cells relies heavily on fatty acid translocase/CD36 (FAT/CD36), fatty acid-binding protein (FABP), fatty acid transport proteins (FATPs) and to a lesser extent on passive diffusion. The transmembrane mechanism of fatty acid transport through FATPs is currently unknown, but numerous

experiments have shown that cellular uptake of fatty acids is closely linked to genes regulating the expression of FATPs. In addition to FATPs, the fatty acid transferase CD36 is able to facilitate the transport of fatty acids, which is closely related to the induction of mesenchymal transition. Small fossil proteins located in the plasma membrane of hepatocytes also contribute to lipid transport and LD formation. CD36 can transport long-chain fatty acids, oxidised LDL, anionic phospholipids and oxidised phospholipids across the cell membrane [42]. CD36 expression was found to be significantly upregulated in malignant tissues, including ovarian [43], gastric [44], breast [45] and hepatocellular carcinoma [46]. In addition, its expression profile was highly correlated with disease stage and metastatic status [47]. Upon uptake by hepatocellular carcinoma cells, the hydrophobicity of fatty acids prevents them from diffusing freely in the cytoplasmic lysis and must instead be shuttled between different organelles by specific FABP1, 2 and 4, of which FABP1 is highly expressed in hepatocellular carcinoma cells and may increase lipid flux and contribute to the transport and storage of exogenous fatty acids in hepatocellular carcinoma cells.

Fatty acid metabolism maintains the biological traits of tumour cells

In most human tissues, cellular requirements for fatty acids are generally met using dietary fatty acids and the fatty acid de novo synthesis pathway is unimportant, with the exception of the liver and to a lesser extent, adipose tissue. The differential importance of the fatty acid ab initio synthesis pathway in normal versus cancerous tissues makes it an attractive therapeutic target. In recent years, there has been a resurgence in the development of lipid inhibitors in anti-cancer therapy. Studies have reported that specific inhibitors of FASN have been developed using the differential FASN activity or expression between normal tissue and cancer cells, including cerulenin, C75, orlistat and more recently TVB-2640, with findings showing that pharmacological inhibition of FASN is effective *in vitro* and *in vivo* against a variety of malignant cells but not normal cells, providing This provides a therapeutic window for intervention. The biological traits and energy metabolism mechanisms of different tumour cells differ from those of normal cells. It has been found that fatty acids required for the growth and proliferation of malignant tumours are mainly derived from ab initio synthetic pathways, and dysregulation of fatty acid metabolism plays an important role in the malignant transformation of many cancers, including liver cancer. Hypoxia represents an important state of the tumour microenvironment due to the rapid growth and uncontrolled angiogenesis of cancer cells. Furuta demonstrated that hypoxia upregulates the expression of SREBP-1, an important transcription factor in FA anabolic metabolism, and verified the synergistic effect of hypoxia and FA metabolism [48]. Important enzymes related to fatty acid synthesis and oxidative metabolism are overexpressed in tumour tissues but not or under-expressed in normal tissues. Key metabolic enzymes involved in fatty acid synthesis and oxidative metabolism play a critical role in the proliferation, migration and invasion of hepatocellular carcinoma cells. Through the invasion-metastasis cascade, cancer cells infiltrate nearby blood vessels and lymphatic vessels, or metastasise to distant tissues, with epithelial mesenchymal transition (EMT) being an important mode in this process. Through EMT cancer cells reverse to an undifferentiated state with invasive, metastatic and anti-apoptotic capabilities. Most of the enzymes associated with epigenetic modifications in this reversible process require the involvement of cofactors, including acetyl coenzyme A, an intermediate product of FA metabolism, which makes EMT vulnerable to changes in intracellular metabolite levels [49].

Relationship between lipid metabolism and the tumour microenvironment (TME) in hepatocellular carcinoma cells

The tumour microenvironment is acidic and hypoxic, and nutritional deficiencies lead to abnormal metabolism of tumour cells and adjacent stromal cells, thereby promoting tumour metastasis, proliferation and survival. In HCC, TME may exhibit different metabolic disorders, with abnormal lipid metabolism being the new domain [50]. There are complex interactions between the immune system and tumour cells during tumorigenesis and progression. Although

the immune system clears malignantly transformed cells at an early stage, surviving tumour cells evade the host's immune defences by various means, even reprogramming the anti-tumour immune response to a pre-tumour phenotype state thereby giving tumour cells the ability to grow and metastasise indefinitely. The high proliferation rate of tumour cells increases their demand for local nutrients and oxygen, which is barely met by poorly organised blood vessels, resulting in an acidic, hypoxic and glucose-deficient tumour microenvironment in which lipids are activated and act as a major source of energy and key regulator of tumour cells and associated immune cells. However, the exact role of lipid metabolic reprogramming in the tumour immune response remains unclear. A comprehensive understanding of dysfunctional lipid metabolism in the tumour microenvironment and its dual impact on the immune response is essential to draw a detailed picture of tumour immunology and to develop patient-specific therapeutic regimens for cancer patients. In this review, we focus on dysregulated lipid metabolism in the tumour microenvironment and discuss its paradoxical role in the tumour immune response. In addition, we summarise current therapeutic strategies targeting lipid metabolism in tumour immunotherapy. This article provides a review of the role of lipid metabolism in the tumour immune response. Cancer-associated adipocytes (CAA) in the tumour microenvironment (TME) play a dynamic and complex role in promoting tumour growth and drug response, with CAA providing fuel, growth factors and cytokines and transdifferentiating into other stromal cells to alter tumour growth, metastasis and drug response [51]. Because lipid metabolism in cancer cells and other cells in the tumour microenvironment, including immune cells, adipocytes, endothelial cells and fibroblasts, is dynamically regulated and interconnected. Efforts have been made to develop therapeutic agents to intervene at different levels of lipid generation [52].

Relationship between lipid metabolism and immunity in hepatocellular carcinoma

Disturbances in lipid metabolism, particularly fatty acid metabolism, due to aberrantly activated oncogenic signalling pathways altering the expression and activity of lipid metabolizing enzymes are important phenomena of metabolic reprogramming within immune cells and cancer cells and may be involved in the development of HCC. Recent studies suggest that immune cells play a key role in TME of HCC and that aberrant lipid metabolism may significantly affect their function and recruitment. Few studies have combined lipid metabolism, immune status and hepatocellular carcinoma progression, and here we provide the following overview of the relationship between HCC and immunity [53]. Reprogramming of cholesterol metabolism is mainly manifested by the upregulation of intracellular cholesterol synthesis and the abnormal accumulation of metabolites. During this process, tumour cells consume large amounts of extracellular cholesterol, resulting in a significant reduction in cholesterol levels in the serum and tumour microenvironment and thus severely limiting cholesterol synthesis in immune cells, which is essential for the maintenance of normal immune cell function. Cholesterol is not only a precursor for the production of bile acids, vitamin D and hormones, which are essential for the normal physiological functions of the body but is also a key component of the lipid rafts in the lipid bilayer structure of the cell membrane. Alikhani et al. found that lung cancer patients with hypocholesterolaemia had significantly lower total lymphocyte, T-lymphocyte and CD8+ T-lymphocyte counts in their peripheral blood than lung cancer patients with hypercholesterolaemia. This led to immune escape of tumour cells and accelerated tumour proliferation and migration. CD8+ T cells are the most important enforcers of anti-tumour adaptive immunity, including HCC. Compared to normal liver, tumour tissue has a lower density of CD8+ T cells and a higher density of Tregs, indicating a poor prognosis [53]. Excess lipids allow activated blast cells to promote NKT cell activation and induce death, leading to a decrease in the number of hepatic NKT cells. High-fat diet (HFD)-induced lipid excess in obese mice activates type I NKT cells and shifts the balance towards a pro-inflammatory cytokine environment. In addition, lipid excess also leads to hepatic steatosis in an NKT-dependent manner [54,55].

Baseline serum cholesterol levels have been reported to be significantly lower in tumor deaths than in survivors, and serum cholesterol levels in tumor patients decrease by 0.13 mmol/L every 3 years. serum lipids consist of two major components, TG and cholesterol (Total cholesterol (TC)), and cholesterol is mainly present as Low density lipoprotein-cholesterol (LDL-C) and High density lipoprotein-cholesterol (HDL-C)[8,8 densitylipoprotein-cholesterol (LDL-C) and high density lipoprotein-cholesterol (HDL-C). It has been shown that serum HDL-C levels are significantly lower in patients with diffuse large B-cell lymphoma (DLBCL)and transformed large B-cell lymphoma (transformed-DLBCL, t-DLBCL) than in normal controls.

Blocking lipid metabolism in hepatocellular carcinoma cells provides a strategy for its treatment

Recent studies have shown that lipid biosynthesis and desaturation are essential for tumorigenesis, survival and progression in primary hepatocellular carcinoma (HCC). Despite the lack of a dedicated and comprehensive assessment of the mechanisms of FA biosynthesis in HCC, several studies have described aberrant overexpression of enzymes in this process, such as FASN, ACL, ACC and stearoyl coenzyme A desaturase-1 (SCD1), and blocking the FA biosynthetic pathway has been shown to inhibit cancer cell growth in a variety of human solid tumours, including HCC, and several of these pathways Several potential targets could serve as effective drug targets as part of the therapeutic strategy for HCC [56,57]. Over the past decade, cancer immunotherapy has achieved great success. In recent years, immune checkpoint inhibitors (ICIs) have emerged as alternative therapies for HCC, and two anti-PD-1 drugs, nabumab (nivolumab) and pembrolizumab (pembrolizumab), are used as second-line treatments for patients with sorafenib-refractory advanced HCC [58], and despite this therapeutic progress, for unknown reasons, approximately 75% of HCC patients do not respond to these immunotherapies. While there is evidence that increasing the activity of tumour-specific T cells may benefit patients with HCC, the underlying chronic inflammation makes the tumour microenvironment (TME) unique and highlights the urgent need to further explore this organ-specific immunity, identify biomarkers to select patients who may respond to such treatments and develop new combinations of immunotherapies [59]. Lipids play an important role in the regulation of cancer immune responses. Cancer cells use lipids to support their aggressive behaviour and allow immune evasion. Metabolic reprogramming of tumour cells disrupts the balance between lipid anabolism and catabolism, leading to lipid accumulation within the tumour microenvironment (TME). Thus, the prevalence of lipids, mainly fatty acids, in the TME affects the function and phenotype of infiltrating immune cells. Determining the complex role of lipids and their interaction with TME will provide new insights into the difficult problem of targeting lipids and thus improving the antitumour immune response. Here, we present a review of recent literature demonstrating how lipid metabolic reprogramming occurs in cancer cells and affects cancer immunity.

Lipotoxicity

Mechanism of action of lipotoxicity in hepatocellular carcinoma cells

The production and consumption of fatty acids follows the law of conservation of energy in normal human tissues and does not accumulate excessively in the body and cause damage to the body, excessive energy intake in the normal body is converted into fatty acids stored in the body's fat cells, and during human exercise or starvation, the plasma level of fatty acids increases to reach the balance of the body's metabolic consumption. Lipid accumulation produces toxic effects that lead to liver cell damage and inflammation. Lipotoxicity refers to the accumulation of liver fat through increased deposition of free fatty acids (FFA) by insulin resistance in the context of diet, lifestyle and gut flora and caloric excess, leading to oxidative stress, protein misfolding, inhibition of autophagy and mitochondrial damage within hepatocytes. Fat accumulation can be damaging when energy intake is excessive, or consumption is greatly reduced. Normal intracellular lipid accumulation can cause damage to different tissues but by different mechanisms.

Liver cancer cells have a particularly high energy demand and therefore require a large intake of food to be converted into sugars for energy use by the cancer cells, while fat is converted into hepatocellular carcinoma cell membranes or intracellular essential substances to promote the rapid growth of liver cancer cells. Therefore, it has been suggested in the literature that starvation therapy can be used to treat cancer cells. We have also found that inhibition of lipid conversion or production can also inhibit the growth of cancer cells. The key pathway is the PPAR signalling pathway, in which lipid metabolism and related kinases are present, and it has been shown that promotion of the PPAR signalling pathway, which activates lipid production leading to lipid metabolism and transport, can lead to excessive accumulation of oxidative factors in hepatocellular carcinoma cells and thus induce cellular lipotoxic necrosis, lipotoxic necrosis is also a type of cellular necrosis.

Lipid accumulation promotes the development of hepatocellular liver cancer

Lipid accumulation leads to the development of a fatty liver, which affects the body's metabolism. Fatty liver develops into hepatocellular carcinoma, but the pathogenesis is unclear. Lipid accumulation produces a range of oxidative substances, including reactive oxygen species, which activate cell death pathways leading to cellular necrosis. Excessive oxidative damage and necrosis in fatty liver cells causes fibrotic growth, promotes the production of inflammatory factors and contributes to the development of hepatocellular carcinoma in a number of ways. In addition, lipid metabolism is associated with the development of non-alcoholic fatty liver disease (NAFLD), which has the potential to progress to steatohepatitis, fibrosis, cirrhosis and hepatocellular carcinoma. Impaired lipogenesis and lipolysis can lead to the accumulation of triglycerides in hepatocytes, which contribute to the progression of NAFLD. However, the pathogenesis of NAFLD remains to be elucidated and there is no established treatment for NAFLD [60]. Non-alcoholic fatty liver disease (NAFLD) is a highly prevalent chronic liver disease worldwide, with 3-5% of patients with NAFLD progressing to non-alcoholic steatohepatitis (NASH) and a higher risk of developing hepatocellular carcinoma [61]. The role of gut microbial, metabolic, immune and endocrine mediators in hepatocarcinogenesis that facilitate the progression of NAFLD to primary hepatocellular carcinoma (HCC) has been reported in the literature. It's worth noting that the progression involves multiple links caused by lipotoxicity, oxidative stress, inhibition of hepatic autophagy and inflammation. Hepatocellular carcinoma cells undergo chronic lipotoxicity in response to lipid oxidative stress as well as stress on the endoplasmic reticulum.

Oxidative stress mediated by reactive oxygen/nitrogen species (ROS / RNS) plays a major role in the pathogenesis and complications of liver cancer. High production of ROS causes mitochondrial damage, lipid peroxidation and LDL oxidation, ultimately leading to inflammation, and hepatic stellate cell (HSC) activation leading to fibrosis, necrosis, cirrhosis and HCC.

Lipid metabolism-related signalling pathways

Cells need to respond appropriately to their environment in order to grow, proliferate and survive. Cellular ligands bind to cellular receptors to deliver external stimuli to the cell interior, and activation of the receptors triggers a series of downstream signalling events leading to altered gene expression. This process of transducing extracellular signals to the nucleus is dysregulated in cancer cells. This section focuses on advances in the study of lipid metabolism-related signalling pathways in hepatocellular carcinoma.

Notch signalling pathway

As a paracrine signalling mechanism mediated by transmembrane ligand-receptor interactions, the Notch pathway allows neighbouring cells to communicate, thereby regulating various life processes including apoptosis, proliferation and asymmetric division. Notch pathway is also involved in liver regeneration, repair, fibrosis and metabolism [62], and activation of Notch signalling pathway can promote hepatocarcinogenesis. The mTOR pathway is known to activate

adipogenesis in the liver by inducing SREBP-1c expression [63]. Notch signalling acts in an mTOR-dependent manner to increase adipogenesis and steatosis [64], and disruption of Notch signalling can lead to liver diseases such as Alagille syndrome, which will result in the inability of the liver to properly form the biliary tree and lead to cholestasis and its sequelae. Notch signalling in hepatocytes can be activated by ligands presented by infiltrating immune cells, as demonstrated by studies of liver metabolism [65]. Although there is no direct evidence for the effect of fatty acid oxidation (FAO) on Notch signalling, studies have found that Notch1 coordinates fatty acid oxidation (FAO) to regulate lipid accumulation in the liver and redox homeostasis in resting endothelial cells. Notch signalling can also be regulated by lipid components of the cell membrane. Studies have found that cholesterol efflux regulates It has also been found that cholesterol efflux regulates the promoter of Notch1, which regulates the activity of the Notch signalling pathway at the transcriptional level, thereby regulating the formation and differentiation of hematopoietic stem cells. These findings suggest a link between Notch signalling pathway and lipid metabolism, especially in cancer, and the mechanism remains to be further investigated, which may provide new ideas or targets for the treatment of cancer.

Hippo signalling pathway

The Hippo signalling pathway consists mainly of the upstream kinase complex and the downstream transcriptional cofactors YAP/TAZ and TEADs. Hippo signalling pathways play a crucial role in the maintenance of organ size and tissue homeostasis. Cells directly recognise glucose, lipids and other metabolic cues and integrate into multiple signalling pathways, including the Hippo signalling pathway, adjusting their proliferation and apoptosis in response to nutritional conditions, so that dysregulation of the Hippo signalling pathway can contribute to tumourigenic progression. this bidirectional regulation between the Hippo signalling pathway and metabolic pathways not only effectively promotes cell growth and proliferation in response to nutritional Hippo signalling is closely linked to lipid metabolism: in response to dietary stimulation, the Hippo signalling pathway transcriptional cofactor phospholipid-lysophospholipid transacylase (TAZ) is directly upregulated in adipocytes. TAZ knockdown directly upregulates the expression profile of a range of secreted proteins, thereby affecting liver tumour growth. Recently, it has been reported that a core component of the Hippo signalling pathway regulates ab initio adipogenesis and that YAP can act as a coactivator with SREBP-1c and SREBP-2 in the nucleus to promote the expression of genes related to lipid synthesis [66]. In addition, high expression of TAZ protein in adipose tissue was found to be associated with poor prognosis in patients with triple-negative liver cancer. SCD1 was found to be involved in the regulation of the Hippo pathway in lung cancer. The study also identified fatty acid metabolism as a key regulator of lung cancer stem cells. SREBP and the pentadienide pathway can regulate Hippo signalling pathway activity, which is important for the proliferation of hepatocellular carcinoma cells. Lipid-mediated Hippo signalling pathways can trigger the progression of liver diseases such as NASH, fibrosis and HCC [67].

Hedgehog signalling pathway

The Hedgehog signalling pathway (HH) receiver system consists of the Patching (PTC) and Smoothened (Smo) families of transmembrane proteins. Hhip is a Hedgehog (Hh) signalling pathway, and Hhip inhibits the expression of Cyclin B, Cyclin D and Cyclin E in preadipocytes by downregulating the expression of these proteins. Hhip increases lipid droplets by inhibiting classical Hh-Gli signalling and increasing the expression of Glut4 and PPARγ [68]. Lipid metabolism regulates the Hedgehog signalling pathway. Cholesterol covalently modifies Hedgehog and its downstream Smo protein. Oxidized cholesterol activates Smo and thus the HH signalling pathway. Some tumour cells in triple negative hepatocellular carcinoma can stimulate tumour-associated fibroblasts to synthesise growth factors by paracrine secretion of HH proteins, which in turn can cause tumour cells to undergo stem cell transformation in a paracrine manner, thereby promoting tumour drug resistance.

Wnt signalling pathway

The Wnt signalling pathway is initiated by the binding of Wnt ligands to a heterodimeric complex formed by transmembrane receptors. The Wnt/β-catenin pathway mainly regulates cell fate during development, whereas the Wnt/PCP pathway's main function is to regulate cytoskeletal organisation; the biological function of the Wnt/Ca^{2+} pathway is not yet clear. The Wnt signalling pathway has been implicated in the metabolic reprogramming of cancer cells, and Wnt signalling plays an important role in the development of adipose tissue, with the classical Wnt signalling being an important endogenous component of adipogenesis. In humans and mice, emerging genetic evidence suggests a central role for Wnt signalling in fat distribution, obesity and metabolic dysfunction [69]. β-catenin plays an important role in the regulation of metabolism and energy homeostasis in hepatocellular carcinoma cells, and sustained activation of the Wnt signalling pathway leads to fat accumulation.

mTOR signalling pathway

The mammalian target of rapamycin (mTOR) is an atypical serine/threonine kinase. The mTOR signalling pathway plays an important role in a variety of diseases, promoting substance metabolism, apoptosis and autophagy. mTOR forms two structurally and functionally distinct multi-protein complexes: mTORC1 and mTORC2, which correspond to the two main branches of the overall signalling network. Since the discovery of mTOR, many studies have revealed how mTOR signalling reprograms metabolism to obtain nutrients from environmental and intracellular sources, resulting in the production of ATP as well as the synthesis of macromolecular intermediates. mTOR regulates SREBP and other regulators of lipid metabolism as well as effectors. mTOR inhibitors can block the expression of genes associated with adipogenesis and prevent mTORC1 also regulates SREBP through the negative regulation of lipin1. Lipids are phosphorylated by mTORC1 at multiple phosphosites, including rapamycin-sensitive and insensitive sites when phosphorylated lipin1 accumulates in the nucleus and represses SREBP-dependent gene transcription. Current strategies to inhibit the mTOR pathway also allow for more effective combination therapy to block key metabolic pathways and other molecules that control metabolic signalling. Combining fatty acid synthesis and mTOR inhibitors is expected to provide benefits for patients with tumours. Preclinical trials of the mTORC1 inhibitor rapamycin and fatty acid synthase (FASN) inhibitors in hepatocellular carcinoma have shown synergistic effects.

Known cancer stem cell-related signalling pathways such as Notch, Hippo, Hedgehog and Wnt are all closely linked to lipid metabolism. Lipid metabolism is a promising target for the inhibition of cancer stem cells and the treatment of cancer. As the key regulators of this pathway are relatively simple and tractable, therapeutic targets of fatty acid and cholesterol metabolism could help to suppress cancer stem cells and reduce chemoresistance *in vivo* and *in vitro*.

The relationship between lipid metabolism and the four modes of death in hepatocellular carcinoma

Autophagy and lipid metabolism

Hepatic autophagy fluctuates with hormone levels, feeding and fasting states, circadian activity and nutrient utilisation. Dysfunctional autophagy in hepatic parenchymal and non-parenchymal cells can lead to a variety of liver diseases, including non-alcoholic fatty liver, alcohol-related liver disease, drug-related liver injury, cholestasis, viral hepatitis and hepatocellular carcinoma [70]. Autophagy is a catabolic process used by cells to remove redundant or dysfunctional organelles and large subcellular structures, and therefore plays an important stewardship role for cells. Although autophagy is important for most normal tissues, tumour cells appear to be particularly dependent on autophagy for survival under conditions of ischaemia or therapeutic stress. The removal of protein aggregates and dysfunctional organelles (e.g., mitochondria and endoplasmic reticulum ER) by autophagy may help to ameliorate

oxidative stress as well as genomic instability and thus prevent cellular transformation. Liver tumour formation is characterised by increased mitochondrial damage, increased peroxisome, ER content, cell death and compensatory hepatocyte proliferation, hepatomegaly, ductal response, inflammation, and fibrosis [71-76].

Lipophagy is a form of autophagy in which lipid droplets produce free fatty acids via β-oxidation of ATP, which is induced in the liver by fasting or high lipid load on hepatocytes [77]. Autophagy and lipid metabolism is a key metabolic process by which cells can recycle their proteins and organelles to regenerate cellular building blocks. Chemotherapy is indispensable in cancer treatment, but it is associated with various side effects, including organ damage. Stem cell therapy is a promising treatment that can reduce the side effects of chemotherapy, however its main drawback is the low survival rate of transplanted stem cells in damaged tissues. One study examined the effect of activating adipose-derived MSC/mesenchymal stromal cell autophagy on tumour cell survival to find its therapeutic value in a model of cisplatin liver injury. One study showed that autophagy was activated by rapamycin (50 nM/L) 2 hours prior to transplantation and compared with unpre-treated ADSCs. Rapamycin pre-treatment activated autophagy in ADSCs by increasing autophagosomes, upregulating the autophagy-specific gene LC3-II, downregulating p62 and mTOR genes, and upregulating the anti-apoptotic gene BCL-2 to improve their survival rate. After transplantation of autophagic ADSCs in the cisplatin liver injury model, liver biochemical parameters (AST, ALT, albumin), lipid peroxidation (MDA), antioxidant profile (SOD, GPX) and histopathological images improved or even approached normal conditions. These promising effects of autophagic ADSCs were achieved by modulating components of the TGF-β1/Smad and PI3K-AKT signalling pathways, in addition to reducing NF-κB gene expression (inflammation marker), TGF-β1 levels (fibrosis marker) and increasing SDF-1 levels (liver regeneration marker). The current findings therefore highlight the importance of autophagy in enhancing the therapeutic potential of stem cells, mitigating cisplatin-related liver injury, and opening the way for improved oncology treatment, particularly chemotherapy.

In tumour cells, the relationships between autophagy, ferroptosis and lipid metabolism are reconnected to support cell survival in response to intrinsic and environmental stresses and identifying strategies to target these adaptations that is an active area of research. We previously described cytoplasmic aspartate aminotransferase (GOT1)-driven pathways in pancreatic cancer that can be used to maintain redox homeostasis. Through a pharmacological approach, we identified cysteine, glutathione, and lipid antioxidant functions as features of metabolic vulnerability following GOT1 withdrawal. We demonstrate that in GOT1 knockout cells, targeting any of these pathways triggers iron sagging, an oxidative, iron-dependent form of cell death. Mechanistically, we reveal that GOT1 inhibits mitochondrial metabolism and promotes a catabolic state. As a result, we found that this enhances the availability of unstable iron through autophagy, thereby enhancing the activity of iron-sensitizing stimuli. In conclusion, our study identifies a biochemical link between GOT1, iron regulation and iron sagging.

Ferroptosis and lipid metabolism

Ferroptosis is a new form of programmed cell death with corresponding changes in lipid metabolism during ferroptosis, and the interaction between ferroptosis and lipid metabolism in cancer could regulate cancer onset, progression, metastasis and tumour immunity, which offers a potential strategy for cancer therapy [78]. Cancer cells are usually defective in performing cell death, and in order to promote their own growth, cancer cells require higher levels of iron and lipid metabolism than normal cells, which also makes them more susceptible to ferroptosis. Lipid metabolism regulates ferroptosis during cancer development and progression.For example, lipophagy promotes ferroptosis in HepG2 cells by reducing lipid stores and lipid peroxidation by RSL3 [79]. Non-viral liver disease is a global public health problem due to its high mortality and morbidity, yet its causative mechanisms are unknown. Iron sagging is known to be a novel form of cell death that is involved in multiple disease processes. Abnormal iron

metabolism (e.g., iron overload) caused by glutathione (GSH) or glutathione peroxidase 4 (GPX4) deficiency, lipid peroxidation and the accumulation of polyunsaturated fatty acid-containing phospholipids (PUFA-PLs) can all trigger iron hypoplasia. In recent years, iron sagging has been implicated in the pathology of non-viral liver diseases (including alcohol-related liver disease (ALD); non-alcoholic fatty liver; hereditary haemochromatosis (HH); drug, ischaemia/reperfusion or immune-induced liver injury; liver fibrosis and hepatocellular carcinoma). Hepatocyte iron sagging is activated in ALD, whereas hepatic stellate cell and hepatoma cell iron sagging is inhibited in hepatic fibrosis and hepatocellular carcinoma, respectively. Thus, upregulation of iron metabolism is an ideal therapeutic target for non-viral liver disease.

Pyroptosis and lipid metabolism

Pyroptosis is cell death induced by caspase-1/4/5/11 in the cell membrane following the release of pro-inflammatory mediators such as interleukin (IL)-18/1β.Pyroptosis is characterized by cell swelling, increased cell membrane permeability, cell lysis, cytoplasmic contents and release of pro-inflammatory mediators [80]. Non-alcoholic fatty liver disease (NAFLD) causes serious health problems associated with an increase in nucleotide-binding oligomeric domain-like receptor family, pyrin structural domain of NLRP3 inflammatory vesicles (NLRP3) and cellular pyroptosis due to high-fat diet (HFD) [81]. In addition, HFD leads to increased hepatic TG, steatosis and pyroptosis [82]. E2 and its receptors are protective against the development of HCC [83], and it has been shown that E2 treatment induces upregulation of caspase-1 and IL-1β in the HCC cell line HepG2, leading to cell pyroptosis in NLRP3 inflammatory vesicles, and that NLRP3 can play an inhibitory role in cancer play an inhibitory role in progression [84]. The branched-chain polyunsaturated fatty acid geranylic acid (GGA; C 20:4), an endogenous metabolite derived from the mammalian mevalonate pathway, induces cellular Pyroptosis in human hepatocellular carcinoma-derived HuH-7 cells [85].

Cuproptosis and lipid metabolism

Tsvetkov identified a new form of cell death, namely copper-dependent cell death, also known as copper sagging. They defined cuproptosis as a non-apoptotic form of cell death. At the same time they have shown that direct binding of copper to lipid acylated components of the tricarboxylic acid cycle leads to aggregation of copper-bound lipid acylated mitochondrial proteins and loss of Fe-S proteins thereby triggering proteotoxic stress and cuproptosis [86]. The effect of intercellular copper concentration on cellular activity suggests that cells can only remain highly biologically active at very narrow copper ion concentrations. Elesclomol is a copper ion carrier that transports copper into cells. DLAT is a target of lipid acylated proteins and mediates the entry of carbon into the TCA cycle. FDX1 promotes DLAT lipid acylation and Cu^{2+} enhances the aggregation of lipid acylated proteins and the reduction of ferritin, thereby triggering proteotoxic stress and cuproptosis [87].

The relationship between lipid metabolism and mitochondria in hepatocellular carcinoma

Mitochondria are involved in lipogenesis and triglyceride synthesis and are associated with lipid droplets in fat-oxidizing tissues [88]. Lipid droplets are unique among organelles because they have a phospholipid monolayer with different biophysical interaction requirements [89]. Jagerstrom and colleagues first demonstrated that isolated mitochondria could interact with isolated LD in a cell-free environment, suggesting that components anchored to the outer organelle membrane are sufficient to mediate mitochondria-LD interactions [90]. One such protein is PLIN5, a lipid droplet encapsidation protein that strongly recruits mitochondria into lipid droplets of a variety of cell and tissue types, including CHO cells [91], liver AML12 cells [92] and cardiac HL-1 cells [93]. We revealed that GOT1 inhibits mitochondrial metabolism and promotes a catabolic state. When complete EMT occurs in HCC cells, a different metabolic switch to TGF-β promotes lipolysis, increases free fatty acid (FFA) transport and utilization, reduces aerobic

glycolysis and increases mitochondrial oxidative metabolism. Saturated FFA induces apoptosis in hepatocytes through multiple mechanisms, such as endoplasmic reticulum stress, death receptor and c-Jun N-terminal kinase signalling, reactive oxygen species, non-coding RNA, autophagy dysregulation and these signalling pathways lead to mitochondrial dysfunction thus causing cell death [94].

The relationship between macrophages and lipid metabolism

The mechanisms by which macrophages and lipid metabolism regulate energy storage remain unclear. We identified by genetic screening a platelet-derived growth factor (PDGF)/vascular endothelial growth factor (VEGF) family homologue, Pvf3, which is produced by macrophages and is required for lipid storage in Drosophila larvae adipose body cells. Genetic and pharmacological experiments have shown that the mouse Pvf3 homolog PDGFcc, produced by adipose tissue macrophages, controls lipid storage in adipocytes in a manner unrelated to leptin receptor and C-C chemokine receptor type 2. PDGFcc production is regulated by diet and controls lipid storage in adipose tissue in neonatal and adult mice in a paracrine manner. At the biological level of PDGFcc blockade, excess lipids are redirected to brown fat for thermogenesis. These data identify macrophage-dependent mechanisms that can help design pharmacological interventions to control energy storage in postnatal animals.

MicroRNAs regulate lipid metabolizing enzymes to influence the development of HCC

MicroRNAs (miRNAs) are a class of small non-coding RNAs that regulate gene expression at the post-transcriptional level and influence the pathogenesis of HCC by regulating lipid metabolism-related proteins in the liver. For example, miRNA1207-5p binds targeting FASN to inhibit the Akt/mTOR signalling pathway to further suppress HCC invasion, while FASN upregulates the reversal of miRNA-1207-5p suppression in HCC cells [95]. a study conducted by Wu showed that to some extent, microRNA-21 inhibits HCC by interacting with the HBP1-p53- SREBP1c pathway to promote hepatic lipid accumulation and HCC tumor progression [96]. miRNA-3941, miRNA-4517 and miRNA-4672 reduce hepatic steatosis by inhibiting the expression of fatty acid binding protein 1 (FABP1), thereby delaying the progression of NAFLD [97,98]. In addition, miRNAs play an important role by regulating lipid metabolizing enzymes through metabolism-related transcription factors. Various miRNAs, including miRNA-33a/b, miRNA-182, miRNA-96 and miRNA-24 have been identified to be involved in the regulation of SREBP [99-101]. MicroRNA-631 and microRNA-155 have been reported to negatively regulate liver-X-receptor α (LXRα), which plays a key role in the regulation of FA metabolism by regulating SREBP1-c as well as downstream targets involved in FA synthesis [102,103]. Fatty acid binding proteins (FABPs) play an important role in lipid metabolism, and microRNAs (miRNAs) can affect lipid metabolism by targeting FABPs. However, the exact mechanism is not known. Methods: The expression of FABP1 in HCC tissues was analysed by immunochemical methods. Lipid content was measured by oil red O staining and the interaction of FABP1 with free fatty acids (FFA) was investigated by marker tracking. miRNA arrays were used to detect miRNA expression in IL-6-stimulated HCC cells. Expression of miR-603 was detected by qPCR. western blot was used to detect each group of proteins. Huh-7 cells were mock transfected by lentivirus and miRNA to assess gain and loss of function, and reactive oxygen species (ROS) were detected by fluorescence. Results: FABP1 expression was significantly reduced in approximately 90% (81/90) of HCC patients. expression of FABP1 in adjacent tissues was strongly correlated with overall survival. Meanwhile, lipids were abundant in paracancerous tissues, whereas lipids were significantly reduced in HCC tissues. FABP1 and FFA mutually promoted uptake by Huh-7 cells. FABP1 overexpression induced apoptosis and inhibited proliferation, migration, invasion and metastasis of Huh-7 cells. miRNAs expression was affected by IL-6 treatment and miR-603 was overexpressed in HCC tissues. miR-603 overexpression promoted proliferation, migration, invasion and metastasis of Huh-7 cells. Bioinformatic analysis predicted that miR-603 targets the 3′-UTR region of FABP1. However, miR-603 overexpression inhibited FABP1

expression and increased CPT1A, PPAR-α and SREBP1 expression. Overexpression of FABP1 decreased ROS in HCC cells, while miR-603 reversed the above results. Conclusion: Our results suggest that in the pathogenesis of HCC, IL-6 induces miR-603 expression, and miR-603 expression inhibits FABP1 expression, promotes the expression of lipid metabolism and synthesis-related proteins, and ultimately increases the level of cellular oxidative stress, leading to hepatocellular carcinoma metastasis.

Competing Interests

The authors have declared that no competing interests exist.

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