Multifaceted roles of lactate dehydrogenase in liver cancer (Review)

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Abstract. Hepatocellular carcinoma (HCC) has high morbidity and mortality rates, and metabolic reprogramming of HCC cells supports the proliferation and development of tumor cells. Lactate dehydrogenase (LDH), a key metabolic enzyme, can maintain the rapid proliferative demand of tumor cells by promoting glycolysis and lactate production in HCC cells. In addition, LDH regulates redox homeostasis and influences lipid synthesis and signaling pathways, further promoting tumor invasion and metastasis. In the tumor microenvironment, LDH affects the function of immune cells and stromal cells by regulating the lactate concentration in and promoting the immune escape and angiogenesis of tumor cells. Since elevated levels of LDH are closely associated with tumor load, invasiveness and poor prognosis, LDH also has promising applications in the early diagnosis, treatment and prognostic assessment of HCC. The present study reviewed the roles of LDH in the occurrence, development, diagnosis, prognosis and treatment of HCC and explored its value as an important biomarker and potential therapeutic target, with the aim of providing a comprehensive reference for HCC-related research and clinical practice.

Contents

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1. Introduction

As an important metabolic organ in the human body, the liver serves a crucial role in maintaining the homeostasis of the internal environment and the normal function of the organism. As a malignant tumor with high morbidity and mortality worldwide, liver cancer has become one of the leading causes of cancer-related deaths. According to the latest statistics, the incidence of liver cancer in 2021 was 6.71/100,000 individuals, and the crude mortality rate of liver cancer was 6.13/100,000 individuals (1,2). Metabolic reprogramming of hepatocellular carcinoma (HCC) cells is one of the central mechanisms of tumor cell proliferation and development (3). In contrast to normal cells, which rely primarily on oxidative phosphorylation (OXPHOS) for energy, HCC cells tend to obtain energy through the glycolytic pathway even under aerobic conditions, a phenomenon known as the 'Warburg effect' (4). Although each glucose molecule produces only two adenosine triphosphate (ATP) molecules through aerobic glycolysis, while 36 ATP molecules can be produced through OXPHOS, the faster rate of aerobic glycolysis better meets the requirements for the rapid proliferation of tumor cells (5). In addition, the glycolytic product lactate can provide fuel for neighboring oxygenated tumor cells, allowing the cooccurrence of glycolytic and oxidative metabolism in the tumor microenvironment (TME) (6). Lactate dehydrogenase (LDH) is an enzyme found in a wide range of tissues (such as heart muscle, liver, kidney, skeletal muscle and lung) and is involved in the final step of the glycolytic reaction, catalyzing the reversible conversion between lactate and pyruvate (5). In tumor cells, LDH not only is closely related to the rate of glycolysis and cofactor ratios but also significantly affects the acidic environment of tumor cells through the regulation of lactate production (7). LDH acts as a key regulator of tumor development through the regulation of the biochemical environment of the tumor, which has an important impact on processes such as tumor cell invasion, immunosuppression, angiogenesis and metastasis (7).

LDH serves an important role in the development, diagnosis, treatment and prognosis of cardiovascular diseases, infectious diseases, cancer and other diseases (8). LDH is not only an important marker of myocardial injury but also serves an important role in the development, progression and treatment of cardiovascular diseases (9). Lactate dehydrogenase A (LDHA) promotes cardiac remodeling by attenuating reactive oxygen species (ROS) levels and promoting M2 macrophage polarization and has the potential to be a target for myocardial infarction repair (10,11). LDHA deficiency may lead to cardiac hypertrophy and heart failure, and serum LDH levels are significantly correlated with mortality in acute heart failure (12,13). In addition, under high-glucose conditions, LDHA may have some therapeutic potential, as it can slow the progression of aortic coarctation (14). In hematologic diseases, elevation of LDH levels is closely associated with a larger tumor load and cell proliferation rate and can be used as an adjunctive diagnostic and monitoring indicator for diseases such as leukemia and pernicious anemia (15-18). Elevation of LDH levels in patients with COVID-19 reflects cytokine-mediated tissue damage, multiorgan dysfunction and hypercoagulability and significantly increases the risk of severe illness and death, suggesting that elevated LDH expression is closely related to poor prognosis (19-23). In scientific research, LDH is often used in combination with other tumor markers as an important marker of malignant tumors, and studies have shown that the degree to which LDH levels are elevated is closely related to tumor load and aggressiveness (8,24).

Although LDH serves an important role in disease development, tumor metabolic reprogramming, regulation of the TME, and has diagnostic and therapeutic potential, a systematic summary and description of the specific role of LDH in liver cancer are currently lacking. By reviewing the biological properties of LDH and its role in the development of HCC, the present study aimed to explore research progress related to the value of LDH in the diagnosis, treatment and prognostic evaluation of HCC and to provide novel targets and concepts for the diagnosis and treatment of HCC.

2. Biological properties of LDH

LDH is an oxidoreductase consisting of four peptide chains with a molecular weight of 134 kDa (25). LDH is a tetrameric enzyme consisting of M (LDHA) and/or H [lactate dehydrogenase B (LDHB)] subunits (7). LDHA and LDHB are encoded by the *LDHA* gene located on chromosome 11 (11p15.1) and the *LDHB* gene located on chromosome 12 (12p12.1), respectively (8). Five isoforms of LDH, namely, LDH-1 (H4), LDH-2 (H3M), LDH-3 (H2M2), LDH-4 (HM3) and LDH-5 (M4), can be produced by combining the A and B subunits in different ways (7). LDH isoforms are distributed in different tissues, with LDH-1 and LDH-2 being detected predominantly in the heart and erythrocytes, LDH-3 being detected predominantly in the brain, and LDH-5 and LDH-4 being detected predominantly in the liver and skeletal muscle (26). There is also a sperm-specific isozyme, LDH6, encoded by the *LDHC* gene (located on chromosome 11) (5).

Of the LDH isoforms, LDH-5 (LDHA) has the strongest ability to convert pyruvate to lactate because subunit M has a strong ability to catalyze this reaction (27). By contrast, subunit H has the ability to convert lactate back to pyruvate through the reverse reaction (28). LDH is active mainly in the cytoplasm and its main primary function is to catalyze the reversible redox reaction between lactate and pyruvate. LDH serves an important role in the balanced regulation of the glycolytic and gluconeogenic pathways and participates in cellular energy metabolism (29). Under aerobic conditions, pyruvate enters mitochondria and the tricarboxylic acid (TCA) cycle to produce large amounts of ATP (30). During hypoxia or high metabolic demand, LDH facilitates the reversible conversion of pyruvate to lactate while oxidizing NADH to NAD^+ (26). Catalysis of the conversion of pyruvate to lactate by LDH helps to regulate the intracellular NADH/NAD^+ ratio, and a normal intracellular NADH/NAD^+ ratio is essential for various cellular processes, including the oxidative stress response, DNA repair and cell signaling (8). Thus, LDH not only serves a key role in energy metabolism but is also involved in maintaining cellular redox homeostasis (27). LDH, an important catalytic enzyme in glycolysis, can further support the metabolic demands of tumor cells by converting lactate to pyruvate and promoting metabolic synergy between glycolysis and OXPHOS (Fig. 1) (31).

LDH is a non-secreted enzyme and serum LDH activity mainly reflects overall enzyme activity. According to standard assays, the baseline activity of serum LDH is usually <247-248 U/l in adults (8,32). LDH activity in organs is closely related to its metabolic activity and the physiological activity of LDH in organs can reach as high as 9,000-25,000 U/g (26,33). There is a significant difference in the expression levels of LDH in different organs and tissues; LDH1 and LDH2 are more abundant in myocardium, while LDH5 and LDH4 are mainly in skeletal muscle and liver (26). LDH expression varies significantly among different organs and is finely regulated by numerous metabolic regulators, including the AMP-activated protein kinase (AMPK) and mTOR signaling pathways (34). These key pathways directly influence cellular metabolic adaptations by regulating LDH expression and enzymatic activity. Under pathological conditions, aberrant expression or activity of LDH is often closely associated with the onset and progression of cardiovascular disease, liver disease and cancer (8). In addition, the metabolic activity of LDH is closely associated with inflammatory responses and immunoregulatory networks, further highlighting its complex role in pathophysiological processes (35). LDH not only is an important metabolic enzyme that serves a key pivotal role in glycolysis and the TCA cycle but also performs multidimensional functions in the regulation of cellular metabolism, tissue-specific gene and protein expression and disease development. Elucidating the biological properties and mechanism of action of LDH in metabolic and pathological processes will provide an important theoretical basis for understanding the pathogenesis of metabolic diseases and tumors and LDH has potential value for the clinical diagnosis and monitoring of diseases, in addition to serving as a potential target for the development of novel therapeutic strategies against these diseases.

3. Roles of LDH in metabolic reprogramming in HCC

As the metabolic center of the body, the liver not only maintains glucose homeostasis by controlling multiple glucose metabolic

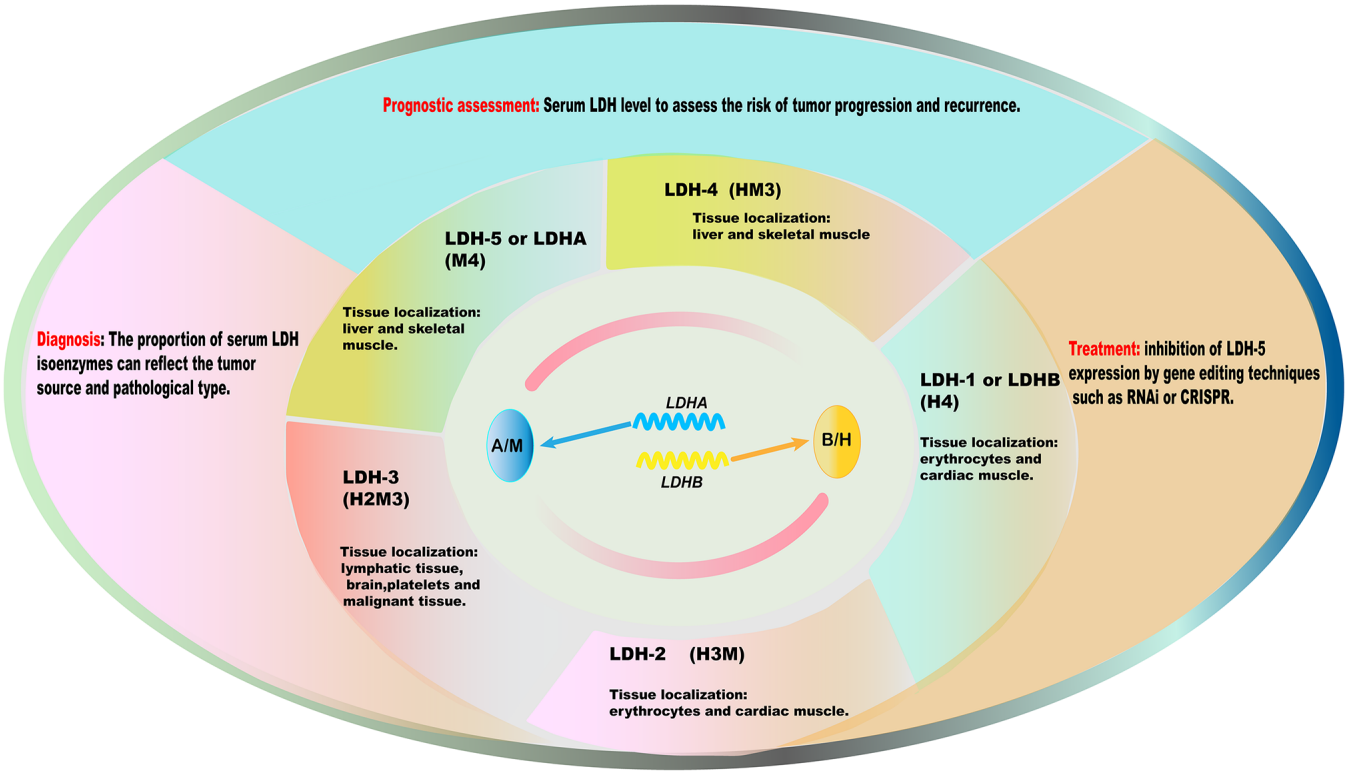

Figure 1. LDH subtypes and associated distribution. LDH is a tetrameric enzyme composed of A (M) and/or B (H) subunits. LDHA and LDHB are encoded by the *LDHA* gene and *LDHB* gene, respectively (7). By altering the combination of A and B subunits, five isoenzyme forms can be produced: LDH-1, H4; LDH-2, H3M; LDH-3, H2M2; LDH-4, HM3; and LDH-5, M4 (7,8). LDH-1 and LDH-2 are primarily detected in the heart and red blood cells, while LDH-3 is found in the brain, and LDH-5 and LDH-4 are found in both liver and skeletal muscle (26). Among these subtypes, LDHA (LDH-5) and LDHB (LDH-1) have a notable association with liver cancer, particularly LDHA. LDHA is highly expressed in liver cancer cells, catalyzing the conversion of lactic acid to pyruvate, maintaining metabolic balance and regulating the tumor microenvironment, thereby promoting invasion and metastasis. High LDHA expression is associated with the invasiveness and resistance to treatment in liver cancer. By contrast, low expression of LDHB in liver cancer may be related to metabolic status and treatment sensitivity. In liver cancer diagnosis, the ratio of serum LDH isoenzymes can reflect the origin of the tumor and its pathological type (96,97). In liver cancer treatment, gene editing techniques such as RNAi or CRISPR to inhibit LDH-5 expression may be used (125-127). In the evaluation of prognosis of liver cancer, serum LDH levels can be used to assess the risk of progression and recurrence of liver cancer (101,102). LDH, lactate dehydrogenase; RNAi, RNA interference.

pathways (36) but also participates in various lipid metabolism processes (37). HCC cells are metabolically reprogrammed to meet the rapid proliferation needs of tumors (34,38). HCC cells often exhibit enhanced aerobic glycolysis, known as the 'Warburg effect' (34). Tumor cells usually produce lactic acid through glycolysis in the presence of LDH (38). The study by Yang *et al* (39) has shown that lactate can promote the lactylation of adenylate kinase 2 at the K28 site, which affects its enzyme activity, leading to an imbalance in energy homeostasis in HCC cells and promoting tumor proliferation, invasion and metastasis. Lactic acid produced by glycolysis can also serve as a nutrient for cancer cells, which is closely related to its ability to alleviate oxidative stress and facilitate lipid synthesis, promoting tumor growth (34,40). Aerobic glycolysis in HCC cells also provides important synthetic raw materials for macromolecular synthesis, such as ribose 5-phosphate, a substrate of the pentose-phosphate pathway, for nucleotide synthesis and the glycolytic intermediates glycerol 3-phosphate and acetyl-coenzyme A for lipid and protein synthesis (41,42). Abnormal lipid metabolism in HCC cells can also drive the development of HCC (43). The increased *ab initio* synthesis of lipids in HCC cells meets the energy and raw material requirements for cell membrane synthesis and cell proliferation (44). However, when the fatty acid oxidation pathway is inhibited, the resulting lipid accumulation enhances immunosuppression and promotes tumor growth and metastasis; thus, it is often suggested that decreased fatty acid metabolism is closely related to the aggressiveness of HCC (45,46). In addition, the loss of branched-chain amino acid catabolism has been shown to promote the development of HCC (47). Metabolic reprogramming in HCC is regulated by oncogene activation or inactivation, signaling pathway abnormalities and the TME (48-50). The activation of oncogenes such as c-Myc, KRAS and PI3K/AKT can promote metabolic reprogramming in HCC cells by increasing the expression of genes related to glycolysis and lipid metabolism (51-53). Hypoxia, a low pH and a tumor environment containing inflammatory cytokines can induce glycolytic reprogramming of HCC cells by activating related signaling pathways, such as the hypoxia-inducible factor (HIF) pathway (54). HIF-1α, which is stably expressed under hypoxic conditions, upregulates the expression of various glycolysis-related genes, such as LDH and promotes glycolysis and lactic acid production (55).

High expression and activity of LDH are key factors for maintaining continuous glycolysis in HCC cells (56). Owing to the rapid proliferation of HCC cells, the local oxygen supply is relatively insufficient and these cells rely on glycolysis for energy (57). LDH catalyzes the conversion of pyruvate

to lactate and ensures the smooth progression to glycolysis through the regeneration of NAD^+ (58,59). The study by Manerba *et al* (60) found that the inhibition of LDH activity or expression significantly reduces the rate of glycolysis in HCC cells, leading to a decrease in intracellular ATP levels, the inhibition of cell proliferation and the induction of apoptosis. LDH deficiency also leads to an intracellular redox imbalance, which affects the normal metabolism and function of cells (61). The catalysis of lactate production by LDH affects the proliferation and invasion of HCC cells through the regulation of the glutathione system and the production of ROS, which subsequently affects the proliferation, invasion and metastasis of HCC cells (38,62,63). LDH also promotes tumor growth by promoting lactate production and enhancing ferroptosis resistance in HCC cells (40). LDH-catalyzed lactate metabolism serves a key role in HCC development, not only providing energy support to tumor cells but also promoting invasion and metastasis through metabolic regulation.

Although LDH is often associated with the glucose metabolism pathway, LDH interacts also closely with other metabolic pathways through glucose metabolism (64). For example, lactate can enter mitochondria through the lactate shuttle and be converted to pyruvate through reverse catalysis by LDH, which participates in the TCA and provides additional energy to cells (65). Lipid metabolism serves a key role in the development and progression of HCC and increased lipid synthesis promotes the progression of HCC (46,66). LDHA indirectly affects the activity of lipid oxidases and reduces the precursors required for lipid synthesis by regulating NAD^+/NADH homeostasis (67,68). LDHA also upregulates sterol regulatory factor binding protein 1 through activation of the HIF-1α/mTOR pathway, which in turn promotes the expression of lipid synthases, such as fatty acid synthase and acetyl-CoA carboxylase (69). Inhibition of LDHA may result in the reduction of precursors required for lipid synthesis by restoring TCA activity (42). Thus, LDH maintains the homeostasis of glucose metabolism while indirectly influencing the balance of other metabolic pathways, thus resulting in the rapid proliferation and survival of HCC cells (Fig. 2) (7).

4. Roles of LDH in the TME in HCC

The TME in HCC is a complex multicomponent environment composed of immune cell populations (including T lymphocytes, macrophages, neutrophils and dendritic cells) as well as non-immune components [such as fibroblasts, vascular and lymphatic endothelial cells and the extracellular matrix (ECM)] (70). The TME not only exerts tumor suppressive effects through immunosurveillance and immunomodulation but also promotes tumor cell invasion and metastasis as well as immune escape to achieve tumor progression (71,72).

Synergistically, LDH and monocarboxylic acid transporter protein coordinate lactate production and transport and serve an important role in the regulation of the tumor immune microenvironment (73-75). LDHA is expressed mainly in bone and liver tissues, but numerous studies have shown that it is also commonly expressed in malignant tumors (73-76,78). The stability of tumor-infiltrating T regulatory cells (Treg cells) is affected by LDHA knockdown or LDH inhibitors (77,78). In a previous study of immune cells in tumors, LDHA levels were found to be significantly elevated in activated lymphocytes, which can exert tumor suppressive effects by upregulating LDHA and engaging in glycolysis (79). LDH can also be involved in modulating the function of suppressor immune cells, such as T lymphocytes, which help tumor cells evade immune surveillance and promote the progression of HCC (80). The important role of LDH in the TME was pointed out in a study by Verma *et al* (78), which reported that the inhibition of LDH not only regulates the glycolytic balance between tumor cells and Tregs, but also alters the functional state of anti-tumor T cells (78). In HCC, LDH regulates tumor-associated macrophages (TAMs) and tumor-associated fibroblasts (TAFs) by modulating lactate production (81). Studies have shown that lactate can contribute to the polarization of TAMs to an M2-like phenotype, causing them to secrete cytokines and chemokines that promote tumor cell growth, angiogenesis and metastasis and facilitate tumor progression (82,83). In TAFs, lactate can stimulate the production of ECM and growth factors to form a supportive stromal environment for HCC cells (84). LDH-mediated production of lactate can also affect endothelial cell function in the tumor vasculature, promoting angiogenesis and increasing nutrient and oxygen supply to the tumor (85). Therefore, LDH can influence tumor development by affecting the function of immune cells and non-immune components in the immune microenvironment of HCC tumors (Fig. 3).

5. Roles of LDH in the diagnosis and prognostic evaluation of HCC

Owing to its wide distribution in tissues and its important role in metabolic reprogramming, LDH serves an important role in the development of different diseases. Numerous studies have suggested that LDH has an important role in the development of liver diseases such as liver injury, liver fibrosis and HCC (34,55,86). In a study of liver disease development, LDHA was found to affect the interaction between LDHA and HIF-1α in the classical Wnt signaling pathway, thereby regulating glycolysis and liver fibrosis in hepatic stellate cells (55). Salvianolic acid B can inhibit M1 macrophage polarization by downregulating the expression levels of LDHA, thus exerting a therapeutic effect on liver injury (87). A recent study has shown that the upregulation of LDHA expression in liver injury contributes to pericentral regeneration of the liver (86). Protein arginine methyltransferase 3 promotes HCC growth by enhancing arginine methylation of LDHA (88).

Since different organs contain different proportions of LDH isoforms, the proportion of LDH isoforms in the blood can help determine the source of released LDH (8,26). By measuring the activity of different LDH isoforms, it is possible to distinguish between different diseases, such as infections, hemolytic anemia, liver disease, kidney disease, heart disease and cancer (8,89). In studies of melanoma and non-Hodgkin's lymphoma, elevated serum total LDH levels and the levels of different subtypes of LDH were found to be useful not only for diagnosing tumors but also for the prognostic assessment of tumors (90,91). Serum LDH levels are often elevated in patients with HCC (92). Elevation of the serum LDH level is thought to be due to the release of

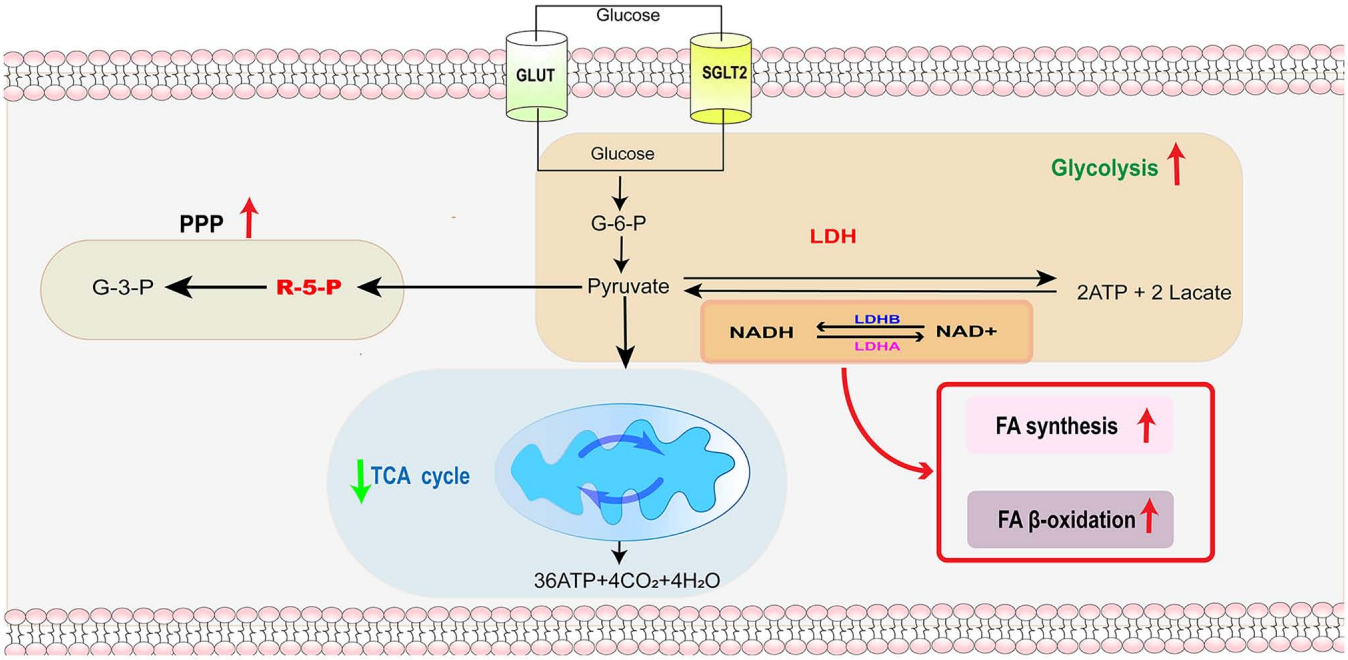

Figure 2. Metabolic reprogramming of HCC cells. HCC cells meet the needs of rapid cell proliferation through metabolic reprogramming and aerobic glycolysis of hepatoma cells is enhanced (3). By reducing pyruvate to lactate, LDH maintains the dynamic balance of NADH/NAD$^+$ in cells and ensures the stability of the intracellular redox environment (8). Glycolysis may also provide the PPP substrate required for nucleotide synthesis (41,42). LDH regulates lipid metabolism through the regulation of NAD$^+$/NADH balance, with increased *de novo* fat synthesis and increased FA β-oxidation in hepatocellular carcinoma cells (67,68). Lactate can enter mitochondria through the lactate shuttle mechanism and be converted to pyruvate under the reverse catalysis of LDH. LDH participates in the TCA and provides more energy to cells (65). HCC, hepatocellular carcinoma; LDH, lactate dehydrogenase; GLUT1, glucose transporter; SGLT2, glucose transporter sodium-glucose cotransporter 2; P, phosphate; G-6-P, glucose-6-P; PPP, pentose phosphate pathway; R-5-P, ribose-5-P; G-3-P, glyceraldehyde-3-P; ATP, adenosine triphosphate; TCA, Tricarboxylic acid cycle; FA, fatty acid.

LDH from tumor cells into the bloodstream, which may be due to cell necrosis or active secretion (27). Serum LDH levels have been shown to be correlated with tumor size, stage and metastasis in HCC (27,93). Measuring serum LDH activity can aid the early screening and diagnosis of HCC (94,95). Changes in the proportions of different LDH isoforms can also reflect the pathological type and stage of HCC to a certain extent, which can improve the accuracy of diagnosis (96,97). Combining serum LDH with other traditional biomarkers, such as a-fetoprotein (AFP), can improve diagnostic accuracy for HCC (98). In certain cases, patients with normal AFP levels but elevated serum LDH levels may still be at increased risk for HCC (99), suggesting that LDH can be used as an adjunctive diagnostic indicator, especially for AFP-negative HCC (100).

The expression patterns of LDH isoforms in tumor tissues can provide valuable information for tumor diagnosis and prognostic evaluation (101,102). LDH5 is usually upregulated in HCC samples compared with that of normal liver tissue, and the expression ratio of LDH5 to other LDH isoforms may be altered (103,104). Increased levels of LDH5 in tumor tissues are associated with more aggressive tumor behavior, including increased rates of proliferation and greater invasion and metastasis abilities (7,105). The expression levels of LDH isozymes can be used to predict the response to therapy in patients with HCC (101). Patients with high LDH5-expressing tumors may have a poorer response to conventional chemotherapy or targeted therapies, suggesting that LDH isoform analysis can aid in selecting personalized treatment regimens for patients with HCC (7). High serum LDH levels are associated with poor prognosis in patients with HCC (106). Patients with HCC with elevated serum LDH levels at multiple time points have shorter overall survival and higher recurrence rates after treatment, including surgical resection, liver transplantation and ablative therapy (2). Previous studies have shown that high preoperative serum LDH levels in patients with HCC tend to portend a poorer prognosis, including shorter survival and higher recurrence rates (2,106,107). The serum LDH level can be an independent prognostic factor, even after adjusting for other clinicopathological factors (108). LDH expression in tumor tissues also has important prognostic significance (101). Patients with high levels of LDH expression have a worse prognosis compared with that of patients with low levels of LDH expression (7,56,101). Monitoring LDH expression in tumor tissue may help clinicians stratify patients according to outcomes and determine more appropriate treatment strategies (109). However, the specificity of serum LDH as a diagnostic biomarker is limited because elevated LDH levels may be observed in other diseases, such as cirrhosis, hepatitis and other malignancies (99,100,110). Therefore, serum LDH has some applications in research as a tumor marker, especially in exploring energy metabolism in and the microenvironment of tumor cells, but it is not a commonly used tumor marker in clinical practice. Owing to its lack of specificity and insufficient sensitivity, serum LDH is usually not used as a preferred indicator for diagnosing or monitoring tumors. In practice, physicians usually use LDH in combination with other more specific tumor markers, imaging techniques and pathology to comprehensively determine a patient's condition (98-100).

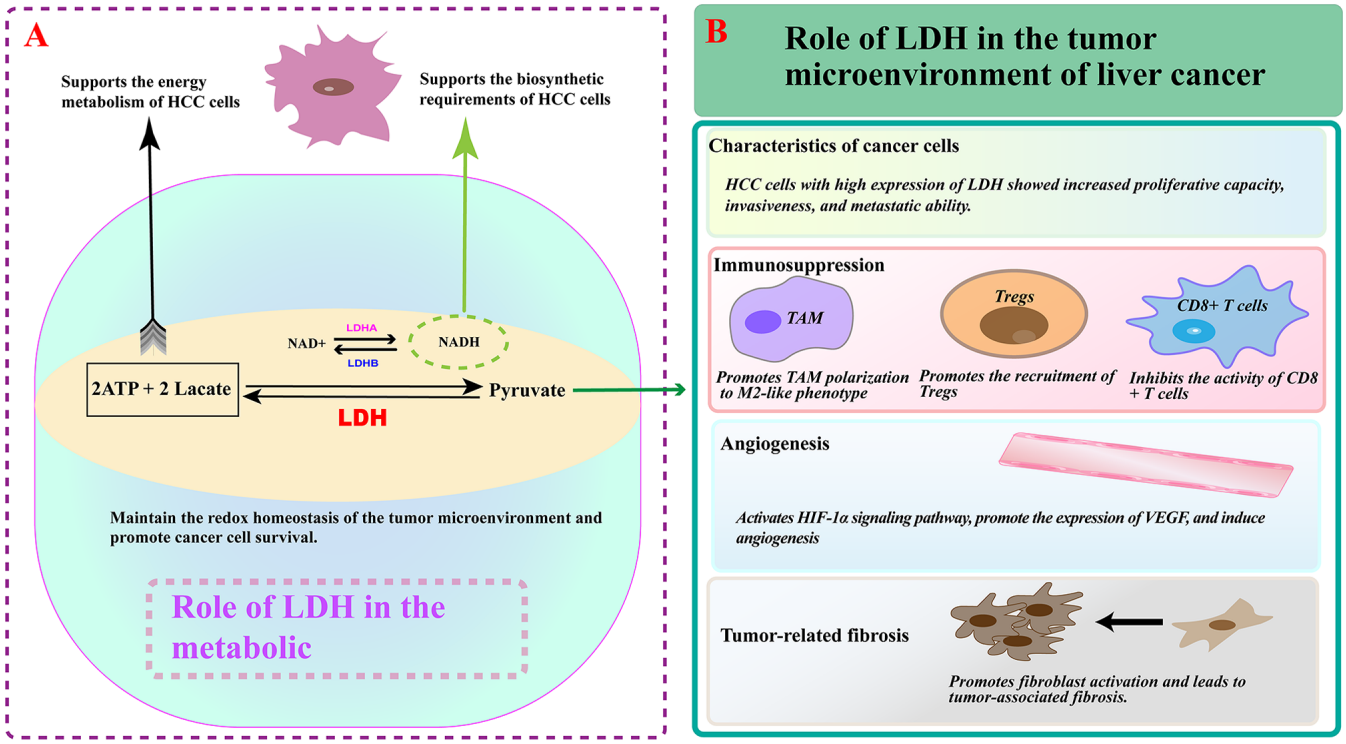

Figure 3. Roles of LDH in the occurrence and development of liver cancer. (A) LDH is involved in numerous aspect of metabolic reprogramming of liver cancer: i) Glycolysis: LDH catalyzes the conversion of pyruvate to lactate, which supports the energy metabolism of HCC cells under hypoxic conditions; ii) pentose phosphate pathway: LDH, through NADH, promotes ribosome, regenerates NADH and supports the biosynthetic requirements of cancer cells; iii) redox balance: LDH maintains the redox homeostasis of the tumor microenvironment through lactate metabolism and promotes cancer cell survival. (B) Roles of LDH in the tumor microenvironment of liver cancer are as follows: i) lactate levels increase in the tumor microenvironment, leading to metabolic abnormalities, acidic environment and fibrosis; ii) immunosuppression: LDH regulates T-cell function through lactate metabolism, whereby the accumulation of lactic acid changes the acidic pH of the tumor microenvironment, inhibits the activity of $CD8^+$ T cells, and promotes the recruitment of Tregs and the polarization of tumor-associated macrophages to the M2-like phenotype (77-83); iii) angiogenesis: Lactate promotes the expression of VEGF by activating the HIF-1 α signaling pathway and then induces VEGF-mediated angiogenesis (85,111); iv) fibrosis: Lactate metabolites promote fibroblast activation, leading to tumor-associated fibrosis; and v) cancer cell properties: HCC cells with high LDH expression showed greater proliferative capacity, invasiveness and metastatic capacity (65). HCC, hepatocellular carcinoma; LDH, lactate dehydrogenase; TAM, tumor-associated macrophages; HIC-1α, hypoxia-inducible factor 1α; regulatory T cells, Tregs.

6. LDH-based therapeutic strategies for HCC

Numerous small-molecule compounds are currently being developed to treat HCC, with the aim of inhibiting the activity of LDH and blocking abnormal glycolysis in cancer cells to suppress the proliferation of HCC cells and induce their apoptosis (111-114). Previous studies have suggested that the regulation of angiogenesis through the VEGF/VEGF-receptor signaling pathway, which is the target of tyrosine kinase inhibitors such as sorafenib, serves a key role in the progression of HCC (111,112). A previous study reported that knockdown of LDHA significantly inhibits the proliferation, migration and invasion of HCC cells and increases sensitivity to sorafenib (113). Polyadenylation-specific factor 6 causes changes in LDH to achieve Warburg effect-mediated immune escape and angiogenesis; contributes to cancer progression through c-Myc via the hexokinase, programmed death-ligand 1 and VEGF pathways, and has the potential to synergize with sorafenib to treat HCC (114). Given the key role of LDH in HCC metabolism and progression, LDH inhibitors have emerged as promising therapeutic agents for HCC (115,116). Several small-molecule inhibitors of LDH, such as FX11 and GNE-140 (117,118), have been developed. These inhibitors target the active site of LDH, block its enzymatic activity and disrupt the glycolytic pathway in HCC cells (116).

In preclinical studies, the targeted inhibition of LDH using drugs and other means has been shown to have significant antitumor effects in HCC cell lines and animal models (119). Treatment with LDH inhibitors results in decreased glycolytic flux, reduced ATP production and induction of HCC cell apoptosis (7,120). In addition, combining LDH inhibitors with other anticancer drugs, such as sorafenib, can, in some cases, enhance antitumor efficacy and overcome drug resistance (121). However, the translation of LDH inhibitors from preclinical to clinical use is hampered by issues such as poor solubility, off-target effects and limited bioavailability (122). The ability of gene therapy approaches such as RNA interference (RNAi) and CRISPR/Cas9-mediated gene editing have also been explored (123). RNAi-based strategies can specifically reduce the expression of the LDH gene, which results in reduced LDH protein levels and enzymatic activity (124). However, there are challenges related to RNAi and CRISPR/Cas9-based, such as achieving effective delivery to tumor cells, potential immune responses and off-target effects (125-127). Overcoming these challenges is critical for the successful development of gene therapy strategies targeting LDH for the treatment of HCC. Combining LDH-targeted therapies with traditional surgery, chemotherapy, radiotherapy and emerging immunotherapies to achieve synergistic effects may further increase the efficacy

Table I. Roles of LDH in hepatocellular carcinoma.

Function	Specific roles	(Refs.)
Development	i) Maintains high-speed glycolysis, energy supply and NADH/NAD^+ balance. ii) Regulates lactate levels, affecting cell behavior. iii) Participates in glucose metabolism and other pathway interactions for homeostasis.	(34-55)
Tumor microenvironment	i) Regulates lactate metabolism, affecting the glycolytic balance between tumor cells and immune cells, and regulates the tumor immune microenvironment. ii) Regulates of tumor-associated macrophages and fibroblasts to promote the growth, angiogenesis and metastasis of tumor cells. iii) Remodels the tumor blood vessels and promotes the tumor growth.	(70-85)
Diagnosis	i) Elevated serum LDH may be used early screening, as related to tumor features. ii) LDH isoenzyme changes can indicate pathology and can be combined with a-fetoprotein for improved accuracy. iii) Tumor LDH isozyme expression levels have diagnostic and prognostic value.	(86-100)
Treatment	i) Targeting LDH shows antitumor effects, combined with drugs for improved results; however, translation is difficult. ii) Gene therapies target LDH, with delivery and off-target challenges, combination may enhance efficacy.	(111-128)
Prognostic assessment	i) High serum LDH linked to poor prognosis. ii) Preoperative LDH as an independent factor and high tumor LDH levels, such as LDH5, are associated with aggressive tumors. iii) Monitoring tumor LDH levels may be used for prognosis stratification.	(101-110)

LDH, lactate dehydrogenase.

of HCC treatment and improve the quality of life and survival of patients (Table I).

7. Conclusion

LDH serves a key multidimensional role in the complex pathology of HCC and influences the developmental trajectory of HCC in numerous aspects. From the perspective of metabolic regulation, LDH actively maintains glycolysis to ensure that tumor cells can efficiently produce energy in an aerobic environment, providing a sufficient energy supply for the rapid proliferation of cancer cells (128). Moreover, LDH also finely regulates the redox balance, maintains the stability of the intracellular environment, and creates favorable conditions for the survival and proliferation of cancer cells (129). LDH also closely interacts with other metabolic pathways, further strengthening the metabolic adaptability and viability of tumor cells and promoting HCC occurrence, development, and metastasis (64). In the TME, LDH regulates the secretion of cytokines and chemokines to remodel the TME and promote the invasion and metastasis of tumor cells (31).

LDH has also shown value in the diagnosis and treatment of liver cancer, as LDH serves a central role in the disease (8). As a potential diagnostic marker for HCC, LDH can act as a sensitive indicator in the early stages of the disease, although it is not commonly used in clinical practice because of its lack of specificity. The combination of LDH with commonly used HCC markers can improve the accuracy of HCC diagnosis and can assist in the early screening and diagnosis of HCC (100). In addition, the expression patterns of different isoforms of LDH are important in the pathological typing and staging of HCC (8). Regarding the prognostic assessment of HCC, serum LDH levels are correlated with survival and recurrence rates and high LDH5 expression in tumor tissues is correlated with aggressive tumor behavior as well as the therapeutic response; thus, by using LDH, clinicians may accurately assess disease progression and therapeutic effects and formulate personalized therapeutic plans (7). Given the important role of LDH in the metabolic reprogramming of HCC as well as in the TME, the use of LDH as a therapeutic target is a key direction for the development of novel anticancer drugs. Despite the potential of LDH as a target for liver cancer therapy, numerous challenges to fully utilizing the therapeutic potential of targeting LDH remain. Currently, more specific and potent LDH inhibitors are needed; specifically, the ability of inhibitors to target LDH in tumor cells, their inhibitory effect and pharmacokinetic properties need to be improved to ensure that the drugs can exert their effects stably and efficiently *in vivo* and to reduce toxicity and side effects on normal tissues. In addition, inefficiency in delivering gene therapy components targeting LDH to cells as well as the risk of off-target effects are key obstacles to clinical application (122). Furthermore, the mechanisms underlying the complex interactions between LDH and other metabolic pathways and signaling pathways are not fully understood and an in-depth analysis of these mechanisms will provide strong support for the development of more precise and effective therapeutic strategies for HCC. In the future, LDH-related biomarkers have potential for use in clinical practice for early diagnosis, precise prognostic prediction and the selection of personalized therapeutic regimens for liver

cancer. With the continuous advances in precision medicine and tumor metabolism research, targeting LDH may become an important approach for the comprehensive treatment of HCC, bringing new treatment opportunities for patients with liver cancer in the future.

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Availability of data and materials

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Authors' contributions

HJ wrote the original draft. QL wrote the original draft and created the figures and tables. JL participated in the literature search and analysis of the data to be included in the review. SZ was assisted in the preparation of the figures and table. BT acquired funding acquisition and helped with review writing and editing. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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