Abnormal expression of HADH, an enzyme of fatty acid oxidation, affects tumor development and prognosis (Review)

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Abstract. Tumor occurrence and progression are closely associated with abnormal energy metabolism and energy metabolism associated with glucose, proteins and lipids. The reprogramming of energy metabolism is one of the hallmarks of cancer. As a form of energy metabolism, fatty acid metabolism includes fatty acid uptake, *de novo* synthesis and β-oxidation. In recent years, the role of abnormal fatty acid β-oxidation in tumors has gradually been recognized. Mitochondrial trifunctional protein (MTP) serves an important role in fatty acid β-oxidation and HADH (two subtypes: α subunit, HADHA and β subunit, HADHB) are important subunits of MTP. HADH participates in the steps of 2, 3 and 4 fatty acid β-oxidation. However, there is no review summarizing the specific role of HADH in tumors. Therefore, the present study focused on HADH as the main indicator to explore the changes in fatty acid β-oxidation in several types of tumors. The present review summarized the changes in HADH in 11 organs (cerebrum, oral cavity, esophagus, liver, pancreas, stomach, colorectum, lymph, lung, breast, kidney), the effect of up- and downregulation and the relationship of HADH with prognosis. In summary, HADH can be either a suppressor or a promoter depending on where the tumor is located, which is closely associated with prognostic assessment. HADHA and HADHB have similar prognostic roles in known and comparable tumors.

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1. Introduction

Reprogramming of energy metabolism is one of the hallmarks of cancer (1). Disordered energy metabolism is closely associated with tumor development and the essence of tumors is the disordered proliferation of cells, which includes not only the dysregulation of genes but also the dysregulation of energy metabolism. The energy metabolism associated with abnormal changes occurs in the metabolic process of tumor development because tumor division (rapid proliferation and DNA replication) requires a large amount of direct energy in the form of ATP (2). Glucose, protein and lipid substances are associated with energy metabolism. In the early days, the focus of research on tumor metabolism was glucose metabolism (3). However, in addition to glucose metabolism, fatty acid metabolism in cancer is dysregulated, specifically in the expression and activity of lipid-metabolizing enzymes (4). Abnormal fatty acid metabolism has also been reported to be involved in tumorigenesis and tumor progression. Lipids are another important energy source that promotes tumor metastasis and tumor metabolism depends on the activity of enzymes involved in fatty acid metabolism (5).

Fatty acid metabolism includes fatty acid uptake, *de novo* synthesis and β-oxidation. Deciphering the complex role of fatty acid β-oxidation in tumors contributes to a comprehensive understanding of its pathogenesis. In fatty acid metabolism, the role of fatty acid β-oxidation is crucial and mitochondrial

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trifunctional protein (MTP) is involved in the second, third and fourth steps of fatty acid β-oxidation (Fig. 1). MTP [the structure of the heterotetramer based on the membrane binding domain (6)] is a protein located on the inner mitochondrial membrane and a heterotetramer consisting of two α subunits (HADHA) and two β subunits (HADHB). Several forms made of α and β subunit coexist (α2β2, α4β4, α6β6), but it is generally accepted that only the α2β2 octomer conserves the enzymatic activities responsible of the beta oxidation (6) (Fig. 1). Therefore, HADH, which participates in and regulates fatty acid metabolism, is a component of MTP. The α subunit of MTP is encoded by the HADHA gene and has the activities of enoyl-CoAhydratase (ECH) and L-β hydroxyacylCoA dehydrogenase (HACD) and the β subunit of MTP is encoded by the HADHB gene and has the activity of β-ketoacylCoAthiolase (KT) (6-8). ECH, HACD and KT are key enzymes in fatty acid β-oxidation.

The HADHA and HADHB genes are located on chromosome 2 (2p23); specifically, the HADHA gene is located at 2p24.1-23.3 of chromosome 2 (9,10). The gene of HADHA mutations may result in LCHAD deficiency (11). Mitochondrial trifunctional protein deficiency (MTPD) is a metabolic disease of fatty acid β-oxidation caused by HADHB gene mutations. It can also be seen that HADH is closely associated with fatty acid β-oxidation (12).

Overall, HADH serves an important role in fatty acid β-oxidation and alterations in fatty acid metabolism are associated with tumorigenesis. However, there is no review summarizing the role of HADH in cancer. The present review summarized the altered fatty acid metabolism of HADHA and HADHB in several tumors and explored their potential clinical value.

2. The roles of HADH in different organs

Cerebrum. Lipid droplets (LDs) are significantly enriched in glioblastoma multiforme (GBM) (13). Studies have shown that fatty acid β-oxidation and immunity mediate radioresistance in GBM (14) and fatty acid β-oxidation is critical for tumor survival (15).

Wang et al (16) showed that telmisartan can inhibit the proliferation of GBM by inducing fatty acid β-oxidation. The increased fatty acid β-oxidation is associated with the high expression level of HADHA. The second and third steps of HADHA-catalyzed fatty acid β-oxidation contribute to the upregulation of fatty acid β-oxidation. This demonstrates that telmisartan can not only affect fatty acid metabolism to treat hypertension but also act on HADHA to interfere with the proliferation of GBM through fatty acid metabolism, which provides a therapeutic strategy for tumor treatment.

Oral cavity. Oral squamous cell carcinoma (OSCC) accounts for >90% of head and neck squamous cell carcinomas (17). Some studies have shown that fatty acid β-oxidation produces a large number of byproducts and some byproducts can also be used as early diagnostic indicators of OSCC (18-20). This suggests that there is an association between oral cancer and fatty acid β-oxidation.

Huang et al (21) constructed a prognostic risk scoring model for OSCC (containing the survival-related metabolic gene HADHB). The HADHB gene was significantly downregulated in this model. This study demonstrated that the risk score is an independent prognostic factor for OSCC and provides a more accurate and personalized prediction of OSCC prognosis. Furthermore, tumor-infiltrating immune cells were negatively correlated with the risk score.

Esophagus. Abnormal fatty acid β-oxidation serves a role in esophageal cancer (EC) (22). Moreover, studies have shown that adipose tissue and adipocytes are closely associated with the occurrence of EC and affect the occurrence and metastasis of EC, which is associated with abnormal fatty acid metabolism (22,23). In addition, esophageal squamous cell carcinoma (ESCC) is particularly prominent in China, accounting for ~88% of EC cases (24). The 5-year survival rate of esophageal adenocarcinoma (EA) is only 20% (25), reflecting the importance of identifying genes or proteins associated with abnormal fatty acid metabolism.

Wang et al (26) found that the HADHA gene was one of 10 hub genes and was identified between EC and normal samples and between EA and ESCC. However, in patients with ESCC and EA, HADHA was not associated with overall survival. In EC, the expression of HADHA is reduced, which suggests that HADHA is a tumor suppressor gene. Compared with EA, the HADHA gene is suppressed in ESCC.

Liver. The liver is one of the most important organs in the body. Liver cancer has a specific metabolic pattern (27) and metabolism in liver cancer is diverse and heterogeneous. It has been reported in the literature that the prognosis and development of liver cancer are closely associated with fatty acid metabolism (27). Accordingly, the present study reviewed and summarized the relationship between enzymes associated with fatty acid metabolism and liver cancer.

Tanaka et al (28) analyzed the interaction of tumor metabolism, differentiation and malignant potential in 41 patients with completely resected liver cancer. They found that dedifferentiation will speed up when the level of HADHA is decreased. HADHA was downregulated in HCC. These results suggest that HADHA is associated with tumor differentiation and altered fatty acid β-oxidation. To verify that fatty acid β-oxidation disorder is associated with the development of hepatocellular carcinoma (HCC) without cirrhosis, Khare et al (29) established a new mouse model. The study revealed that a mouse model deficient in long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) developed HCC at an early age and demonstrated altered expression of early cancer markers. The HADHA mRNA transcript was significantly downregulated. Impairment in the oxidation of long-chain fatty acids due to a reduction in HADHA transcript may serve a cancer-promoting role in HCC. This suggests that mitochondrial dysfunction serves an important role in HCC. Micro RNA (miR)-612 inhibits epithelial-mesenchymal transition (EMT) in HCC. Liu et al (30) investigated its biological role in HCC expression and found that miR-612 reduction leads to HADHA upregulation and that miR-612 can inhibit pseudopodia (mainly responsible for extracellular matrix degradation, local cell migration and invasion, extravasation of blood itself and spatiotemporal spread to distant organs), EMT and HCC metastasis through HADHA-mediated fatty
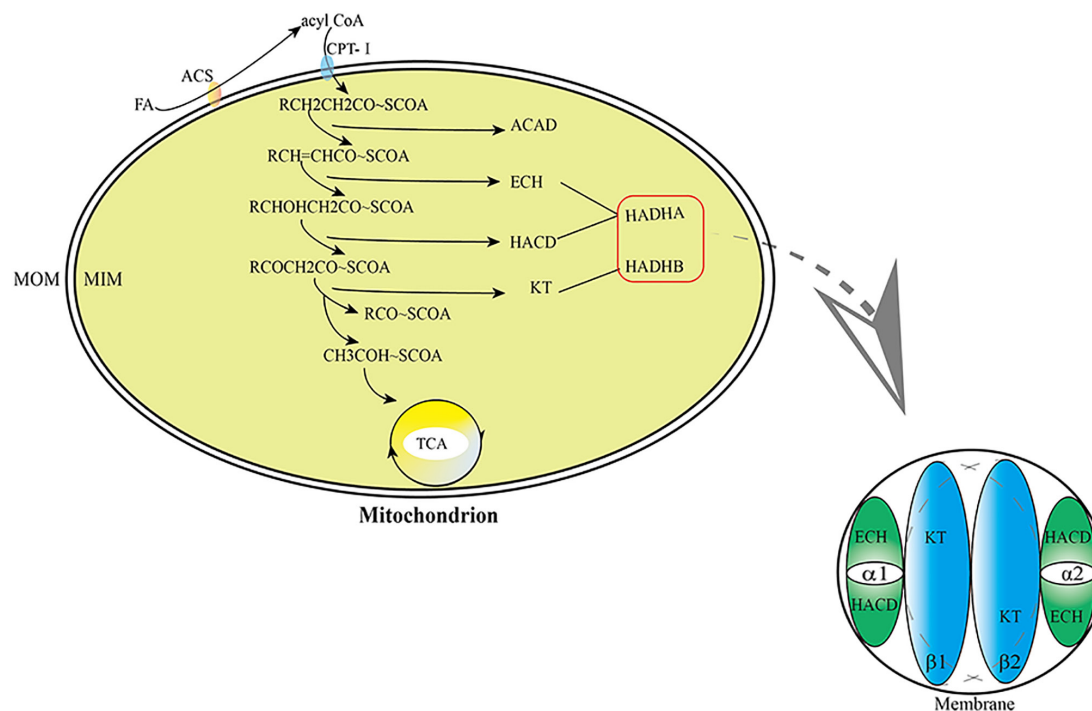
Figure 1. Steps of fatty acid β-oxidation and the structure of HADH. MOM, mitochondrial outer membrane; MIM, mitochondrial inner membrane; FA, fatty acid; ACS, acetyl CoA synthase; CPT-I, carnitine palmitoyltransferase-I; ACAD, acyl-CoA dehydrogenase; ECH, enoyl-CoAhydratase; HACD, L-β hydroxyacylCoA dehydrogenase; KT, β-ketoacylCoAthiolase; TCA, tricarboxylic acid cycle.

acid programming. Shi et al (31) constructed a computational framework to predict HCC prognosis. Its risk score [Metabolic genes derived from Pathways (MGP) score] consists of the HADHA gene. The metabolic pathway involved in HADHA is downregulated in liver cancer. The HADHA gene is a risk factor for HCC. Shi et al (31) propose that the MGP score can predict the prognosis of liver cancer and provide a basis for precise treatment.

Pancreas. Hypoxia is a common phenomenon in pancreatic cancer and is a key determinant of, and an important therapeutic target for, pancreatic cancer. To adapt to hypoxic conditions, pancreatic cancer cells proliferate by altering their own metabolism and increasing the uptake of fatty acids to ensure tumor progression (32). Signaling pathways regulating pancreatic cancer stem cell (PCSC) growth, survival and metabolomic plasticity are poorly understood (33).

Di Carlo et al (34) showed that PCSCs have specific and common proteome and lipidome regulation. Their study revealed that HADHA protein was upregulated in PCSCs. This may be a new target for pancreatic cancer treatment.

The published research about the gene of HADH on the site of pancreas is poor and further experimental or meta-analysis investigations will yield some significant results. Perhaps these new findings will bring good prospects in treating this tumor.

Stomach and colorectum. Fatty acid metabolism is an important pathway of cellular energy metabolism. Fatty acid β-oxidation supports intestinal stem cell renewal, which is associated with the HADH gene (35). A study revealed that HADH is a noncanonical target gene in colon cancer (36). However, the exact role of fatty acid metabolism in gastric cancer (GC) and

colorectal cancer (CRC) is poorly understood and there is no fatty acid metabolism therapy for CRC (37). GC and CRC are difficult to diagnose early, and treat in the advanced stage, and they have a poor prognosis (38,39). The 5-year survival rate of patients with GC is low, although great progress has been made in the treatment of GC (40). Therefore, it is urgent to explore the relationship among fatty acid metabolism and GC and CRC.

Du et al (39) found that HADH has prognostic value in GC and that HADH is significantly associated with disease-free survival. The analysis of the HADH gene shows that low expression levels lead to improved chances of survival. This finding reveals that the HADH gene may act as a tumor suppressor. Shen et al (41) studied the mechanism of GC and found that HADH was decreased in GC samples compared with normal gastric tissue, which significantly promoted the development of GC. The mechanism may be associated with increased expression of phosphorylated (p-)Akt and reduced expression of PTEN. Gao et al (42) reported that the phosphorylation of sirtuin 6 (SIRT6) is significantly increased following palmitic acid treatment in colon cancer cells. This is the result of increased binding of SIRT6 to the promoter of HADHB.

There are no predictors for routine neoadjuvant chemotherapy (nCRT) in patients with rectal cancer. Croner et al (43) successfully verified the expression of the regulatory protein HADHA following nCRT-II (5-fluorouracil ± oxaliplatin). HADHA protein is upregulated in good responders (patients who are sensitive to nCRT-II) following nCRT-II, which serves as the basis for nCRT-II. The difference in HADHA protein expression between nCRT-I (5-fluorouracil) and nCRT-II may provide new research directions for imbalances in genomic

methylation leading to carcinogenesis. Imbalances in genomic methylation lead to carcinogenesis. Zhu *et al* (44) found that hypermethylation of the HADHB gene in CRC correlates with its transcriptional downregulation. HADHB reduces the migration and invasiveness of cancer cells, suggesting that HADHB may be a tumor suppressor gene (TSG). Peng *et al* (45) found significant changes in the expression of the HADHB gene in a differentially expressed gene study of metformin-treated type-2 diabetes and colorectal cancer. The expression level of HADHB is upregulated following metformin treatment in CRC cells. The authors suggest that the HADHB gene may regulate the functions of ATPase, basal transcription factor and the mitochondrion by mutations and/or structural changes. Hu *et al* (46) were the first to explore the genes associated with cetuximab (CTX) sensitivity in colorectal cancer through clustered regularly interspaced short palindromic repeats Cas9. It was also confirmed that HADHB is associated with the CTX sensitivity of colorectal cancer, which provides a theoretical basis for further research on the drug sensitivity mechanism of colorectal cancer. In addition, Ren *et al* (47) also confirm that the expression of HADH is a relevant prognostic indicator in intestinal cancer.

Lymph. Malignant lymphoma is a malignant tumor of lymph nodes and lymphoid tissue (48). Oncogene mutations and cancer metabolic programming provide distinctive perspectives on tumor initiation and progression (49). Reprogramming of energy metabolism also exists in lymphoma and its association with fatty acid β-oxidation is gradually becoming known.

A study on malignant lymphoma by Yamamoto *et al* (49) demonstrated that HADHA tends to be overexpressed in its high-grade subtype. This was associated with significantly lower overall survival and was an independent prognostic predictor for diffuse large B-cell lymphoma. This result suggests that the HADHA target may provide a new therapeutic strategy for malignant lymphoma. Sekine *et al* (50) studied the antitumor effect of HADHB in malignant lymphoma. HADHB is overexpressed in high-grade lymphoma subtypes. This is an independent predictor of poor prognosis. These studies provide new directions for the treatment of malignant lymphoma.

Lung. Metabolic differences persist even within the same tumor (51). For example, compared with nonoxidative lung cancer, oxidative lung cancer is characterized by different carbon sources involved in the tricarboxylic acid cycle. The carbon source of oxidative lung cancer is derived from substances other than glucose, and fatty acid β-oxidation can provide it with ATP. This reveals whether there is a potential mechanism between fatty acid β-oxidation and the occurrence and development of lung cancer (51).

Amoedo *et al* (52) analyzed lung adenocarcinoma with a high-resolution respiration method and found that [^{18}F] fluorodeoxyglucose binding was poor in tumors with high mitochondrial respiration, the expression of mitochondrial trifunctional fatty acid oxidase (MTP; HADHA) increased and the genetic inhibition of MTP changed the growth of tumors with high mitochondrial respiration in the body. These findings provide proof-of-concept data for preclinical, precise, bioenergetic medicine in oxidative lung cancer. A study by

Madhusudhan *et al* (3) revealed that mitochondrial complex I is a target of non-small cell lung cancer (NSCLC), while QDC (selective toxin for NSCLC cell lines) interacts with mitochondrial complex I of the electron transport chain and catalytic long chain HADHA binding of fatty acid β-oxidation.

Breast. Breast cancer (BC) is a systemic metabolic disease for which no significant improvement in morbidity and mortality has occurred and in which metastasis, relapse and drug resistance are common (53). Fatty acids may affect the progression of BC (54).

A study by Zhou *et al* (55) showed that estrogen has two receptors: ERα and ERβ. ERβ is located in mitochondria and binds to ERα. A previous study (56) demonstrated that ERα interacts with the mitochondrial protein HADHB (affecting thiolytic cleavage activity in β-oxidation). Thus, it was demonstrated that HADHB is associated with ERβ and colocalized in the mitochondria of BC cells. The enzymatic activity of HADHB is enhanced when ERβ expression is specifically inhibited, suggesting that ERβ serves an inhibitory role in HADHB enzymatic activity. Orogen affects the primary role of mitochondria, producing most of the cellular energy and reactive oxygen species (ROS). Compared with ERα, ERβ affects the enzymatic activity of HADHB in an opposite manner; specifically, ERα activates the enzymatic activity of HADHB and ERβ inhibits the enzymatic activity of HADHB. The authors speculate that the increase in ROS production may be due to the stimulation of HADHB enzymatic activity by ERα when ERα positivity is present and that when ERα negativity is present or the ERα/ERβ ratio is low, ERβ inhibits HADHB enzymatic activity, thereby affecting fatty acid β-oxidation. There is no difference in the expression of HADHA in ER (+) and ER (-) and HADHA is unlikely to have been influenced by ER status (57). A meta-analysis by Mamtani *et al* (57) assessing the risk of BC occurrence, metastasis and recurrence showed that HADHA is expressed at low levels in BC (especially ER-negative BC). In addition, HADHA is also underexpressed in metastatic and relapsed patients. This study supports the possibility that HADHA is involved in the occurrence of BC and suggests that alteration of the metabolism of long-chain fatty acids in breast tissue should be an indicator of possible carcinogenesis. This provides the basis for the primary prevention of BC. Ji *et al* (58) found that 5-7 exons of the HADHA gene (located at chr2:26453059-2645723) produced hsa-circ-0053063 (with a unique closed-loop structure). The authors confirmed that it functions as a tumor suppressor gene.

Kidney. Clear cell renal cell carcinoma (ccRCC) is histologically characterized by the presence of numerous LDs in the cytoplasm (59,60). There is evidence of a link between obesity and ccRCC and ccRCC is a metabolic disease (61). Abnormal fatty acid metabolism occurs in ccRCC (62) and the β-oxidase of ccRCC is changed (63).

Zhao *et al* (64) showed that HADHA is a prognostic indicator of ccRCC. In tumor tissues, the expression of HADHA is downregulated; the expression of HADHA is also significantly correlated with tumor grade, stage, size, metastasis and tumor-specific survival. Downregulation of HADHA expression is associated with poor tumor prognosis and HADHA is
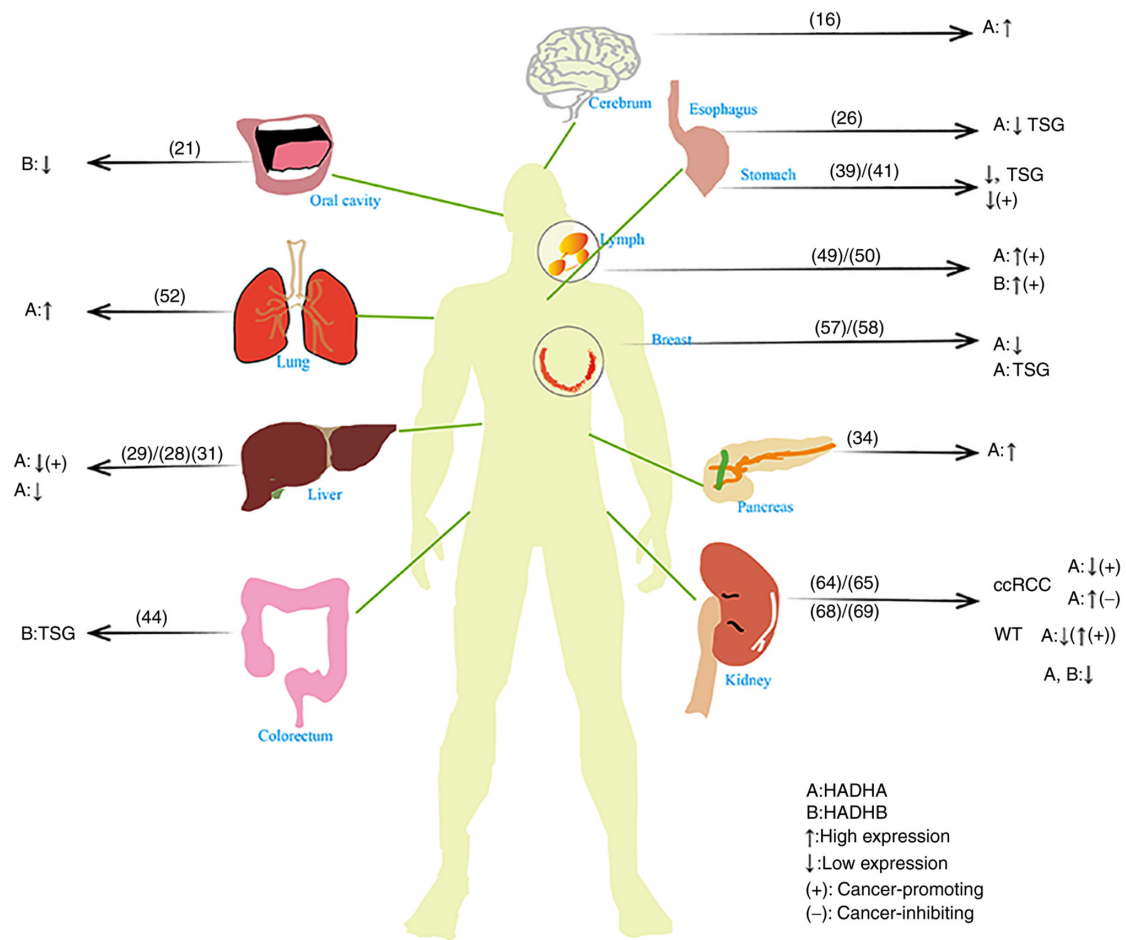
Figure 2. Expression of HADH in different organs. High HADHA expression inhibiting tumorigenesis or low HADHA expression promoting tumorigenesis: HCC, GC and ccRCC; High HADHA expression promoting tumorigenesis: Lymphoma. High HADHB expression promoting tumorigenesis: Lymphoma. A, HADHA; B, HADHB; ↑, high expression; ↓, low expression; (+), cancer-promoting; (-), cancer-inhibiting.

an independent prognostic factor. Liu *et al* (65) further studied the tumor suppressor effect of HADHA overexpression in ccRCC. HADHA overexpression inhibits the formation of cytoplasmic LDs and tumor cells take up fatty acids and store them as LDs, leading to proliferation. Overall, overexpression of HADHA disrupts fatty acid metabolism and inhibits tumor growth. A study by Zhao *et al* (66) also suggests that abnormal fatty acid metabolism may be involved in the occurrence and development of ccRCC, with downregulation of fatty acid oxidation. HADHA and HADHB are involved in fatty acid oxidation and HADHA and HADHB are protective factors. In studying the relationship between enzymes and prognosis, both HADHA and HADHB were associated with good overall survival rates. Taken together, these results suggest that HADHA is a potential prognostic marker for ccRCC.

Although the survival rate of children with Wilms tumor (WT) is high, the mortality rate of recurrent WT is increased (67). Chemotherapy is usually required to treat WT and enhancement of fatty acid metabolism can alleviate the hypoxic state caused by chemotherapy (68).

In a study by Wang *et al* (69), the expression levels of HADHA and HADHB were low in tumor tissue. The reason for this finding may be that the majority of the tissues did not undergo chemoradiotherapy; therefore, the tumor was not under hypoxic conditions. Wu *et al* (68) found that the

expression level of HADHA in tumors was lower than in adjacent normal tissues and correlated with histopathological type. In a prognostic analysis, it was found that high HADHA expression was closely associated with poor prognosis. The reason for the differential expression of HADHA in ccRCC and WT may be associated with the different tumor tissue origins. Specifically, ccRCC originates from mutated kidney cells, whereas WT does not.

3. Conclusions

With the increase in research, the role of energy metabolism reprogramming in tumors is gradually becoming known and fatty acid β-oxidation serves an important role. The present review summarized the expression of HADH in some tumors of 11 organs to explore its role in tumor intervention and prognosis. Compared with HADHB, there are more studies on HADHA.

Different tumors yield different HADHA expression results. For example, tumors with high HADHA expression inhibiting tumorigenesis or low HADHA expression promoting tumorigenesis include HCC, GC and ccRCC (Fig. 2). In contrast, tumors with high HADHA expression that promote tumorigenesis is lymphomas. In GBM, pancreas and lung, the expression of HADHA is high. In

OSCC, esophagus, HCC, GC, BC and WT, the expression of HADHA is low.

Relatively few studies have been performed on HADHB. A tumor with high HADHB expression that promote tumorigenesis is lymphoma. The low expression of HADHB is included in OSCC and WT. (Fig. 2).

In addition, a number of scholars have constructed predictive models for tumors or screened out related genes. In a model of oral cancer, HADHB is expressed at low levels (21); HADHA is a TSG in esophageal cancer (26) and BC (58) and HADHB is a TSG in CRC (44). HADHA is one of the liver cancer models and HADHA is expressed at low levels (29).

In 11 organs, the HADH is involved in fatty acid oxidation and located in 2p23 (70). However, the dissimilarities of organs are unclear in cancers. The gene of HADH is not only expressed in mitochondria but also in cytoplasm (71). Research about the mechanisms of HADH is not plentiful in various types of cancer. There are some relevant articles about the mechanisms of HADH, including PPARγ (72), p-Akt and PTEN (41), RoR2, Dvl2, ATF2 and ATF4 (36), LCL-K and MD901 (50) and TNFα, IL6-JAK-STAT3 and interferon-γ (73).

HADHA, a key enzyme in fatty acid oxidation, serves a significant role in tumors by influencing fatty acid metabolism. For example, in HCC, reduction in the levels of HADHA is significantly correlated with the progression of de-differentiation which influence fatty acid oxidation and the progression of HCC (28). It has been found that HADHA can promote invadopodium formation, Wnt/β-catenin signaling-mediated EMT and HCC metastasis via lipid programming (30). In addition, in lymph, downregulation of HADHA can cause G_0/G_1 arrest which is similar to treatment with the inhibitor of fatty acid oxidation (FAO) (49). HADHA is association with mitochondrial complex I to influence fatty acid oxidation (3). HADHA is regulated by the way of VHL/HIF-2α-independent and high expression HADHA decrease the formation of cytoplasmic lipid droplets in ccRCC.

The majority of articles describe the expression of HADH as an essential enzyme in cancer, but the precise mechanism remains to be elucidated. Under the background of tumor energy metabolism, acidic and hypoxic conditions are the usual environment in tumor metabolism (74). In addition, resistance to radiotherapy and chemotherapy is association with hypoxia (75). With the response to hypoxia, a number of tumor cells will regulate special ways of energy, such as glucose and fatty acid metabolism (76). Under hypoxia, although some cells initiate programmed apoptosis, other tumor cells adapt to the hypoxic environment, which is closely associated with tumor recurrence (77). Energy metabolism is associated with hypoxia. Hypoxia inducible factor-1 (HIF-1) can promote the occurrence of tumors (78) which serves a significant role in adapting hypoxic environment (75). HIF-1 regulates glycolysis and pyruvate metabolism (75). At the same time, fatty acid metabolism also can be influenced by HIF-1 and HIF-2 (79). Fatty acid oxidation can be affected by HIF-1a; the high expression of HIF-1a and the low expression of the fatty acid oxidative gene is association with reduced PPARγ-mediated fatty acid oxidation (80). The gene of HADH is an essential gene of fatty acid oxidation, which seems to be a survival strategy for tumor cells in an anoxic environment (80). It is hypothesized that the interaction between the gene of HADH and HIF might be the potential mechanism regulating fatty acid oxidation. Further basic experiments are required.

Overall, the abovementioned studies have shown that the expression of HADH is different in tumors occurring in different organs. However, HADH is closely associated with tumors and can be used as a prognostic indicator and therapeutic target for tumors. Exploring its specific mechanism in tumors is the next undertaking and one which could eventually aid in clinical decision-making.

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Availability of data and materials

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

Authors' contributions

XW and HS performed the literature search and wrote the manuscript. JL, YJ and YZ supervised and revised the manuscript. 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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