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Upregulated Lactate Dehydrogenase C4 Promotes Hepatocellular Carcinoma Progression Via Accelerating Glycolysis and Triggering the AKT/mTOR Signaling Pathway

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ABSTRACT

Background: Lactate dehydrogenase C4 (LDHC4) plays a crucial role in regulating the interconversion between lactate and pyruvate during glucose metabolism. Yet, its expression patterns and biological roles in hepatocellular carcinoma (HCC) remain largely unknown. This study endeavors to elucidate the expression and biological function of LDHC4 in HCC.

Methods: The expression of LDHC4 was analyzed in HCC tissues and adjacent non-tumorous tissues utilizing bioinformatics tools and immunohistochemical analysis. Additionally, an in vitro study was conducted to investigate the impact of LDHC4 on HCC progression.

Results: Our findings revealed that LDHC4 is upregulated in HCC tissues. Furthermore, LDHC4 facilitates the migration and invasion of HCC cells in vitro. Notably, overexpression of LDHC4 accelerates the conversion of pyruvate to lactate and upregulates the expression of AKT and mTOR.

Conclusions: LDHC4 enhances HCC invasion and migration in vitro, promotes glycolysis, and activates the AKT/mTOR pathway. This study provides novel insights for future investigations into the functionality and mechanisms of LDHC4 in HCC.

Keywords: Lactate Dehydrogenase C4; Hepatocellular Carcinoma; Glycolysis; Mechanism

Abbreviations: LC: Liver Cancer; HCC: Hepatocellular Carcinoma; (CTA): Cancer/Testis Antigen; NSCLC: Non-Small Cell Lung Cancer; ATCC: American Tissue Culture Collection; STR: Short Tandem Repeat

Introduction

Liver cancer (LC) represents one of the most prevalent malignant tumors affecting the digestive tract in China, with hepatocellular carcinoma (HCC) accounting for over 80% of all liver cancer cases [1]. Clinically, HCC primarily arises from viral infections, liver cirrhosis, and inherited metabolic conditions [2,3]. Surgical resection currently stands as the optimal treatment for HCC; however, the 5-year recurrence rate post-radical resection is alarmingly high at 61.5% [4]. Metastasis and recurrence are pivotal factors contributing to the poor prognosis observed in LC patients [5]. Early diagnosis, intervention, and treatment remain pivotal in reducing mortality and mitigating disease progression in HCC patients [1,6]. Current research indicates that the fundamental pathogenesis of HCC hinges on the abnormal expression of genes and their translation products, ultimately leading to tumorigenesis [7]. Therefore, a thorough investigation of the potential molecular mechanisms underlying the occurrence and development of HCC, focusing on abnormal gene and protein expression, may offer crucial insights for the identification and development of biomarkers and therapeutic targets for HCC.

Cancer/testis antigen (CTA) constitutes a class of antigens exclusively expressed in the germinal epithelium of mammalian testes and certain tumor tissues [8], and is recognized as a potential immuno-

therapy target for HCC [9]. LDHC4, encoded by the LDHC (lactate dehydrogenase C) gene, stands out as the first LDH isoenzyme identified to be expressed solely in testes and tumors, and serves as a significant CTA molecule [10]. LDHC4 is a crucial LDH isoenzyme that regulates glycolysis and plays a vital role in catalyzing the interconversion between lactate and pyruvate [11]. Studies by Wang et al. on the enzymatic kinetic properties of LDHC4 in plateau pika revealed that the Michaelis constant (Km) for pyruvate and lactate is notably higher in LDHC4 compared to the other five isoenzymes [12]. Furthermore, LDHC4 exhibits a 90-fold higher affinity for pyruvate than for lactate [12]. When compared to LDH1 to LDH5, LDHC4 demonstrates superior enzymatic activity and glycolysis rates. Odet et al. found that LDHC4 accounts for 80% of the total LDH activity in mouse spermatozoa [11]. Functional deficiency of LDHC4 results in a rapid decline in ATP levels and progressively decreased motility in spermatozoa; spermatozoa from LDHC4-deficient male mice produce extremely low lactate levels, at only one-thirtieth of that in wild-type male mice, and display inefficient glucose utilization [11]. These findings highlighted that LDHC4 yielded critical role in energy supply during reproduction and energy metabolism. As a CTA, LDHC/LDHC4 has been reported to play a pivotal role in the development of malignant tumors such as lung cancer, renal cancer, and breast cancer [13-16]. Study has identified LDHC as the only molecule positively expressed in all pathological tissues of non-small cell lung cancer (NSCLC) among the seven CTAs tested, suggesting its potential as a robust biomarker for NSCLC diagnosis [17]. In lung adenocarcinoma, the expression rate of LDHC4 in patient tumor tissues was 81.8%, and LDHC4 expression correlated with patient prognosis and TNM staging; overexpression of LDHC4 exerts oncogenic functions by activating the PI3K/Akt/GSK-3β pathway, thereby promoting the growth, proliferation, and tumorigenicity of lung cancer cells in vivo [13].

Studies in renal cell carcinoma demonstrated that positive LDHC4 expression was significantly associated with decreased patient survival and an increased risk of poor clinical prognosis [14]. Our research group has previously found that LDHC4 expression is upregulated in breast cancer [15] and lung adenocarcinoma [18] tissues, with LDHC4 protein expression levels inversely correlated with overall survival in cancer patients. Currently, the expression and biological functions of LDHC/LDHC4 in HCC remain elusive. This study analyzed the differential expression of LDHC in LIHC (liver hepatocellular carcinoma) based on online databases and further validated LDHC4 expression at the protein level using high-throughput commercial tissue microarrays. At the cellular level, the study explored the impact of LDHC4 overexpression on HCC cell growth, invasion, and migration, while preliminary investigations were conducted into the underlying molecular mechanisms. Our research aims to provide novel insights and clues for future in-depth studies on the functions and mechanisms of LDHC4 in HCC.

Materials and Methods

Public Data and Bioinformatics Tools

The UALCAN database offers insights into gene expression and survival analyses, grounded in clinical data derived from TCGA [19]. In this study, the UALCAN database was harnessed to evaluate the disparity in LDHC mRNA expression between cancerous and noncancerous tissues in liver hepatocellular carcinoma (LIHC). Additionally, pan-cancer and correlation analyses were conducted leveraging the UALCAN database.

Main Reagents

LDHC overexpression was achieved using the GV492 lentiviral vector sourced from GENECHEM (Shanghai, China). EliVisionTM Plus Two-step Detection Kit was from Fuzhou Maixin (Fuzhou, China). SDS-PAGE Kit was purchased from Beyotime Biotechnology (Shanghai, China). ECL AB color development solution (chemiluminescence) was sourced from Meilunbio (Dalian, China). Matrigel was provided by Corning Lifesciences (China). Glucose Detection Kit was obtained from Beijing Pleili Company (Beijing, China), while Pyruvate and Lactate Detection Kits were sourced from Nanjing Jianguo Company (Nanjing, China). Rabbit anti-human GAPDH monoclonal antibody, rabbit anti-human PI3K monoclonal antibody, rabbit anti-human AKT monoclonal antibody, rabbit anti-human mTOR monoclonal antibody, mouse anti-human HIF-1α monoclonal antibody, and HRP-labeled goat anti-mouse/rabbit secondary antibody are all sourced from Abcam (UK).

Immunohistochemical (IHC) Analysis

Paraffin-embedded tissue samples were processed for immunohistochemical analysis. A high-density hepatocellular carcinoma (HCC) tissue microarray (Cat. no. HLivH180Su10) containing 77 HCC tissue cores and 76 matched adjacent non-tumor tissue cores was utilized. IHC staining was performed using the EliVisionTM Plus two-step detection system (Product no. KIT-9903, Fuzhou Maixin) following the manufacturer's protocol. Tissue sections were incubated with human anti-LDHC rabbit monoclonal antibody (Abcam, cat. no. Ab52747) at a dilution of 1:200, with phosphate-buffered saline (PBS) serving as the negative control. Chromogenic detection was performed using 3,3'-diaminobenzidine (DAB) substrate for 2 minutes, followed by counterstaining with hematoxylin. Stained sections were visualized and imaged using light microscopy.

Cell Culture

Human Bel7402 cells were maintained in RPMI-1640 (Gibco, USA), supplemented with 10% fetal bovine serum (Gibco, USA) and 1% penicillin-streptomycin (Gibco, USA). These cells were cultured at 37°C in an atmosphere containing 5% CO_2. The Bel7402 cell line was sourced from the American Tissue Culture Collection (ATCC) and verified through short tandem repeat (STR) profiling. The experimental design comprised the LDHC4 overexpression group (Bel7402-OE), GV492 empty lentivirus vector (Bel7402-NC), and blank cells (Bel7402-CON). The cells were infected at an appropriate multiplicity of infection (MOI) value, followed by the addition of Puromycin at a

concentration ranging from 1.0-10 μg/mL for a three-day screening period. This procedure led to the establishment of stably infected cell lines, which were subsequently used for further experiments.

Real-Time Quantitative PCR (RT-qPCR) Analysis

Total RNA was isolated from Bel7402 cells using a commercial RNA Extraction Kit (Promega Corp). Complementary DNA was synthesized using a Reverse Transcription Kit from Roche (Basel, Switzerland). PCR primers were acquired from Sunya (Fuzhou, China), with sequences detailed in a previous study [15]. RT-qPCR reactions were conducted on the ABI 7500 System (ABI, Vernon, CA, USA) using the SYBR Green kit from Roche, adhering to the manufacturer's instructions. Relative gene expression values were calculated using the formula (2-ΔΔct), where ΔCt was determined by subtracting the Ct value of each target gene from the corresponding glyceraldehyde-3-phosphate dehydrogenase (GAPDH) Ct value.

LDHC4 Protein Activity

Based on LDHC4's capacity to catalyze the specific substrate sodium 2-hydroxybutyrate, resulting in color development and the formation of an insoluble colored product known as formazan, detailed operational steps are outlined in our published study [20].

CCK-8 Assay

Bel7402 cells were inoculated into a 96-well plate at a density of 1×10^3 cells per well and incubated for 0, 24, 48, 72, and 96 hours, respectively. Subsequently, 10 μL of CCK-8 solution was added to each well. After an additional 2 to 4 hours of incubation, the mixture was homogenized by oscillation, and the optical density values were measured at dual wavelengths of 450 nm and 630 nm using a microplate reader. A cell growth curve was plotted, with OD values on the vertical axis and incubation time on the horizontal axis.

Wound Healing Assay

BC cells in logarithmic growth phase were seeded into a 6-well plate. Using a 10 μL pipette tip, scratches were created on the surface of BC cells from different groups, followed by an additional 24 hours of incubation. The widths of the scratches at 0 and 24 hours were observed under a microscope. Cells treated with incomplete medium alone served as the control group, and the wound healing rates of each group were compared.

Transwell Assay

For the invasion experiment, Matrigel was added to the upper chamber of the Transwell insert, with complete medium in the lower chamber. Subsequently, 1×10^4 cells were added to the upper chamber and cultured for 48 hours. Non-invading cells were washed away, and the cells were fixed with 20% methanol and stained with 0.2% crystal violet. Five random fields were selected under an inverted microscope, and the number of invading cells in each field was counted to calculate the average. For the migration experiment, matrigel was omitted, with the other steps remaining the same as those for the invasion experiment.

Lactate Detection

Cellular lactate content was detected using a commercial Lactate Detection Kit. The detection principle relies on LDH catalyzing lactate dehydrogenase to produce pyruvate, with NAD+ serving as the hydrogen acceptor and converting to NADH. PMS transfers hydrogen to reduce NBT into a purple colorant, which exhibits a linear relationship with lactate content at 530 nm. Detailed operations followed the instructions provided.

Pyruvate Detection

Cellular pyruvate content was detected using a commercial Pyruvate Detection Kit. The detection principle involves the reaction of pyruvate with a color reagent, resulting in a red-brown color in an alkaline solution. The color depth is proportional to the pyruvate content. Detailed operations were performed according to the instructions.

Glucose Testing

Cellular glucose content was detected using a commercial Glucose Detection Kit. Based on the Trinder reaction principle, glucose is converted into gluconic acid and hydrogen peroxide (H_2O_2) by glucose oxidase (GOD). Peroxidase (POD) then catalyzes hydrogen peroxide to generate a quinone imine from a chromogen (4-aminoantipyrine). The color depth is proportional to the glucose concentration. Detailed operations adhered to the instructions.

Immunoblotting

Cells were lysed with RIPA protein lysis buffer. Following centrifugation at 12,000 r/min for 10 minutes, the supernatant was collected as total protein. Protein concentration was determined using the BCA method. An appropriate amount of protein was mixed with loading buffer and boiled at 100°C for 5 minutes for denaturation. SDS-PAGE gel electrophoresis was performed with 30 μg of protein per lane. After electrophoresis, proteins were transferred to a PVDF membrane, which was then blocked in 5% skimmed milk for 1 hour. The following antibodies were used: rabbit anti-human GAPDH monoclonal antibody (1:1000), rabbit anti-human PI3K monoclonal antibody (1:1000), rabbit anti-human AKT monoclonal antibody (1:500), rabbit anti-human mTOR monoclonal antibody (1:1000), and mouse anti-human HIF-1α monoclonal antibody (1:1000), and followed by incubation at room temperature for 4 hours or at 4°C overnight. The membrane was washed with TBST three times, and HRP-labeled goat anti-rabbit and goat anti-mouse secondary antibodies (1:10000) were added, respectively, with incubation continued for 1 hour. AB color developing solution was added for exposure and development, with GAPDH serving as the internal reference protein.

Statistical Analysis

All experiments were conducted with three replicate wells/samples. Data were presented as mean ± standard deviation (SD) and analyzed using SPSS 19 software. One-way ANOVA was performed, with pairwise comparisons using the t-test. Homogeneity of variances was analyzed, and if variances were heterogeneous, adjusted t-tests, vari-

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able transformations, or rank sum tests were utilized. Statistical significance was indicated by $P < 0.05$.

Results

LDHC/LDHC4 is Highly Expressed in HCC Tissues

Pan-cancer expression analysis using the UALCAN database revealed LDHC upregulation in various malignant tumor tissues compared to corresponding normal controls (Figure 1A). LDHC expression in LIHC tissues was higher than in the control group (Figure 1B). Subgroup analysis showed LDHC expression increasing with clinical stage and pathological grade (Figure 1C & 1D). Correlation analysis demonstrated a positive correlation between LDHC expression in LIHC tissues and the expression of ZGPAT (zinc finger CCCH-type and G-patch domain containing), APOBEC3B (apolipoprotein B mRNA editing enzyme catalytic subunit 3B), MGC3771 (ZNF205 antisense RNA 1), LOC147727 (ILF3-DT ILF3 divergent transcript), among others (Figure 1E). High-throughput tissue microarrays combined with immunohistochemical techniques were used to detect LDHC4 protein expression in HCC. LDHC4 was predominantly expressed in the cytoplasm of HCC tissue cells (Figure 1F). LDHC4 protein expression was significantly higher in HCC tissues compared to adjacent tissues (Figure 1G & 1H). The proportion of high LDHC4 expression was 55.84% (43/77), which was higher than the proportion of high LDHC4 expression in adjacent tissues (26.32% or 20/76, P<0.0001).

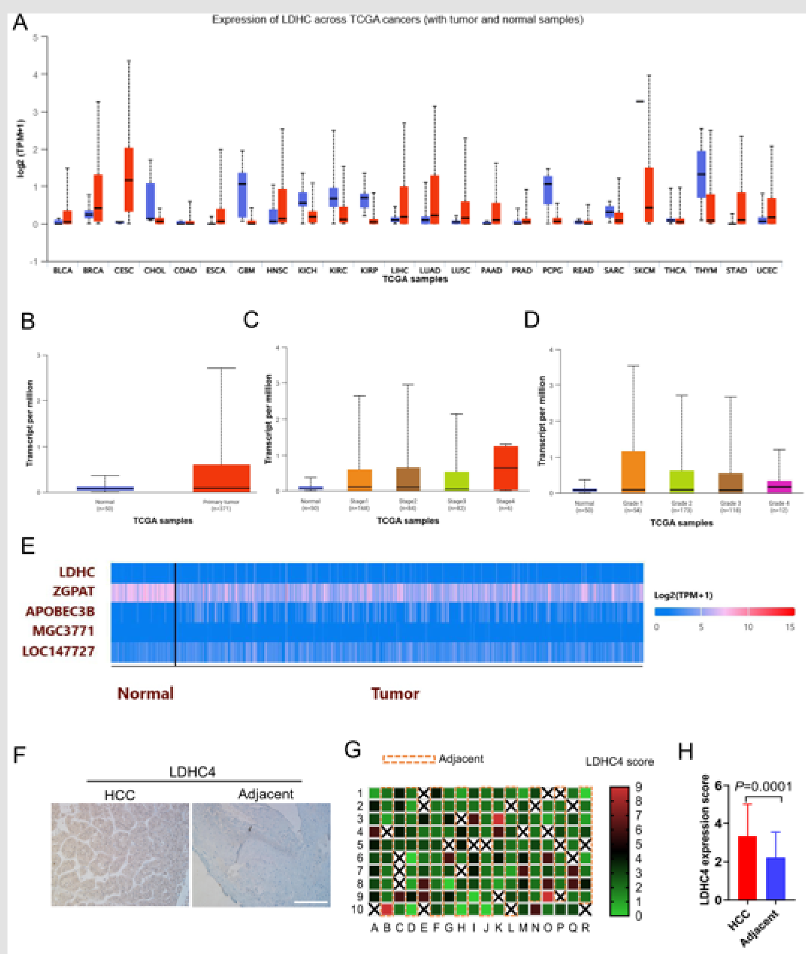

Figure 1: Analysis of LDHC/LDHC4 Expressions in LIHC Based on the UALCAN Database and Tissue Chip.

A. Pan-cancer perspective of LDHC mRNA derived from the UALCAN database.
B. LDHC mRNA expressions in LIHC analyzed through the UALCAN database.
C. LDHC mRNA expressions in LIHC analyzed according to clinical stage.
D. LDHC mRNA expressions in LIHC examined based on tumor grade.
E. Genes positively correlated with LDHC in LIHC.
F. (F, G) Examination of LDHC4 protein expression in HCC tissue utilizing a commercial tissue chip.
G. (H) Quantification of LDHC4 expression based on rating scores.

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Overexpression of LDHC4 Enhances the Invasion and Migration Capabilities of Bel7402 HCC Cells

We selected the Bel7402 HCC cell line with relatively low LDHC4 expression and overexpressed exogenous LDHC4 protein through lentiviral infection, obtaining a Bel7402 cell line stably transfected with LDHC4 based on puromycin selection (Figure 2A). Specific enzymatic activity staining of LDHC4 protein showed significantly higher staining intensity in the Bel7402-OE group compared to the Bel7402-NC group (Figure 2B). Additionally, RT-qPCR demonstrated increased LDHC levels in the Bel7402 group (Figure 2C). These results indicated successful construction of the Bel7402 cell line stably transfected with LDHC4. A cell growth curve plotted based on the CCK-8 assay showed no statistical difference in OD values between the Bel7402-OE group and the Bel7402-NC and Bel7402-CON groups at 24 to 96 hours (Figure 2D). However, the wound healing assay results indicated a significantly higher number of migrating cells in the Bel7402-OE group compared to the Bel7402-NC and Bel7402-CON groups. Furthermore, the Transwell assay showed that the number of migrating and invading cells in the Bel7402-OE group was significantly higher than in the corresponding control groups (Figure 2E-2G). These experiments confirmed LDHC4 overexpression promotes the invasion and migration capabilities of Bel7402 cells.

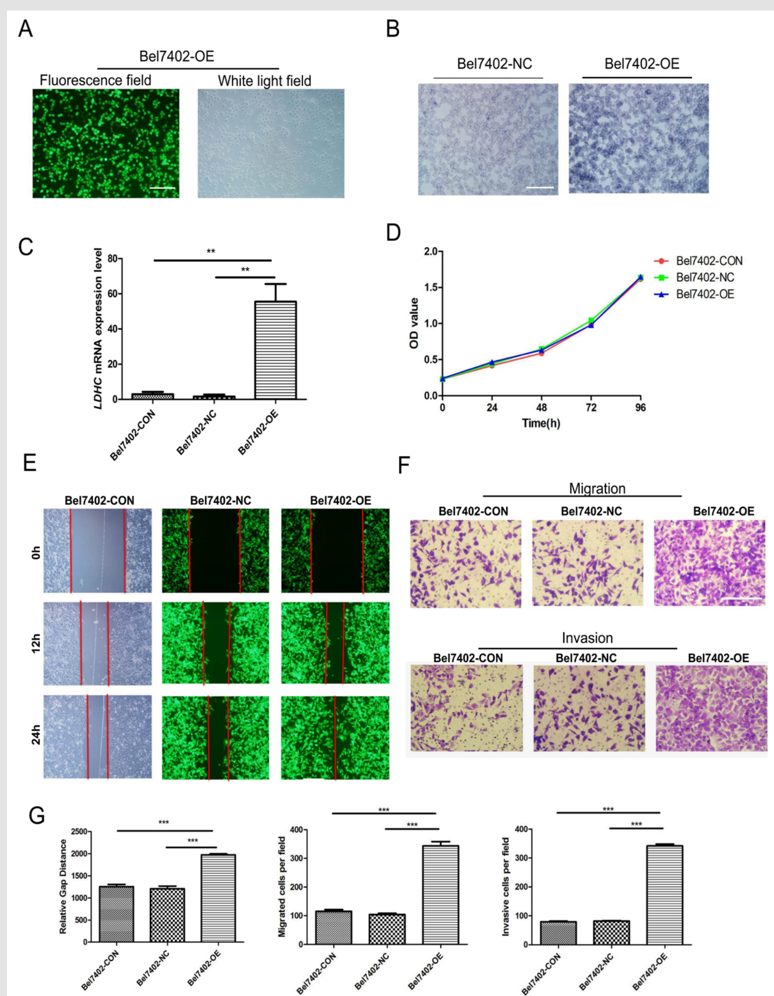

Figure 2: Functional Role of LDHC4 in Bel7402 HCC Cells In Vitro.

A. Stable LDHC4-expressing cell lines were screened using puromycin.
B. LDHC4 protein activity staining.
C. LDHC mRNA levels in variably treated Bel7402 HCC cells.
D. CCK-8 assay results.
E. Wound healing assay.
F. Transwell assay.
G. Quantitative results of Wound healing and Transwell assays. **P<0.01, ***P<0.001.

Overexpression of LDHC4 Promotes Glycolysis

Considering LDHC4 as a key enzyme regulating glycolysis, we further detected lactate, pyruvate, and glucose levels. Results showed higher lactate and glucose levels in the Bel7402-OE group compared to corresponding control groups, while pyruvate content in the Bel7402-OE group was lower than in the Bel7402-NC and Bel7402-CON groups (all with P<0.001; Figure 3A-3C). These results suggest LDHC4 promotes the conversion of pyruvate to lactate during glycolysis in Bel7402 cells.

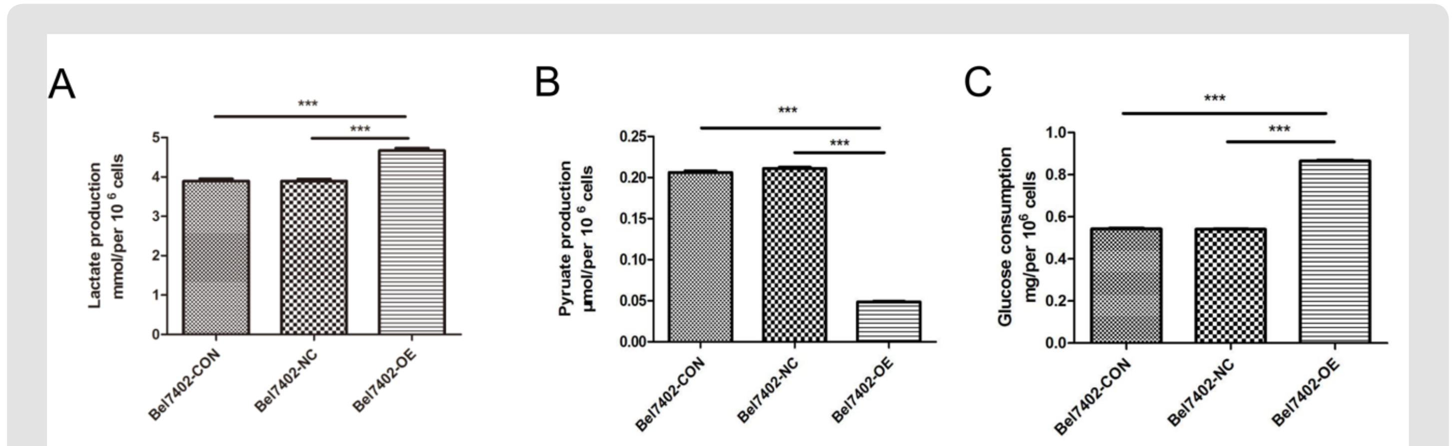

Figure 3: Impact of LDHC4 Overexpression on Glycolysis.

A. Lactate levels,

B. Pyruvate levels, and

C. Glucose levels were measured. ***P<0.001.

Overexpression of LDHC4 Activates the AKT/mTOR Pathways

We verified changes in AKT/mTOR pathway-related molecule expression after LDHC4 overexpression and found that AKT and mTOR protein expression levels in the Bel7402-OE group were higher than in the corresponding Bel7402-NC and Bel7402-CON groups (all with P<0.001). There was no difference in PI3K and HIF-1α expression among the three groups (Figure 4A & 4B). These results suggest LDHC4 may promote Bel7402 cell invasion and migration by activating AKT/mTOR pathway-related protein expression.

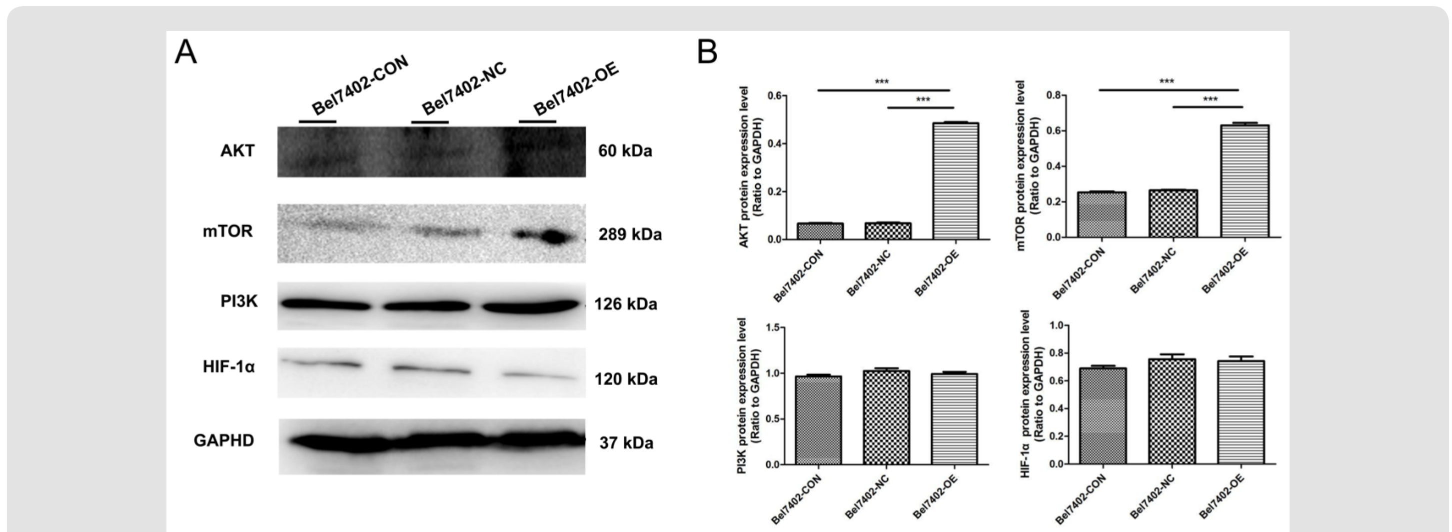

Figure 4: Effects of LDHC4 Overexpression on the Regulation of AKT, mTOR, PI3K, and HIF-1α Expressions.

A. Immunoblotting images.

B. Quantified results of targeted proteins normalized to GAPDH. ***P<0.001.

Discussion

Currently, there is a lack of clinically effective biomarkers for diagnosing and treating HCC. At diagnosis, most HCC patients often exhibit varying degrees of metastatic lesions, which not only elevate post-surgical recurrence rates but also heighten mortality risks [21]. Delving into the genetic and proteomic abnormalities underpinning HCC progression and metastasis could pave the way for discovering novel diagnostic and therapeutic biomarkers. As a CTA, LDHC4 holds notable potential in tumor immunotherapy [22], yet there are scant reports on its expression and functionality in malignant tumors, especially HCC. Our study revealed LDHC/LDHC4 upregulation in HCC, where its overexpression fuels in vitro invasion and metastasis, augments glycolysis, and activates the AKT/mTOR pathway. Our prior research has confirmed LDHC4 expression in tumors like breast cancer [15] and lung cancer [18], with high LDHC4 expression negatively correlating with patient prognosis. To further elucidate LDHC4 expression in HCC, this study, leveraging online database analysis and immunohistochemical analysis, confirmed significant LDHC/LDHC4 overexpression in HCC tissues, aligning with current studies reporting high LDHC4 expression in tumor tissues. We also examined how upregulated LDHC4 impacts HCC cell line biology, finding that LDHC4 overexpression bolsters the invasion and migration capabilities of Bel7402 cells. However, CCK-8 assay results were insignificant, potentially due to Bel7402's rapid growth and the time required for exogenous LDHC4 expression, obscuring LDHC4's overexpression effect. As a glycolysis-regulating enzyme crucial in mammalian sperm metabolism [10,11], our study also showed that LDHC4 upregulation in HCC affects lactate, pyruvate, and glucose levels in glycolysis, suggesting LDHC4 influences tumor metabolism via glycolysis regulation.

Currently, few studies have explored LDHC4's functional mechanisms in tumors. The PI3K/AKT/mTOR pathway is established in regulating HCC invasion and metastasis [23], while HIF-1α, a constituent subunit of hypoxia-inducing factor 1 [24], has been implicated in influencing the progression of HCC through modulation of the cell cycle, suppression of apoptosis, activation of pro-proliferative signaling pathways, facilitation of epithelial-to-mesenchymal transition (EMT), and glycolysis [25-28]. Chen et al. reported LDHC4 acting as an oncogene in lung adenocarcinoma (LUAD), enhancing cell growth, proliferation, and tumorigenicity by activating the PI3K/Akt/GSK-3β pathway [6]. In breast cancer (BC), LDHC silencing in four BC cell lines significantly increased giant cells, nuclear aberrations, DNA damage, and apoptosis [13]. Our study found LDHC4 overexpression upregulates AKT and mTOR expression but does not alter total PI3K and HIF-1α proteins. Since phosphorylated PI3K wasn't detected, phosphorylation-level changes in PI3K cannot be discounted. Additionally, as HIF-1α is a transcription factor [24], nuclear-cytoplasmic expression differences were undetected and require further exploration. In summary, this study examined LDHC4 expression in HCC and, for the first time, demonstrated in vitro that LDHC4 promotes HCC invasion and metastasis, enhances glycolysis, and activates the AKT/mTOR pathway. Our findings are poised to offer fresh perspectives on LDHC4's role and potential molecular mechanisms in HCC onset and progression.

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