Iranian Journal of Basic Medical Sciences

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The miR-383-LDHA axis regulates cell proliferation, invasion and glycolysis in hepatocellular cancer

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ARTICLE INFO

Article type:
Original article

Article history:
Received: Apr 1, 2016
Accepted: Oct 20, 2016

Keywords:
Hepatocellular cancer
LDHA
MiR-383

ABSTRACT

Objective(s): To explore the correlation between expression patterns and functions of miR-383 and LDHA in hepatocellular cancer (HCC).

Materials and Methods: We detected the expression of miR-383 and LDHA in 30 HCC tissues and their matched adjacent normal tissues using qRT-PCR. Then we performed MTT assay, foci formation assay, transwell migration assay, glucose uptake assay and lactate production assay to explore the function of miR-383 in cell proliferation, invasion and glycolysis in HCC cell lines. Luciferase reporter assay was used to explore whether LDHA was a target gene of miR-383. Western blot and qRT-PCR were used to further confirm LDHA was targeted by miR-383. Then the above functional experiments were repeated to see whether the function of LDHA could be inhibited by miR-383.

Results: The results of qRT-PCR showed that miR-383 was down-regulated in HCC tissues compared with their matched adjacent normal tissues. Functional experiments showed that overexpression of miR-383 significantly suppressed cell proliferation, invasion and glycolysis. Luciferase reporter assay showed LDHA was a target gene of miR-383 and expression of LDHA was inversely correlated with that of miR-383 in HCC. Besides, increased cell proliferation, invasion and glycolysis triggered by LDHA could be inhibited by overexpression of miR-383 in HCC cell lines.

Conclusion: Our study proved that miR-383 is down-regulated in HCC and acts as a tumor suppressor through targeting LDHA. Targeting the miR-383-LDHA axis might be a promising strategy in HCC treatment.

► *Please cite this article as:*
Fang Zh, He L, Jia H, Huang Q, Chen D, Zhang Zh. The miR-383-LDHA axis regulates cell proliferation, invasion and glycolysis in hepatocellular cancer. Iran J Basic Med Sci 2017; 20:187-192; http://dx.doi.org/10.22038/ijbms.2017.8246

Introduction

Liver cancer is a common malignant disease. It is estimated that there were 782,500 new cases and 745,500 deaths during 2012 worldwide (1). Most primary liver cancer cases are hepatocellular cancer (HCC), which tends to be diagnosed at advanced stage, and the curative treatments are surgical resection or transplantation. Despite the improvement of surgical technique and radio-chemotherapy regimens in the past decades, the prognosis of HCC remains poor (2-4). Although it has been reported that many genes relate to the carcinogenesis of HCC, the molecular mechanisms remain mostly obscure (5). Therefore, it urges us to search novel molecular targets to help improve the clinical management and long-term prognosis of HCC.

MicroRNAs (miRNAs) are endogenous, highly conserved, 19-25 nucleotides non-protein-coding RNAs. Through binding to the 3'untranslated regions (3'UTRs) of target messenger RNAs (mRNAs), miRNAs play important roles in post-transcriptional regulations (6). Increasing evidence demonstrates that miRNAs are regulated in cancers and play important roles in cancer progression (7, 8). Many miRNAs have been revealed to take part in the development and progression of HCC. Therefore, clarifying the function of a specific miRNA to develop a novel therapeutic strategy may shed some light on the effective management of HCC.

It is reported that miR-383 acts as a tumor suppressor in many cancers, including esophageal squamous cell carcinoma, glioma, testicular embryonal carcinoma, medulloblastoma and others (9-15). In esophageal squamous cell carcinoma, miR-383 inhibits cell proliferation by down-regulating 5S rRNA and enhancing c-Myc–rpL11 interaction (9). In glioma, miR-383 inhibits cell invasion through down regulating insulin-like growth factor 1 receptor (10) and induces cell cycle arrest through targeting CCND1 (11). In HCC, miR-383 is also reported to inhibit cell proliferation via targeting APRIL (16).

Lactate dehydrogenase A (LDHA) is an important enzyme for cell metabolism. Recently, LDHA was reported to play critical roles in the progression of multiple cancers, such as cell proliferation and glycolysis in gastric

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cancer, renal cancer, pancreatic cancer, esophageal cancer and colorectal cancer (17-23). But the functions and regulations of LDHA are still not clear in HCC.

In this study, we investigated the expression levels of miR-383 in HCC tissues and performed functional studies to see the effects of miR-383 on cell proliferation, invasion and glycolysis in HCC cells. We used luciferase reporter assay to explore whether LDHA was a target gene of miR-383. Then functional experiments were performed to see whether the function of LDHA could be inhibited by miR-383. Our study demonstrates the function of miR-383-LDHA axis in carcinogenesis and progression of HCC. Targeting LDHA by miR-383 might be a novel effective therapeutic strategy in HCC treatment.

Materials and Methods

Cell lines and culture

The HCC cell lines HepG2 and SMMC-7721 were obtained from American Type Culture Collection (ATCC) and cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum, penicillin and streptomycin (Gibco BRL, NY, USA) at 37°C in humidified atmosphere with 5% CO_2.

Clinical samples

Thirty HCC tissues (HC) and their matched adjacent normal tissues (Normal) were achieved from Cancer Research Institute, University of South China. Tissues were immediately stored in RNAlater (Ambion) and subjected to quantitative real-time PCR (qRT-PCR) analysis. The tumors were graded pathologically according to the World Health Organization classification system. The pathological staging was performed according to the 2002 tumor-node-metastasis (TNM) classification of malignant tumors. The clinicopathologi - cal characteristics of the patients are as follow: Male, 17 cases, Female, 13 cases, ≥50 years, 16 cases, <50 years, 14 cases. This study was approved by the Ethics Committee of University of South China Health Authority. The collection and use of tissues were performed in accordance with the ethical standards formulated in the Declaration of Helsinki. Informed consent was obtained from all patients.

Quantitative RT-PCR analysis (qRT-PCR)

Total RNA was extracted with TRIzol (Invitrogen, USA) then reverse transcription and qRT-PCR reactions were performed according to the manufacturer's instructions with qSYBR-green-containing PCR kit (Qiagen, USA), using the Bio-Rad IQTM5 Multicolour Real-Time PCR Detection System (USA). The primers for LDHA were: forward, 5′-TTGGTCCAGCGTAACGTGAAC-3′ and reverse, 5′-CCAGGATGTGTAGCCTTTGAG-3′. The threshold cycle (Ct) value for LDHA was normalized against that for β-actin. The Ct value for miR-383 was normalized against that for U6 snRNA. The relative fold-change was calculated by the 2-ΔΔCt method.

Cell proliferation assay

HepG2 and SMMC-7721 cells were transfected with scrambled oligonucleotide or miR383 mimics then MTT assays were performed according to the manufacturer's instructions (Roche Applied Science, Mannheim, Germany).

Foci formation assay

HepG2 and SMMC-7721 cells were plated into six-well plates at 2000 cells/well and transfected with scrambled oligonucleotide or miR383 mimics. When most cell clones had exceeded 50 clones, we stained the cells with 0.06% crystal violet and counted the foci number.

Transwell migration assay

Transwell migration assay was used to determine the invasion capacity of HCC cells. Briefly, cells were seeded onto the basement membrane matrix (EC matrix, Chemicon, USA) of 24-well culture plates. Fetal bovine serum was added to the lower chamber as a chemo-attractant. Then the EC matrix together with non-invading cells were gently removed after 48 hr, while the invasive cells were stained with crystal violet, counted and imaged.

Measurement of glucose uptake and lactate production

To determine cell glucose uptake and lactate production, we collected the cell culture media 48 hr after transfection. Then Amplex® Red Glucose/Glucose Oxidase Assay Kit (Invitrogen, USA) and lactate assay kit (Sigma, USA) were used according to the manufacturer's instructions.

Luciferase reporter assay

The full-length of LDHA 3′-UTR was amplified and inserted into pGL3 control vector (Promega, WI). Then we generated mutations by deletion of 4 bp from the perfectly complementary site of the LDHA 3′-UTR using the QIAGEN XL-site directed Mutagenesis Kit (QIAGEN, CA). Next, we co-transfected HepG2/SMMC-7721 cells with 0.5 μg firefly luciferase report vector and 0.5 μg control vector containing Renilla luciferase, pRL-TK (Promega), followed by 50 nM miR-383 mimics or scrambled oligonucleotide. Finally, the relative luciferase activities (RLA) were measured 48 hr after transfection using the dual luciferase assay (Promega).

Western blot

HepG2 and SMMC-7721 cells were transfected with either miR-383 mimics or scrambled oligonucleotide. Protein was extracted using RIPA lysis buffer 48 hr after transfection. Protein concentrations were measured using the Protein BCA Assay Kit (Bio-Rad, USA). Then 20 μg protein mixed with 2 × SDS loading buffer was loaded. Protein was separated by 12% SDS-polyacrylamide gel electrophoresis then transferred to PVDF membranes (Millipore, USA). The membranes were incubated with 5% skim milk powder for 1 hr at room temperature

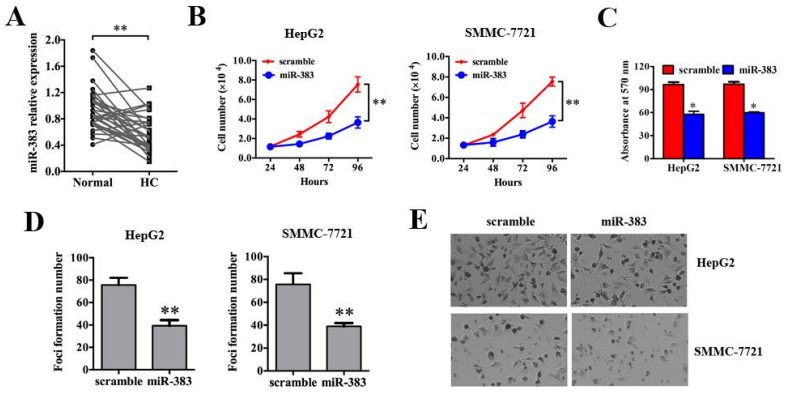

Figure 1. miR-383 inhibits cell proliferation and invasion and is decreased in hepatocellular cancer. A. qRT-PCR was performed to determine the expression of miR-383 in 30 HCC tissues (HC) and their matched adjacent normal tissues (Normal). B. HepG2 and SMMC-7721 cells were transfected with scrambled oligonucleotide or miR383 mimics. After transfection, the number of cells was counted. C. HepG2 and SMMC-7721 cells were transfected as described before. After transfection, MTT assay was performed. D. HepG2 and SMMC-7721 cells were transfected as described before. Cell proliferation capacity was assessed by foci formation assay. E. HepG2 and SMMC-7721 cells were transfected as described before. Cell invasion capacity was assessed by transwell migration assay. All of the data are shown as the means ± SEM * P<0.05, ** P<0.01

to block nonspecific binding, followed by antibody against LDHA (Affinity, USA) at 4 ˚C overnight. To visualize the target proteins, peroxidase-conjugated secondary antibody (dilution 1:400) and ECL Western blotting detection reagents (ECL New England Biolabs, USA) were used, which were quantified with a Bio Image Intelligent Quantifier 1-D (Version 2.2.1, Nihon-BioImage Ltd., Japan). Anti-β-actin antibody (Affinity, USA) was used as an internal control.

LDHA-expressing vector

The full-length of LDHA cDNA was purchased from GeneCopeia (USA) then it was sub-cloned into the expression vector pcDNA3.1(+) (GeneCopeia, USA); the vector pcDNA3.1(+) was used as a negative control.

Statistical analysis

Comparisons between groups were analyzed using t tests and χ^2 tests. All of the differences were statistically significant when P<0.05 was achieved. The statistical analyses were performed with SPSS 16.0 software.

Results

miR-383 inhibits cell proliferation and invasion, and is down-regulated in hepatocellular cancer

To determine the expression of miR-383, 30 pairs of HCC tissues (HC) and their matched adjacent normal tissues (Normal) were subjected to qRT-PCR analysis. Compared with adjacent normal tissues, we found that 80% (24 of 30 patients, P<0.0001) of tumor tissues revealed a decrease in miR-383 levels (Figure 1A).

To explore the biological effects of miR-383 in HCC, HepG2 and SMMC-7721 cells were transfected with miR-383 mimics or scrambled oligonucleotide then the number of cells was counted. We found that overexpression of miR-383 markedly inhibited cell proliferation compared with the control group (Figure 1B). MTT assay was performed to further confirm the inhibition of cell proliferation after miR-383 transfection. The results showed that transfection of miR-383 indeed inhibited cell proliferation (Figure 1C). Next we performed foci formation assay and found that overexpression of miR-383 led to decreased foci formation capacity of HCC cells (Figure 1D).

To further explore the function of miR-383 in HCC, we performed transwell migration assay to evaluate the invasion capacity of HepG2 and SMMC-7721 cells. The result showed that overexpression of miR-383 inhibited cell invasion compared with the control group (Figure 1E).

miR-383 inhibits glycolysis in hepatocellular cancer

To explore the role miR-383 plays in glycolysis in HCC, we detected the differences in metabolic parameters after HepG2 and SMMC-7721 cells were transfected with scrambled oligonucleotide or miR383 mimics. The results showed that overexpression of miR-383 largely decreased glucose uptake and lactate production of HCC cells (Figure 2).

LDHA is a direct target of miR-383

To identify the possible target genes of miR-383 that associate with cancer cell proliferation, invasion and

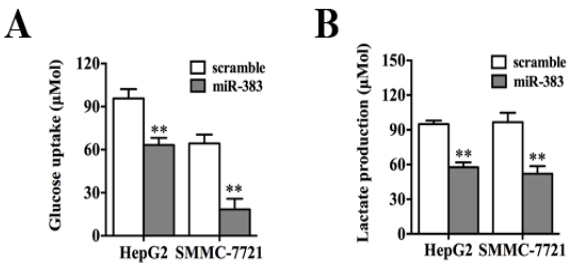

Figure 2. miR-383 inhibits glycolysis in hepatocellular cancer. A. HepG2 and SMMC-7721 cells were transfected with scrambled oligonucleotide or miR383 mimics. The glucose uptake levels were measured after transfection. B. HepG2 and SMMC-7721 cells were transfected as described before. After transfection, the lactate production levels were measured. All of the data are shown as the means ± SEM ** P< 0.01

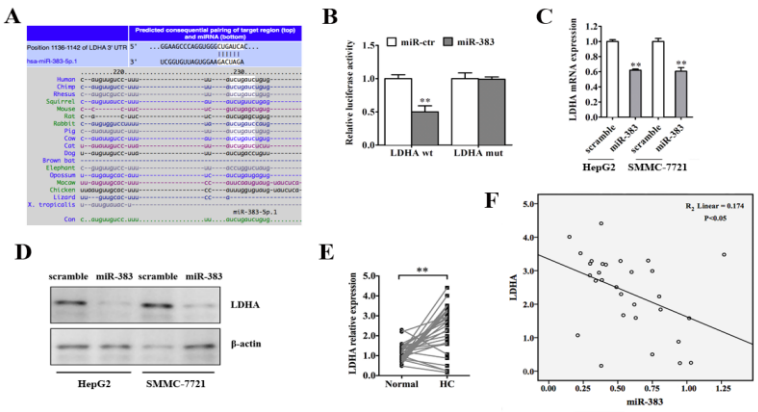

Figure 3. LDHA is a direct target of miR-383. A. Predicted binding site between miR-383 and LDHA 3′UTR. B. Luciferase assay of HepG2/SMMC-7721 cells co-transfected with miR-383 mimics or scrambled oligonucleotide and a luciferase reporter containing LDHA 3′UTR (LDHA wt) or mutant constructs (LDHA mut). C. HepG2 and SMMC-7721 cells were transfected with miR-383 mimics or scrambled oligonucleotide. Overexpression of miR-383 down-regulated the levels of LDHA mRNA. D. Overexpression of miR-383 inhibited the LDHA protein expression. β-actin was used as an internal control. E. qRT-PCR was performed to determine the mRNA level of LDHA in 30 HCC tissues (HC) and their matched adjacent normal tissues (Normal). F. The correlation between LDHA expression level and that o fmiR-383 in 30 HCC tissues. All of the data are shown as the means ± SEM ** $P< 0.01$

glycolysis, we used miRNA target-predicting algorithms TargetScan and miRanda. And both algorithms predicted LDHA among all the possible target genes (Figure 3A). Considering the metabolic function of LDHA, we therefore selected LDHA for further study.

To confirm this finding, we performed luciferase reporter assays in HCC cell line HepG2/SMMC-7721. Briefly, the full-length of LDHA 3′UTR was subcloned downstream of the firefly luciferase gene then it was co-transfected with miR-383 mimics or scrambled oligonucleotide. Then we measured the luciferase activity 48 hr after transfection. The relative luciferase activity (RLA) of the wild-type LDHA 3′UTR in HepG2/SMMC-7721 cells co-transfected with miR-383 mimics showed an approximately 50% reduction compared with those co-transfected with scrambled oligonucleotide (Figure 3B).

Furthermore, mutation of the miR-383 binding sites in LDHA 3′UTR abrogated the luciferase response to miR-383 (Figure 3B).

Next we performed qRT-PCR and Western blot analyses to further confirm LDHA is a target gene of miR-383. We transfected HepG2 and SMMC-7721 cells with miR-383 mimics or scrambled oligonucleotide then checked whether LDHA expression was regulated by miR-383. The result showed that compared with the control groups, cells transfected with miR-34a mimics showed a notable reduction in both the mRNA and protein levels of LDHA (Figure 3C and 3D).

To further confirm the regulations between miR-383 and LDHA described above are also relevant clinically, 30 HCC tissues (HC) and their matched adjacent normal tissues (Normal) were subjected to qRT-PCR assay to detect the LDHA expression level. The result showed that LDHA expression level in 80% (P<0.0001, 24 of 30 patients) of HCC tissues were higher compared with that in normal tissues (Figure 3E). Moreover, there was a negative correlation between LDHA expression level and that of miR-383 in 30 HCC tissues (Figure 3F).

miR-383 inhibits cell proliferation, invasion and glycolysis of hepatocellular cancer by targeting LDHA

To validate that miR-383 inhibited cell proliferation, invasion and glycolysis of HCC through targeting LDHA, we transfected HepG2 and SMMC-7721 cells with control

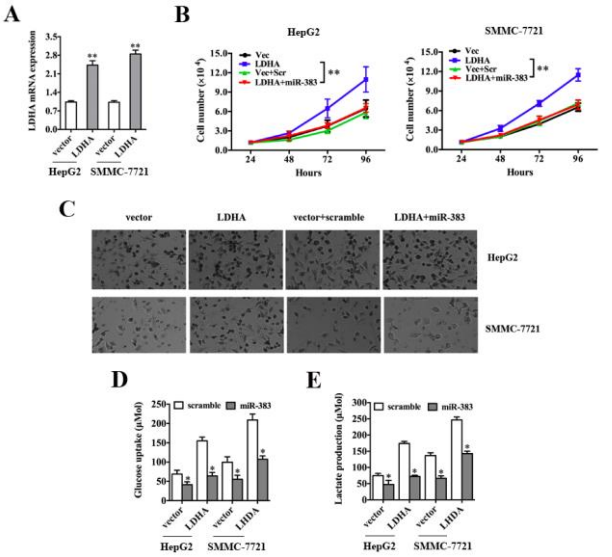

Figure 4. LDHA-induced cell proliferation, invasion and glycolysis can be inhibited by miR-383. A. HepG2 and SMMC-7721 cells were transfected with LDHA-expression vector or control vector. qRT-PCR demonstrated that the transfection was successful. B. HepG2 and SMMC-7721 cells were transfected with control vector, LDHA-expression vector, control vector + scrambled oligonucleotide or LDHA-expression vector + miR383 mimics. After transfection, the number of cells was counted. C. HepG2 and SMMC-7721 cells were transfected as described before. Cell invasion capacity was assessed by transwell migration assay. D. HepG2 and SMMC-7721 cells were transfected with control vector or LDHA-expression vector followed by scrambled oligonucleotide or miR-383 mimics. After transfection the glucose uptake levels were measured. E. HepG2 and SMMC-7721 cells were transfected then the lactate production levels were measured after transfection. All of the data are shown as the means ± SEM. * $P< 0.05$, ** $P< 0.01$

vector, LDHA-expressing vector, control vector +scrambled oligonucleotide or LDHA expressing vector +miR-383 mimics, respectively. The transfection was successful (Figure 4A). The number of cells was counted to explore whether miR-383 could suppress cell proliferation by targeting LDHA. We found that overexpression of LDHA could induce cell proliferation. But after co-transfection with miR-383 mimics, increased cell proliferation induced by LDHA was abrogated by miR-383 (Figure 4B).

Then we performed transwell migration assay to determine the invasion capacity of HepG2 and SMMC-7721 cells transfected as described before. The result showed that enhanced invasion capacity induced by LDHA could be abrogated by miR-383 (Figure 4C).

We also detected the differences in metabolic parameters after HepG2 and SMMC-7721 cells were transfected as described before. We found that increased glycolysis triggered by LDHA could be abrogated by miR-383, which led to decreased glucose uptake (Figure 4D) and lactate production (Figure 4E).

Discussion

Although surgical technique and radio-chemotherapy regimens have been improving in the past decades, the survival rate of HCC has not substantially increased as we expect. Therefore, it is urgent to thoroughly explore the molecular mechanisms of carcinogenesis and progression in HCC so as to develop novel strategies to better improve the prognosis of HCC (3, 24).

To date, more and more miRNAs have been found to take vital parts in the pathogenesis and progression of cancers. Increasing studies has found that miRNAs are related to HCC carcinogenesis and progression (25, 26). Since different miRNAs have different functions in HCC, it is important to clarify the function of a certain miRNA to develop a novel therapeutic target.

Researchers have found that miR-383 is down-regulated and acts as a tumor suppressor in multiple cancers, such as glioma, testicular embryonal carcinoma and medulloblastoma (10-15). It is reported that miR-383 inhibits cell proliferation via targeting APRIL in HCC (16). In this study, we detected the expression level of miR-383 in 30 HCC tissues and their matched adjacent normal tissues. The result showed that miR-383 was markedly down-regulated in HCC tissues, which was consistent with previous studies. Besides, functional experiments demonstrated that overexpression of miR-383 significantly inhibited cell proliferation, invasion and glycolysis in HCC cell lines, indicating that miR-383 might function as a tumor suppressor in HCC.

Reprogramming of metabolism is very common in cancer. Aberrant metabolism has been proved to help the progression and metastasis of cancers. A series of enzymes have been identified to play vital roles in regulation of cancer metabolism. Among them, LDHA is reported to involve in proliferation and glycolysis of cancer cells in gastric cancer, renal cancer, pancreatic cancer, esophageal cancer and colorectal cancer and so on (17-23). But how LDHA functions in HCC is still unclear. Using the miRNA target-predicting algorithms TargetScan and miRanda, we found that LDHA might be a target gene of miR-383. The functions of miR-383 in HCC might be partly due to its regulation on LDHA. Therefore, in this study we explored the functional regulations of LDHA by miR-383 in HCC cells. As expected, increased cell proliferation, invasion and glycolysis triggered by LDHA could be inhibited by miR-383 in HCC cell lines. These findings indicated that miR-383 suppressed HCC progression partly via targeting LDHA and miR-383-LDHA axis could be a promising therapeutic strategy in HCC treatment.

However, carcinogenesis and progression of HCC is very complicated. Besides LDHA, miR-383 also targets APRIL in HCC (16). There must be multiple miRNAs and their targets genes involved in HCC. Therefore, further studies are still needed to clarify potential molecular mechanism for HCC.

In summary, our study explores the expression of miR-383 and LDHA in HCC and validates that LDHA is indeed a target gene of miR-383. miR-383 suppresses proliferation, invasion and glycolysis of HCC cells via targeting LDHA. Our study proved the function of miR-383-LDHA axis in carcinogenesis and progression of HCC. Targeting LDHA by miR-383 might be a novel effective therapeutic strategy in HCC treatment.

Conclusion

Our study proves that miR-383 is down-regulated in HCC and acts as a tumor suppressor via targeting LDHA. Targeting the miR-383-LDHA axis might be a promising therapeutic strategy in HCC treatment.

Acknowledgment

This work was supported by funds from the National Natural Science Foundation of China (81100106).

Conflict of Interest

The authors declare no competing financial interests.

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