

# *miR-183-5p* Promotes HCC Migration/Invasion via Increasing Aerobic Glycolysis

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**Background:** The mortality and morbidity of hepatocellular carcinoma (HCC) are still unacceptably high, despite decades of extensive studies. Aerobic glycolysis is a hallmark of cancer metabolism, closely relating to invasion and metastasis of HCC. MicroRNAs (miRNAs) are involved in the regulation of aerobic glycolysis. *miR-183-5p*, an oncogenic miRNA, is highly expressed in HCC, but the regulatory mechanism of *miR-183-5p* in migration, invasion and aerobic glycolysis in HCC remains unclear.

**Purpose:** To elucidate whether *miR-183-5p* affects aerobic glycolysis to regulate the migration and invasion of HCC, and to explore its regulatory mechanism.

**Methods:** We attempted to observe the effects of *miR-183-5p* on the migration and invasion of HepG2 cells by a wound-healing assay and Transwell assays. The effect of *miR-183-5p* on glycolysis was determined by glucose uptake and lactate generation. Western blot and qPCR were used to detect the relevant proteins and miRNA expression.

**Results:** Our results show that *miR-183-5p* promoted migration and invasion, enhanced glycolysis via increasing glucose uptake and lactate generation, and up-regulated glycolysis-related gene (*PKM2*, *HK2*, *LDHA*, *GLUT1*) expression in HepG2 cells. Further experiments indicated that *miR-183-5p* could decrease PTEN expression, but increased Akt, p-Akt and mTOR expression in HepG2 cells.

**Conclusion:** These findings suggest that *miR-183-5p* may promote HCC migration and invasion via increasing aerobic glycolysis through targeting PTEN and then activating Akt/mTOR signaling.

**Keywords:** *miR-183-5p*, aerobic glycolysis, migration, invasion, PTEN/Akt/mTOR, hepatocellular carcinoma

## Introduction

Hepatocellular carcinoma (HCC), accounting for the majority of primary liver cancers, is the sixth most common cancer and the third leading cause of cancer-related deaths globally.<sup>1</sup> Despite advances in diagnosis and treatment, the prognosis of HCC patients is not satisfactory, mainly owing to metastasis and recurrence.<sup>2,3</sup> Therefore, it is critically important to understand the underlying molecular mechanisms of HCC progression.

Several studies have demonstrated that metabolic reprogramming, in particular the Warburg effect (aerobic glycolysis), provides favorable conditions for the growth of cancer cells and promotes tumor invasion and metastasis by increasing glucose uptake and lactic acid production under normoxic conditions.<sup>4-6</sup> Many studies have found that the metastasis and invasion of HCC are correlated with the enhanced aerobic glycolysis in HCC.<sup>7</sup> These phenomena are also common in

**Table 1** Sequence of Hsa-miR-183-5p Inhibitor, Inhibitor NC, Hsa-miR-183-5p Mimics and Mimics NC

Reagent	Sequence
hsa-miR-183-5p inhibitor	5'-AGUGAAUUCUACCAGUGCCAUA-3'
inhibitor NC	5'-CAGUACUUUUGUGUAGUACAA-3'
hsa-miR-183-5p mimics	sense: 5'-UAUGGCACUGGUAGAAUUCACU-3' antisense: 5'-UGAAUUCUACCAGUGCCAUAUU-3'
mimics NC	sense: 5'-UUCUCCGAACGUGUCACGUTT-3' antisense: 5'-ACGUGACACGUUCGGAGAATT-3'

breast cancer, prostate cancer, cervical cancer, and head and neck cancers.<sup>8</sup> Tumor-related energy regulation and abnormal energy metabolism have been used as biochemical pathways and drug targets for tumor therapy.<sup>9</sup> Elucidating the molecular mechanism of aerobic glycolysis in tumor cells has become the focus and direction of future research.

MicroRNA (miRNA), small non-coding RNA regulating post-transcriptional gene expression, is involved in many biological processes, such as cell proliferation, differentiation, metabolism, metastasis and apoptosis.<sup>10,11</sup> It has been demonstrated that non-coding RNAs, especially miRNAs, play a crucial role in mediating the metabolic transformation of cancer. Accumulating evidence suggests the role of the abnormal expression of miRNAs in aerobic glycolysis, both directly and indirectly.<sup>12,13</sup> Increased attention has been focused on the role of *miR-183-5p* in the development, invasion and metastasis of malignant tumors.<sup>14</sup> *miR-183-5p*, abnormally expressed in many tumors including HCC, is a significant cancer-related miRNA.<sup>14–18</sup> *miR-183/96/182* are involved in aerobic glycolysis in breast cancer.<sup>19</sup> Previous studies have found that *miR-183-5p* is up-regulated in HCC tissues and cells and is associated with invasion, metastasis and poor prognosis.<sup>20–23</sup> However, the effects of *miR-183-5p* on aerobic glycolysis in HCC are still unknown.

In the present study, we demonstrated that *miR-183-5p* promotes HCC invasion and metastasis via aerobic glycolysis by targeting the PTEN-mediated Akt/mTOR signaling pathway. Our data may provide insight into the mechanism of HCC progression.

## Materials and Methods

### Cell Culture

The HepG2 human HCC cell line was purchased from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China). HepG2 cells were cultured in Dulbecco's modified Eagle's medium (DMEM) (HyClone Laboratories, Logan,

UT, USA) containing 10% fetal bovine serum (FBS; Yeasen, Shanghai, China) with 1% penicillin–streptomycin (Solarbio, Beijing, China) in a humidified chamber at 5% CO<sub>2</sub> and 37°C.

### Cell Transfection

Hsa-miR-183-5p inhibitor, inhibitor NC, hsa-miR-183-5p mimics and mimics NC were designed and synthesized by GenePharma (Shanghai, China) and the sequences are listed in Table 1. HepG2 cells were seeded in a six-well cell culture plate (Corning, ME, USA) until they reached 70% confluence. Then, these cells were transfected with hsa-miR-183-5p inhibitor, inhibitor NC, hsa-miR-183-5p mimics and mimics NC using Lipofectamine 2000 Reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions, and cultured for 24–48 h before analysis.

### Quantitative Real-Time Polymerase Chain Reaction (qPCR)

Trizol (Tiangen Biotech, Beijing, China) was used to extract total RNA from cells according to the manufacturer's procedure. PrimeScript™ RT Master Mix (Takara, Beijing, China) was used to perform reverse transcription. qPCR was performed using a Mir-X™ miRNA First-Strand Synthesis Kit (Takara, Beijing, China) and SYBR Green kit (Yeasen, Shanghai, China). *U6* and *β-actin* were used as internal controls for *miR-183-5p* and target genes, respectively. The primers for *miR-183-5p* and *U6* were obtained from Bioscience (Shanghai, China). The sequences of the primers are shown in Table 2.

### Cell Wound-Healing Assay

HepG2 cells, seeded in a six-well cell culture plate until 90% confluent, were transfected with hsa-miR-183-5p inhibitor, inhibitor NC, hsa-miR-183-5p mimics and mimics NC. Wound healing was generated using a single

**Table 2** Primers Used in This Study

Gene	Primer Sequence (5'→3')
<i>miR-183-5p</i>	Forward: GCGGCTATGGCACTGGTAGAA Reverse: GTGCAGGTCCGAGGTATTC
<i>U6</i>	Forward: CTTAGTTGCGTTACACCTTTCTTG Reverse: CTGTCACCTTACCAGTTCCAGTTT
<i>PTEN</i>	Forward: ACACCGCCAAATTTAATTGCAG Reverse: TGTCATCTTCACTTAGCCATTGGTC
<i>Akt</i>	Forward: CTCATTCCAGACCCACGAC Reverse: ACAGCCCCGAAGTCCGTTA
<i>mTOR</i>	Forward: ATGACGAGACCCAGGCTAA Reverse: GCCAGTCTCTACAATACGC
<i>HK2</i>	Forward: CGGTACTCAATGACATCCGA Reverse: TTCACCAGGATGAGTCTGACC
<i>PKM2</i>	Forward: TGTCTGGAGAAACAGCCAAG Reverse: TCCTCGAATAGCTGCAAGTG
<i>LDHA</i>	Forward: CATGGCCTGTGCCATCAGTATC Reverse: TGCCAGAGACAATCTTGGGTGTTT
<i>GLUT1</i>	Forward: ACATAGCTTGCCTAATGGCTTTCAC Reverse: CCTGCCTGCTGACAACACCTA
<i>β-actin</i>	Forward: CTTAGTTGCGTTACACCTTTCTTG Reverse: CTGTCACCTTACCAGTTCCAGTTT

scratch with a 10  $\mu$ L pipette. Then, the HepG2 cells were washed with PBS and grown in FBS-free medium for a further 48 h. The intersections of the wounds and horizontal lines were observed under a Leica DMI6000 B Fully Automated Inverted Research Microscope (Leica Microsystems, Germany), and the cells were photographed at 0, 24 and 48 h. Image-Pro Plus software was used for measuring the cell migration distance.

### Cell Migration and Invasion Assays

Transwell® chambers (Millipore, Burlington, MA, USA) were used for cell migration and coated with Matrigel® (BD Biosciences, Bedford, MA, USA) for cell invasion assays. For migration assays, after treatment with hsa-miR-183-5p inhibitor, inhibitor NC, hsa-miR-183-5p mimics and mimics NC, HepG2 cells ( $1 \times 10^4$ ) in the upper chamber were cultured with FBS-free DMEM, and the lower chamber was filled with 10% FBS-containing DMEM. For invasion assays, HCC cells ( $1 \times 10^4$ ) were seeded on Matrigel-coated membrane inserts. Then, the chamber was put into the cell culture plate and incubated at 37°C for 48 h. Subsequently, cells that migrated or invaded across the Transwell membrane were fixed with 4% paraformaldehyde for 10 min and then stained with

0.1% crystal violet for 20 min. Finally, the migratory and invasive cells were examined and counted under the microscope.

### Lactate Production and Glucose Consumption

HepG2 cells were cultured for 24 h following treatment with hsa-miR-183-5p inhibitor, inhibitor NC, hsa-miR-183-5p mimics and mimics NC. The supernatant was then harvested for the measurement of lactate production and glucose consumption. Lactate or glucose levels were quantified, using the Lactate Assay kit (JianCheng Bioengineering Institute, Nanjing, China) or the Glucose Assay kit (Rongsheng Biotech, Shanghai, China), respectively, according to the manufacturer's instructions.

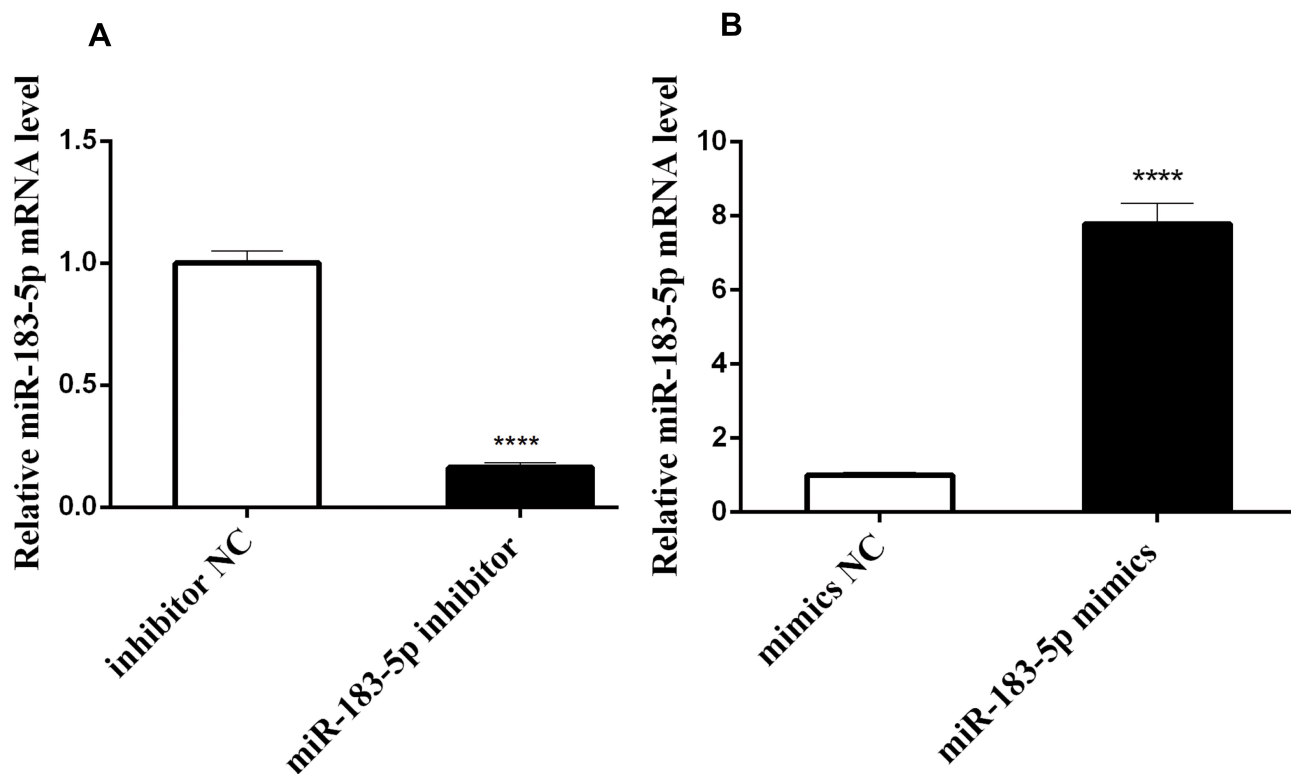
### Western Blot

The total protein was lysed with lysis buffer (Solarbio, Beijing, China) and BCA Protein Assay Kit (Solarbio, Beijing, China) for quantification. The proteins were electrophoresed by 10% SDS-PAGE and transferred to polyvinylidene fluoride (PVDF) membranes (Servicebio, Wuhan, China). The protein-transferred membrane was blocked in TBST with 5% non-fat milk powder, incubated for 30 min at room temperature. The non-specific blocked membrane was incubated with specific primary antibodies at 4°C overnight. GAPDH, AKT, mTOR, PKM2, HK2, LDHA (1:1000; Servicebio, Wuhan, China), GLUT1 (1:1000; Bioss, Beijing, China), PTEN and p-AKT (Ser473) (1:1000; Affinity, ME, USA) antibodies were used. After that, the membranes were incubated with horseradish peroxidase-conjugated secondary antibodies (Servicebio, Wuhan, China) and analyzed by Image Lab analysis software (Bio-Rad). PTEN, AKT, pAKT, mTOR, PKM2, HK2, LDHA and GLUT1 were normalized to GAPDH.

### Statistical Analysis

Data were analyzed using SPSS 23.0 software and presented as mean  $\pm$  SD. The Student's *t*-test was used to assess the significance of differences between two groups, and one-way analysis of variance (ANOVA) and Dunnett's multiple comparisons test were used for multiple-group comparisons. All

## HepG2



**Figure 1** Relative expression of *miR-183-5p* in transfected HepG2 cells through qPCR.

**Notes:** (A) Expression of *miR-183-5p* in inhibitor-treated cells. (B) Expression of *miR-183-5p* in mimics-treated cells. n=3, Student's t-test. \*\*\*\* $P < 0.0001$ .

statistical tests were two sided.  $P < 0.05$  was considered statistically significant. Single and multiple asterisks indicate statistical significance: \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$  and \*\*\*\* $P < 0.0001$ .

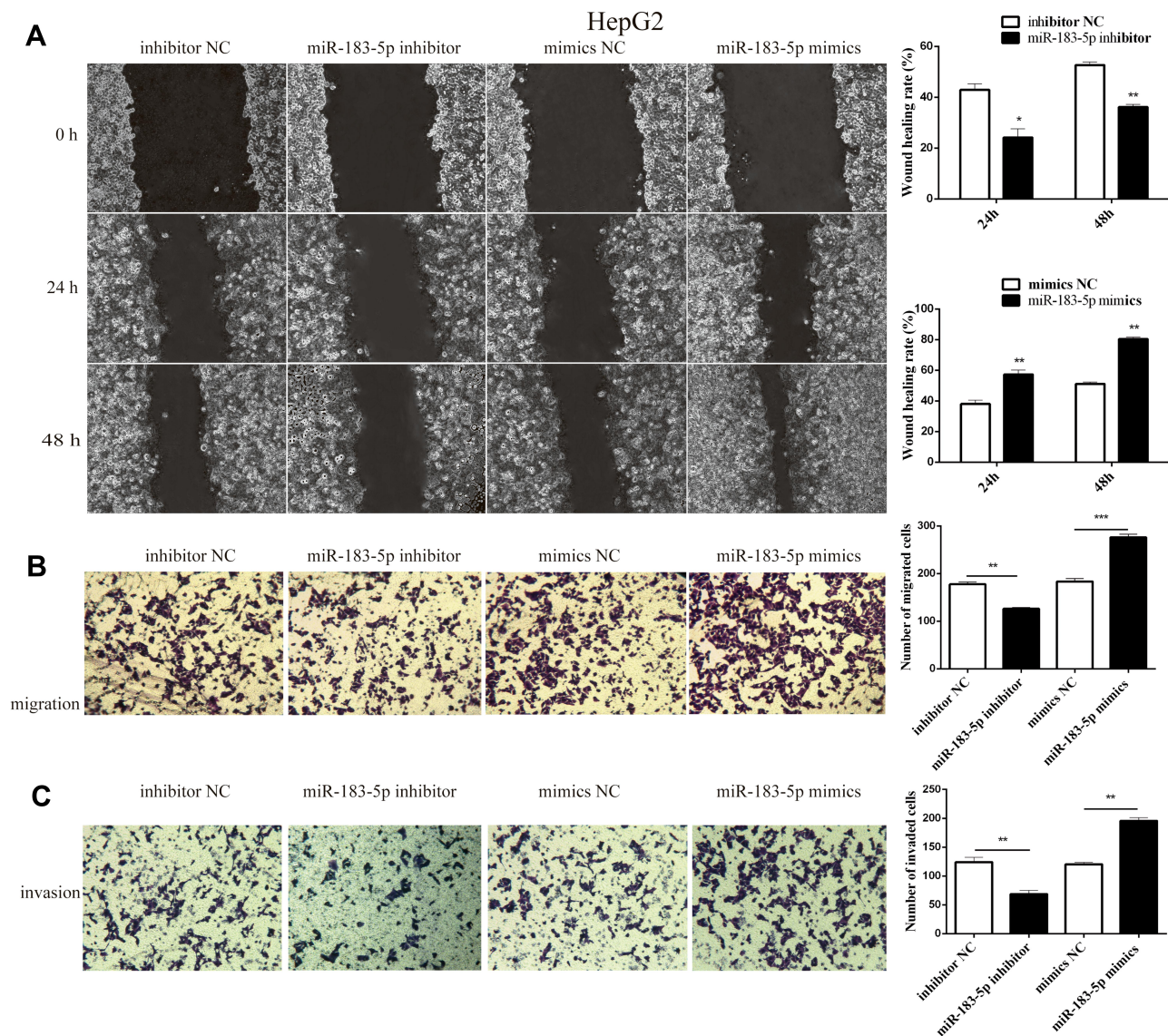
## Results

### Efficiency of Transfection in HepG2 Cells

We constructed both *miR-183-5p* overexpression and low expression in HepG2 cell using miR-183-5p mimics and inhibitor, respectively. Transfection efficiency in HepG2 cells was confirmed by qPCR, showing that the expression of *miR-183-5p* was significantly decreased in the miR-183-5p inhibitor-treated group compared with the inhibitor NC-treated group (Figure 1A). In addition, the expression of *miR-183-5p* was significantly increased in miR-183-5p mimics-treated HepG2 cells, compared with mimics NC (Figure 1B).

### *miR-183-5p* Promotes Migration and Invasion of HepG2 Cells

Cell wound-healing assay, cell migration and invasion assays were used to clarify the effect of *miR-183-5p* on the migration and invasion of HepG2 cells. Our results showed that the degree of healing was notably reduced in the miR-183-5p inhibitor-treated HepG2 cells compared to that in inhibitor NC-treated HepG2 cells; in contrast, the degree of healing increased significantly in miR-183-5p mimics compared with mimics NC (Figure 2A). The results of the Transwell assay with or without Matrigel showed that suppression of *miR-183-5p* significantly inhibited HepG2 cell migration and invasion compared with controls, whereas overexpression of *miR-183-5p* increased HepG2 cell migration and invasion compared with controls (Figure 2B and C).



**Figure 2** Effect of migration and invasion in HepG2 cells after transfection with miR-183-5p inhibitor.

**Notes:** (A) Scratch healing rate of lateral migration of HepG2 cells detected by a scratch healing experiment. (B and C) Longitudinal migration and invasion of HepG2 cells detected by Transwell migration and invasion assay under the microscope ( $\times 200$ ).  $n=3$ , Student's *t*-test. \*\* $P<0.01$ , \*\*\* $P<0.001$ .

## miR-183-5p Promotes Aerobic Glycolysis in HepG2 Cells

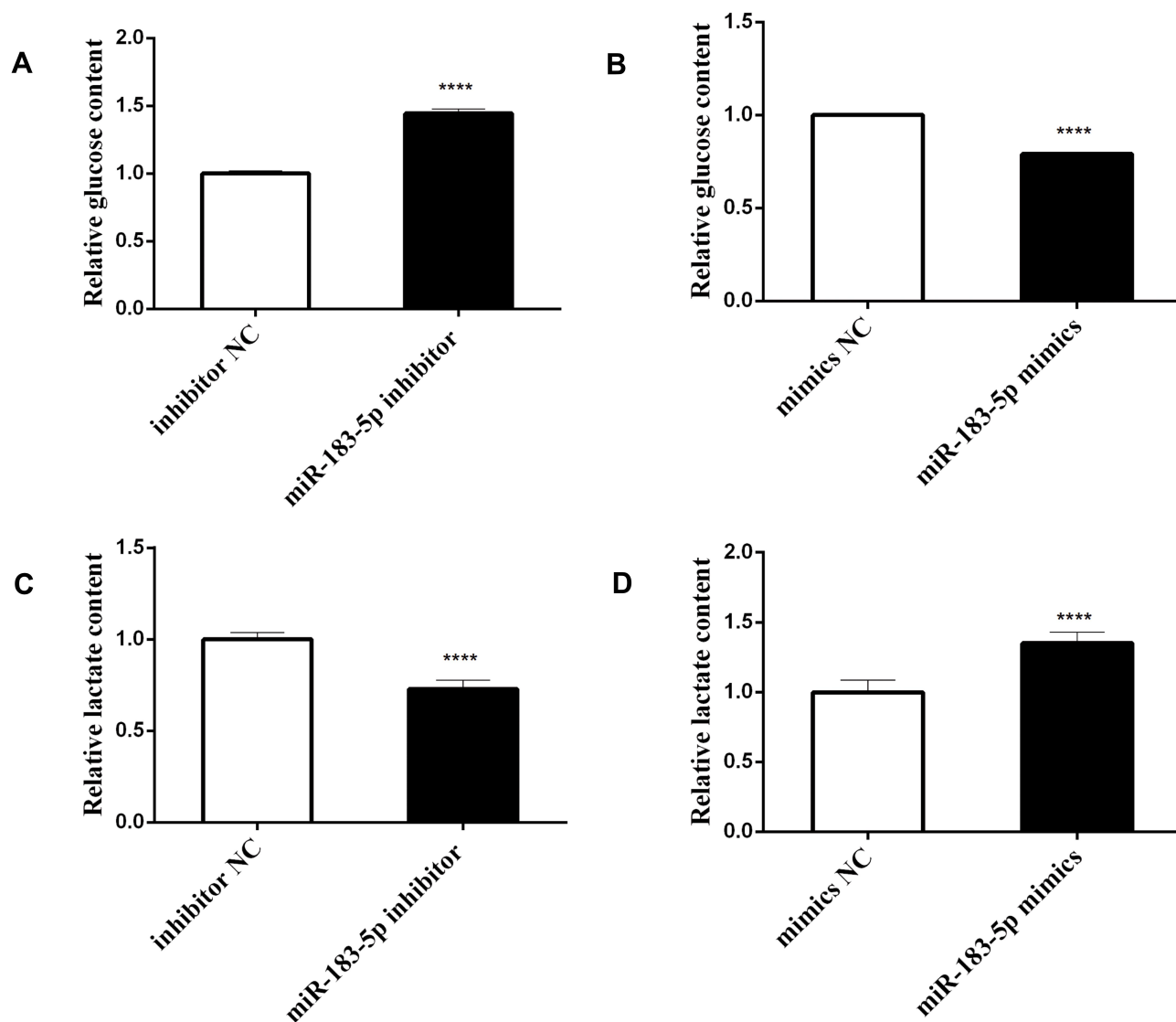
Subsequently, when investigating whether *miR-183-5p* could modulate glucose metabolism in HepG2 cells, we found that the glucose content was increased by 1.5-fold, but lactate production was reduced by 30%, in the miR-183-5p inhibitor-treated HepG2 cells compared to the values in inhibitor NC-treated HepG2 cells (Figure 3A and C). In contrast, overexpression of miR-183-5p reduced the glucose content and increased the lactate production (Figure 3B and D). Furthermore, it was observed that the expression of PKM2, HK2, LDHA and GLUT1 (related to

aerobic glycolysis) was lower in miR-183-5p inhibitor-treated HepG2 cells compared with those in inhibitor NC-treated cells (Figure 4A, C and D); compared with mimics NC, the expression of PKM2, HK2, LDHA and GLUT1 was significantly higher (Figure 4B, E and F).

## PTEN is a Direct Downstream Target of miR-183-5p

To determine how *miR-183-5p* influenced aerobic glycolysis in HepG2 cells, we predicted that *PTEN* is a potential target gene of *miR-183-5p*, using miRDB and TargetScan, which has been demonstrated in the study of lung cancer.<sup>24</sup>

## HepG2

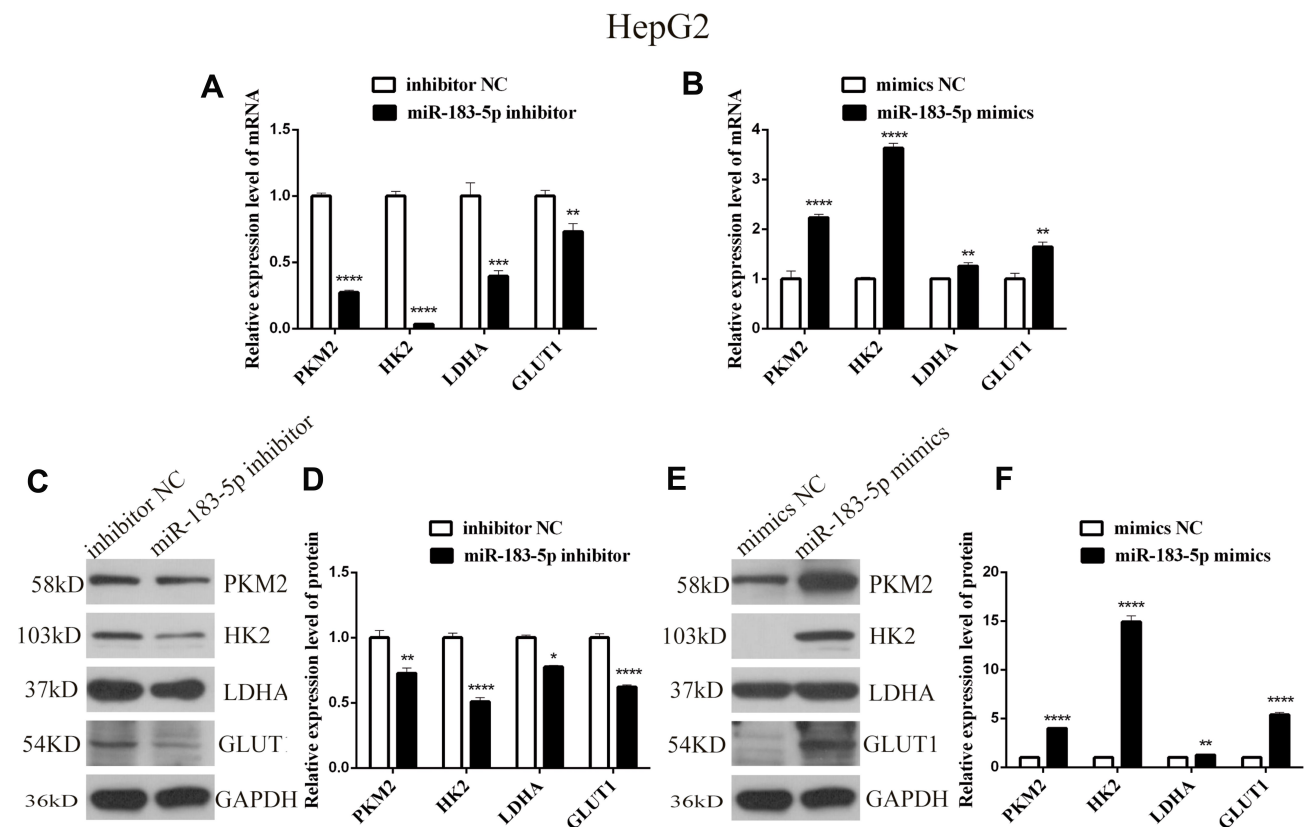


**Figure 3** Effect of aerobic glycolysis in HepG2 cells after transfection with miR-183-5p inhibitor and mimics. **Notes:** (A and B) Glucose content. (C and D) Lactate content. n=3, Student's t-test. \*\*\*\*P<0.0001.

Subsequently, qPCR and Western blotting were performed to test the level of PTEN in transfected HepG2 cells. The results revealed that the expression of PTEN was increased in miR-183-5p inhibitor-treated HepG2 cells compared to that in inhibitor NC-treated HepG2 cells (Figure 5A, C and D). In addition, miR-183-5p mimics dramatically decreased the mRNA and protein levels of PTEN in HepG2 cells compared with mimics NC (Figure 5B, E and F); compared with inhibitor NC, the expression of PTEN was higher.

### *miR-183-5p* Promotes Hepatocellular Carcinoma Aerobic Glycolysis Through Activating Akt/mTOR Signaling

Because *PTEN* is a major negative regulator of the Akt/mTOR pathway, *miR-183-5p* may target *PTEN* in HepG2 cells; thus, we examined Akt, p-Akt and mTOR levels. The expression of Akt, p-Akt and mTOR was much lower in miR-183-5p inhibitor-treated HepG2 cells than in inhibitor NC-treated cells (Figure 6A, C and D). In contrast, the expression of Akt, p-Akt and mTOR increased



**Figure 4** mRNA and protein expression levels of genes related to aerobic glycolysis in HepG2 cells transfected with miR-183-5p inhibitor and mimics.

**Notes:** (A and B) mRNA levels of PKM2, HK2, LDHA and GLUT1 in HepG2 cells, as suggested by qPCR. (C–F) Protein levels of PKM2, HK2, LDHA and GLUT1 in HepG2 cells, as suggested by Western blot analysis. n=3, Student's *t*-test. \*\*\*\**P*<0.0001, \*\*\**P*<0.001, \*\**P*<0.01, \**P*<0.05.

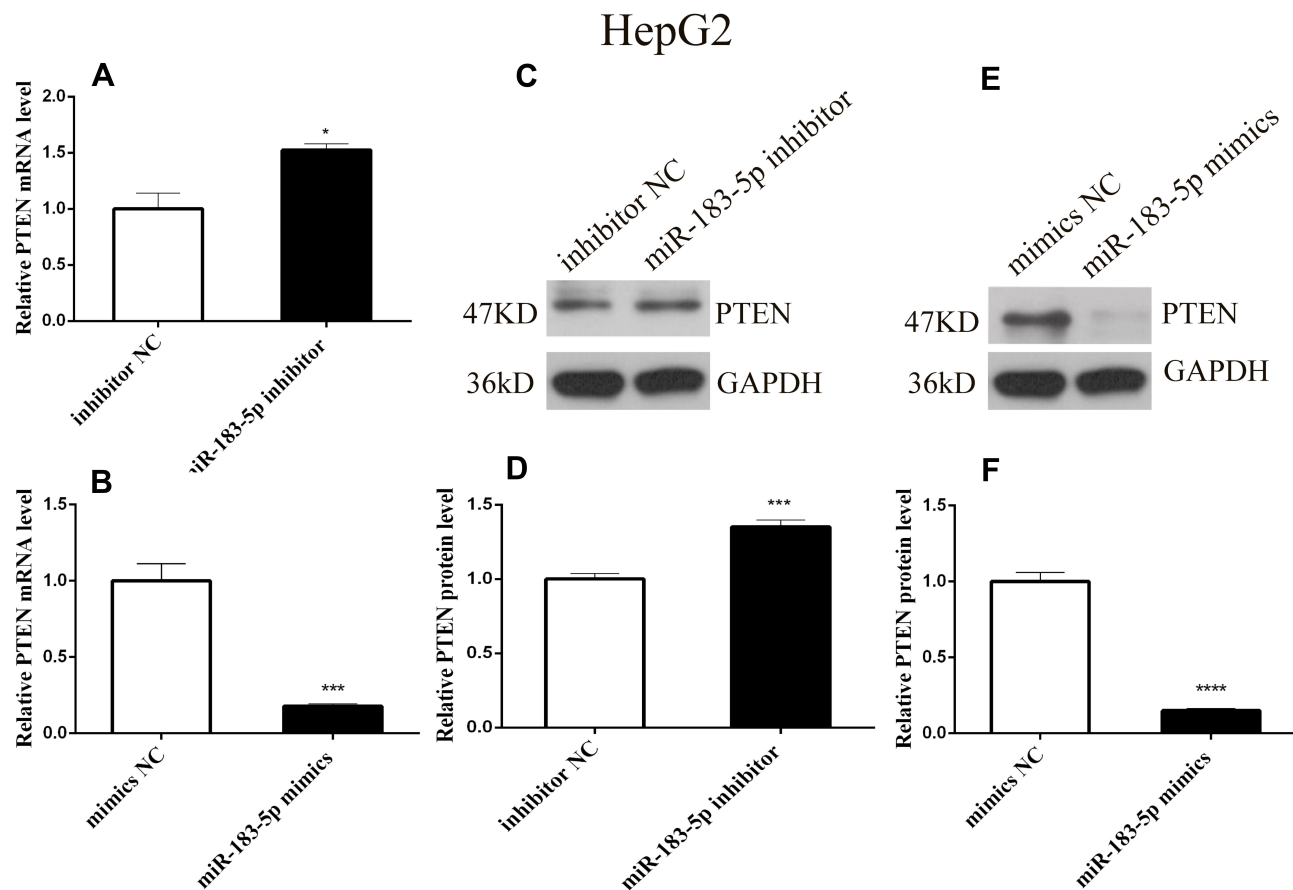
significantly in miR-183-5p mimics compared with mimics NC (Figure 6B, E and F).

## Discussion

The Warburg effect (increased aerobic glycolysis and impaired oxidative phosphorylation) is a major abnormal metabolic feature in cancer, which may also play an important role in biological processes such as tumorigenesis, proliferation, metastasis and drug resistance.<sup>25</sup> The dysregulation of glucose metabolism in cancer is coordinated by genetic changes, including activation of oncogenes but inhibition of oncosuppressor genes. Therefore, understanding the mechanism of aerobic glycolysis disorder in cancer cells is essential for targeted tumor therapy.<sup>26,27</sup> Increasing evidence demonstrates that miRNAs play a vital role in the regulation of HCC aerobic glycolysis.<sup>28–30</sup> Up-regulated *miR-183-5p* in HCC promotes the progress of HCC.<sup>19</sup> This is in line with our preliminary research, showing that miR-183-5p inhibitor significantly inhibited the invasion

and migration of HepG2 cells. Given that aerobic glycolysis is the foundation of invasion and metastasis, our further studies suggest that *miR-183-5p* could promote glucose uptake and lactate secretion.

Our results showed that the expression of glycolytic regulators (PKM2, HK2, LDHA and GLUT1) was positively correlated with the expression of *miR-183-5p* in HepG2 cells, which plays an important role in the process of glycolysis. Overexpressed GLUT1 in liver cancer cells accelerates the uptake of glucose,<sup>31</sup> and several key enzymes related to glycolysis, such as hexokinase (*HK*),<sup>32</sup> pyruvate kinase 2 (*PKM2*)<sup>33</sup> and lactate dehydrogenase A (*LDHA*)<sup>34</sup> in HCC, consistent with an increasing glycolysis process. This process not only provides the ATP and intermediates needed for HCC cell proliferation, but also leads to the accumulation of a large amount of lactic acid to create an acidic tumor microenvironment for cancer invasion and metastasis.<sup>35</sup>



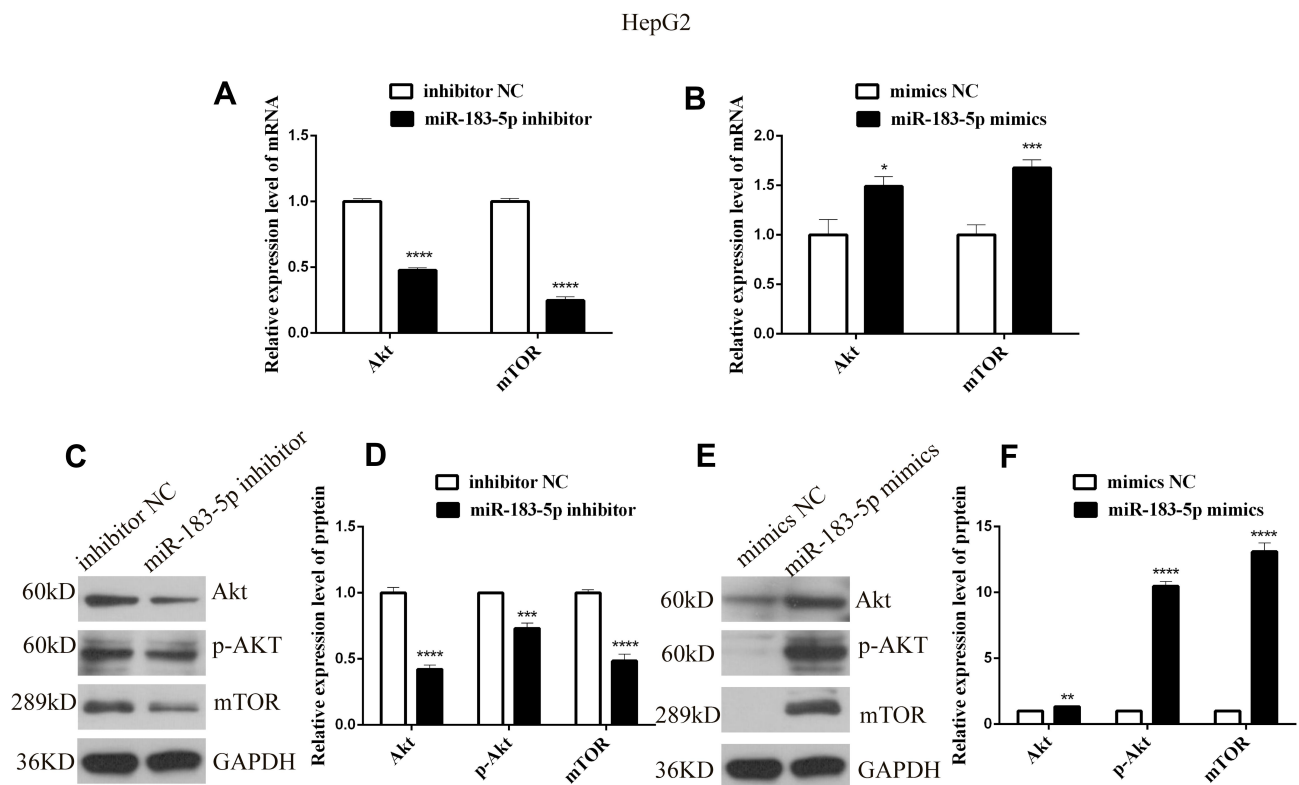
**Figure 5** *PTEN* is a potential target gene of *miR-183-5p*.

**Notes:** (A and B) mRNA levels of *PTEN* in HepG2 cells, as suggested by qPCR. (C–F) Protein levels of *PTEN* in HepG2 cells, as suggested by Western blot analysis.  $n=3$ , Student's *t*-test. \*\*\*\* $P<0.0001$ , \*\*\* $P<0.001$ , \* $P<0.05$ .

In order to reveal the possible mechanism by which *miR-183-5p* promotes aerobic glycolysis in HepG2 cells, we examined the changes in the PTEN/Akt/mTOR pathway. It can be found from our data that the expression of PTEN is negatively correlated with *miR-183-5p*, while Akt, p-Akt and mTOR are positively correlated with *miR-183-5p*. This finding is consistent with previous research showing that the expression of *PTEN* is down-regulated in HCC cells, while the expression of *Akt* and *mTOR* is up-regulated.<sup>36</sup> *PTEN* is a specific protein tyrosine phosphatase and an important tumor suppressor, and negatively regulates and inhibits the Akt/mTOR signaling pathway.<sup>37</sup> Akt is one of the most common activated protein kinases in human cancers and is closely related to energy metabolism in cancer cells.<sup>38</sup> Meanwhile, Akt activates mTOR by regulating ATP and AMPK activity.<sup>39</sup> mTOR, a highly conserved serine–threonine kinase, is an important intracellular energy-sensing molecule that can respond to a variety of nutritional signals.<sup>40</sup>

These findings suggest that *miR-183-5p* may promote HCC migration and invasion via increasing aerobic glycolysis through targeting PTEN and then activating Akt/mTOR signaling. These findings outline the importance of *miR-183-5p* in the Warburg effect and HCC tumorigenesis. Therefore, blocking this specific pathway may provide a novel approach for HCC therapeutics. Our project team will further use Akt inhibitors or PTEN-overexpressing vectors in liver cancer cell lines overexpressing *miR-183-5p* to fully explain whether *miR-183-5p* can affect the aerobic glycolysis process through the PTEN/Akt/mTOR pathway. As the metabolic pathway is composed of complex networks and the tumor microenvironment in the human body is changeable, the regulatory mechanism of aerobic glycolysis needs further intensive research in vivo.





**Figure 6** mRNA and protein expression levels of genes related to Akt/mTOR in HepG2 cells transfected with miR-183-5p inhibitor and mimics. **Notes:** (A and B) mRNA levels of Akt and mTOR in HepG2 cells, as suggested by qPCR. (C-F) Protein levels of Akt, p-Akt and mTOR in HepG2 cells, as suggested by Western blot analysis. n=3, Student's ttest. \*\*\*\* $p < 0.0001$ , \*\*\* $p < 0.001$ , \*\* $p < 0.01$ , \* $p < 0.05$ .

## Abbreviations

HCC, hepatocellular carcinoma; miRNA, microRNA; PTEN, phosphatase and tensin homolog deleted on chromosome ten; Akt, protein kinase B; mTOR, mammalian target of rapamycin; PKM2, pyruvate kinase 2; HK2 hexokinase 2; LDHA, lactate dehydrogenase A; GLUT1, glucose transporter 1; p-Akt, phospho-protein kinase B.

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## Disclosure

The authors report no conflicts of interest in this work.

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