MiR-590 Suppresses Proliferation and Induces Apoptosis in Pancreatic Cancer by Targeting High Mobility Group A2

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Abstract

Background: Pancreatic ductal adenocarcinoma is a common malignancy with high morbidity. MicroRNAs have been demonstrated to be critical posttranscriptional regulators in tumorigenesis. This study aimed to investigate the effect of microRNA-590 on the proliferation and apoptosis of pancreatic ductal adenocarcinoma.

Material and Methods: The expression of microRNA-590 and high mobility group AT-hook 2 were examined in clinical pancreatic ductal adenocarcinoma tissues. Pancreatic ductal adenocarcinoma cell line Capan-2 was employed and transfected with microRNA-590 mimics or inhibitor. The correlation between microRNA-590 and high mobility group AT-hook 2 was verified by luciferase reporter assay. Cell viability and apoptosis were detected by MTT and flow cytometry assay. The protein level of high mobility group AT-hook 2, AKT, p-AKT, mTOR, and phosphorylated mTOR were analyzed by Western blotting.

Results: MicroRNA-590 was found to be negatively correlated with the expression of high mobility group AT-hook 2 in pancreatic ductal adenocarcinoma tissues. Further studies identified high mobility group AT-hook 2 as a direct target of microRNA-590. Moreover, overexpression of microRNA-590 downregulated expression of high mobility group AT-hook 2, reduced cell viability, and promoted cell apoptosis, while knockdown of miR-590 led to an inverse result. MicroRNA-590 also suppressed the phosphorylation of AKT and mTOR without altering total AKT and mTOR levels.

Conclusion: Our study indicated that microRNA-590 negatively regulates the expression of high mobility group AT-hook 2 in clinical specimens and in vitro. MicroRNA-590 can inhibit cell proliferation and induce cell apoptosis in pancreatic ductal adenocarcinoma cells. This regulatory effect of microRNA-590 may be associated with AKT signaling pathway. Therefore, microRNA-590 has the potential to be used as a biomarker for predicting the progression of pancreatic ductal adenocarcinoma.

Keywords
miR-590, HMGA2, pancreatic cancer, proliferation, apoptosis

Abbreviations
mRNA, messenger RNA; PDAC, pancreatic ductal adenocarcinoma; HMGA2, High mobility group AT-hook 2; miR, microRNA; 3′UTR, 3′untranslated region; PCR, polymerase chain reaction; 3′UTR, 3′untranslated region.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a common malignancy and the fifth cause of cancer-related mortality in developed countries.1,2 Although the treatment improved rapidly, PDAC still remains one of the most malignant cancer with high mortality rate, showing an unsatisfactory status.3 According to the report, nearly 80% of patients with locally advanced or metastatic diseases have poor prognosis.4,5 Therefore, exploring the
molecular interactions occurred in the initiation and progression of PDAC will be helpful in developing effective therapies.

High mobility group AT-hook 2 (HMGA2) is a member of HMGA family, which comprises the high mobility group AT-hook1 and high mobility group AT-2 proteins. The HMGA family proteins are characterized by their ability to bind to specific regions of DNA sequences rich in adenine and thymine. Among the HMGA family proteins, HMGA2 is reported to be an oncofetal protein that is hardly expressed in the differentiated tissues whereas is highly expressed in a variety of tumors. Notably, it has been verified that aberrant expression of HMGA2 is highly correlated with malignancies, including cancers of lung, breast, liver, kidney, and colon. Recent studies showed that the expression of HMGA2 positively related to tumor size and progression of PDAC; moreover, high level of HMGA2 may lead to poor prognosis, which implied that HMGA2 may play an important role in the tumorigenesis and progression of PDAC.

MicroRNAs (miRNAs or miRs) are a group of small non-coding RNA molecules, containing about 20 nucleotides in length, which posttranscriptionally regulate the target genes by binding to their 3’ untranslated region (3’UTR). Accumulating studies have confirmed that miRNAs are widely involved in biological processes. Abnormal expression of miRNAs may contribute to tumorigenesis and malignance through the modulation of tumor suppressor genes. For example, miR-221 promotes metastasis of PDAC by targeting PTEN-Akt, miR-200a regulates the proliferation and metastasis of pancreatic cancer through modulating DEK gene. miR-543 is downregulated in colorectal cancer samples and acts as tumor suppressor by targeting KRAS, MTA1, and HMGA2.

In the present study, we observed the negative relationship between the expression of miR-590 and HMGA2 in PDAC tumor tissues and identified HMGA2 as a direct downstream target of miR-590. Our study demonstrated the regulatory effect of miR-590 on the proliferation and apoptosis of PDAC cells through downregulation of HMGA2, suggesting that miR-590 may be used as a potential therapeutic target of PDAC.

**Cell Lines and Cell Culture**

Human pancreatic cancer cell lines Capan-2 were purchased from Cell Bank of Type Culture Collection of Chinese Academy of Sciences and cultured in minimal Roswell Park Memorial Institute 1640 medium (Gibco) supplemented with 10% fetal bovine serum (Gibco), 2 mM L-glutamine, 100 U/mL of penicillin G, and 100 mg/mL of streptomycin (Biofavor Biotech) at 37 °C under normoxic conditions (5% CO2, 95% O2).

**Transfection and Plasmid Construction**

Capan-2 cells were seeded at a density of 1.0 × 10⁶ cells/mL. After 6 hours of incubation, cells were transfected with miR-590 mimics, miR-590 inhibitors, and their negative controls (Biofavor Biotech) by using Lipofectamine 2000 (Invitrogen) according to manufacturer’s instructions. Cells were provided a 24-hour starvation for further analyses before reaching a confluence of 90%. The wild-type sequence of the HMGA2 3’UTR containing predicted miR-590 binding sites was amplified from Capan-2 cells by polymerase chain reaction (PCR). Then, both wild-type and mutant sequences were subcloned into a psiCHECK-2 vector (Promega).

**Luciferase Reporter Assays**

For luciferase reporter assay, Capan-2 cells were seeded into 24-well plate and then co-transfected with miR-590 mimics and HMGA2-3’UTR-luciferase plasmids. Following culture for 48 hours, cells were collected and lysed. The luciferase activity was measured by a Dual-Luciferase Reporter Assay System (Promega). Each experiment was performed in triplicate.

**Western Blotting**

Capan-2 cells were collected and lysed in radioimmunoprecipitation buffer (Beyotime). The protein concentration was determined using a bicinchoninic acid assay (Beyotime). Briefly, equivalent weights of protein samples (40 μg/lane) were separated on 10% sodium dodecyl sulfate–polyacrylamide gel electrophoresis and subsequently electrotransferred onto polyvinylidene fluoride membranes (Bio-Rad). Subsequently, all membranes were incubated with the following primary antibodies against HMGA2 (ab97276; Abcam), AKT (sc-8312; Santa Cruz), phosphorylated AKT (sc-33437; Santa Cruz), mTOR (sc-8319; Santa Cruz), and phosphorylated mTOR (p-mTOR, sc-101738; Santa Cruz) at 4 °C overnight. After incubation with secondary antibodies for 1 hour at room temperature, all bands were determined using an enhanced chemiluminescence system kit (MultiSciences).

**Quantitative Real-Time PCR**

Total RNA was extracted from clinical specimens and Capan-2 cells using Trizol Reagent (Invitrogen). After that, all RNAs were reversed transcribed into complementary DNA using reverse
tissues, we explored the expression of HMGA2 in the TCGA data portal from Starbase version 2.0. As the result showed in Figure 1A, HMGA2 significantly increased in PDAC tissues when compared to normal tissues (P = .034). Moreover, data from Starbase 2.0 showed that patients with high expression of HMGA2 had a poor overall survival time compared to patients with low HMGA2 expression (Figure 1B). Then, we determined the expression of HMGA2 in PDAC and normal tissues collected from our department (Figure 1E; \( P = .009 \)). The result was in accordance with that from database. On the other hand, database revealed a lower expression of miR-590 in PDAC samples than in paired normal samples (Figure 1C; \( P = .045 \)). Then, we verified that result using tissues from our department in the same way (Figure 1F; \( P = .037 \)). A Pearson correlation analysis was performed, and the result showed that the expression of miR-590 was negatively correlated with HMGA2 expression (Figure 1D).

MicroRNA-590 Directly Regulates the Expression of HMGA2

To further investigate the correlation between miR-590 and HMGA2, a PDAC cell line Capan-2 was employed. We transfected Capan-2 cells with miR-590 mimics or inhibitors and then obtained miR-590 overexpressed or knockdown cells (Figure 2A, \( P = .006 \); Figure 2B, \( P = .013 \)). By using Western blots, we measured the expression of HMGA2. As the data revealed, the expression of HMGA2 was significantly down-regulated in miR-590 overexpressed cells while moderately increased in miR-590 knockdown cells (Figure 2E, \( P = .017 \); Figure 2F, \( P = .032 \)). Subsequently, we predicted that HMGA2 was a downstream target of miR-590 by using open access databases (Targetscan, miRanda, and miRwalk 2.0), and a putative binding site in the 3'UTR of HMGA2 for miR-590 was identified (Figure 2C). To confirm this prediction, a luciferase reporter assay was performed. As the result revealed, the reporter activity of HMGA2 3'UTR was significantly abrogated in miR-590 overexpressed cells. However, this effect was reversed when the putative binding site in the 3'UTR of HMGA2 was mutated (Figure 2D; \( P = .041 \)). Taken together, abovementioned results indicated that miR-590 can negatively regulate the expression of HMGA2 by directly binding to it.

MicroRNA-590 Regulates the Proliferation and Promotes Apoptosis of PDAC Cells

To delineate the role of miR-590 in the proliferation of PDAC cells, MTT assay was performed and the result revealed that the viability of Capan-2 cells transfected with miR-590 mimics were remarkably inhibited when compared with control group, while transfection with miR-590 inhibitors strongly promoted cell viability (Figure 3A, \( P = .029 \); Figure 3B, \( P = .044 \)). Moreover, we investigated the role of miR-590 in the apoptosis of PDAC cells. Data from flow cytometry showed that over-expression of miR-590 caused a significant apoptotic rate compared to the control group and that promotive effect was abrogated by the usage of miR-590 inhibitors (Figure 3C, Table 1. RT-PCR Primer Sequences.

| GENE    | Primer sequences (5’-3’)          |
|---------|-----------------------------------|
| HMGA2   | F: CAAAGGTCGCTGGGCAGCTCCGG       |
|         | R: CCATTCTCATGTTCTGGCTCTTG        |
| miR-590 | F: AAAGATTCCAAGAAGCTAAGGGTG       |
|         | R: CCTAAGTGTTCTTCAAATTGCCTCA     |
| U6 snRNA| F: CTGRGCTTCGGGCACAGCATAACT       |
|         | R: ACCTTCACGAATTGCTGTC            |
| GAPDH   | F: TGAAGGTCGTTGGAACCGATTTGTC      |
|         | R: CATGATGCCATGAAGGTCCACCAC       |

Abbreviations: HMGA2, High mobility group AT-hook 2; miR, microRNA.

Cell Proliferation Assay

The effect of miR-590 on cell viability was determined using an MTT assay. Capan-2 cells were cultured in 96-well plates (2 \( \times 10^3 \) cells per well) for 24, 48, 72, and 96 hours. Then, cells were stained with 10 \( \mu \)L of 5 mg/mL MTT per well (Sigma-Aldrich) for 4 hours at 37 °C. Then culture medium was discarded and 150 \( \mu \)L of dimethyl sulfoxide was added. The absorbance was detected at 490 nm with an ELX-800 spectrometer reader (Bio-Tek Instruments).

Cell Apoptosis Assay

Cell apoptosis was measured by Annexin V-fluorescein isothiocyanate/propidium iodide staining (BD PharMingen) following the manufacturer’s instructions. In brief, Capan-2 cells were collected in 6-well plates at a concentration of \( 10^5 \) cells/mL. Then, Annexin V-fluorescein isothiocyanate (5 \( \mu \)L) and PI (5 \( \mu \)L) were distributed to each well and the cells were incubated in the dark for 15 minutes to undergo flow cytometry (BD LSRII).

Statistical Analysis

All data were presented as means ± standard deviation. Differences were assessed by 2-tailed Student t test and \( \chi^2 \) test as appropriate. \( P \) values of .05 or less were considered as statistically significant. Each experiment was performed in triplicate. Statistical analyses were carried out using SPSS 20.0 (SPSS Inc).

Results

Expression of miR-590 Negatively Correlates With the Expression of HMGA2 in PDAC Samples

To investigate the expression of HMGA2 in PDAC and normal tissues, we explored the expression of HMGA2 in the TCGA
Taken together, abovementioned results implied that miR-590 may regulate the proliferation and apoptosis of PDAC cells.

**Influence of miR-590 on AKT Signaling Pathway**

To verify whether miR-590 was involved in the regulation of AKT signaling pathway, we analyzed the phosphorylation level of AKT and mTOR. Western blotting was performed, and results showed that overexpression of miR-590 markedly reduced the phosphorylation of AKT \( (P = .025) \) and mTOR \( (P = .039) \). The total level of AKT \( (P = .14) \) and mTOR \( (P = .54) \) remain the same related to the expression of miR-590. These results demonstrated that miR-590 involves in the regulation of AKT signaling pathway, which may be an important factor to the tumorigenesis of Capan-2 cells (Figure 4).

**Discussion**

Pancreatic ductal adenocarcinoma is the fourth cause of cancer-related death among all cancers. The 5-year survival rate of PDAC is just 7% to 8%. Due to its early metastasis and invasion, PDAC is difficult to be diagnosed early until it has developed into advanced stages or distant metastasis. The underlying mechanisms of invasion and metastasis remain to be unfolded. Previous studies have indicated that miRNAs involve in...
multiple biological processes, and they can regulate tumor proliferation and apoptosis in cancer cells by targeting specific genetic markers. Based on these discoveries, we have therefore analyzed and identified miRNAs that regulate the progression of PDAC.

It has been well-known that miRNA regulates gene expression at the posttranscriptional level in the way of translational inhibition and mRNA destabilization. Accumulating studies have reported that miRNAs act as oncosine or tumor suppressor in different cancers. MicroRNA-590 has been reported to be downregulated in breast cancer and suppresses cell survival by targeting sirtuin-1 and deacetylation of P53. It has also been reported that miR-590 acts as a tumor suppressor in osteosarcoma by targeting SOX9. Latest research unfolded that miR-590 can be used as a prognostic biomarker for glioma. However, the role of miR-590 on PDAC and the
molecular mechanism have not been investigated. In the present study, we found a negative correlation between miR-590 and HMGA2 in PDAC tissues. MicroRNA-590 was significantly downregulated in PDAC tissues compared to paired normal tissues, while HMGA2 was remarkably increased in tumors. Subsequently, we verified a binding correlation between miR-590 and HMGA2 via open access bioinformatic databases and identified HMGA2 as a direct downstream target of miR-590 by luciferase reporter assay.

High mobility group AT-hook 2 has been reported to be aberrantly expressed in a variety of cancers and plays a critical role in the regulation of cell growth.\textsuperscript{11,26} Its regulatory effect on cell proliferation and metastasis of tumors may be ascribed to the activation of by tumor growth factor \(\beta\)/Smad3 signaling pathway.\textsuperscript{27,28} In our \textit{in vitro} studies, we observed that overexpression of miR-590 caused a reduction in HMGA2 expression, while knockdown of miR-590 led to a significant increase in HMGA2. These data indicated that miR-590 negatively regulates the expression of HMGA2 in PDAC cells, which is in accordance with the results from clinical specimens.

Previous study has reported that HMGA2 promotes cell proliferation by activating AKT pathway.\textsuperscript{16,29} Based on these

**Figure 3.** MicroRNA-590 regulates the proliferation and apoptosis of PDAC cell line. A, MTT assay was performed to analyze cell viability after the transfection of miR-590 mimics, miR-590 inhibitors. The absorbance value was examined at 24, 48, 72, and 96 hours after transfection. B and C, Flow cytometry was performed 48 hours post-transfection. Apoptotic cell rate was showed in histogram. Data are presented as means \(\pm\) SD of 3 independent experiments (*\(P < .05\) compared to control). PDAC indicates pancreatic ductal adenocarcinoma.
findings, we investigated whether AKT signaling pathway mediated tumor suppression that induced by miR-590. As results showed, overexpressed miR-590 markedly stagnated the phosphorylation of AKT and mTOR rather than total AKT and mTOR expression. Collectively, our data suggested that miR-590 may somehow involve in the regulation of AKT signaling. Moreover, this regulation might be initiated after the modulation of the expression of HMGA2 by miR-590.

Conclusion

In conclusion, our present study indicated that miR-590 may play a critical role in the tumorigenesis of PDAC cells by inducing cell apoptosis and restraining cell proliferation, and this regulatory effect may, at least in part, be ascribed to the modulation of HMGA2 through AKT signaling pathway. These results implied that miR-590 has a potential to be used as a diagnostic biomarker in the progression of PDAC.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Figure 4. Effects of miR-590 on AKT signaling pathway. The protein level of AKT, p-AKT, mTOR, and p-mTOR were examined by western blotting. GAPDH was used as an internal control. Data are presented as means ± SD of 3 independent experiments (*P < .05 compared to control).
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