European Review for Medical and Pharmacological Sciences 2019; 23: 10248-10256

MicroRNA-588 regulates migration capacity and invasiveness of renal cancer cells by targeting EIF5A2

J.-S. DONG[1], B. WU[2], Z.-L. ZHA[2]

[1]Department of Urology Surgery, Lianshui County People's Hospital, Huaian, China
[2]Department of Urology Surgery, Affiliated Jiangyin Hospital of Southeast University Medical College, Jiangyin, China

Abstract. – OBJECTIVE: To investigate whether microRNA-588 was involved in the development and progression of renal cancer, and to explore its possible regulatory mechanisms.

PATIENTS AND METHODS: Tumor tissues excised from renal carcinoma and adjacent normal tissues were selected for the experiment. Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) was performed to analyze the expression level of microRNA-588 in tissue specimens. The relationship between the expression of microRNA-588 and the prognosis of patients with renal cell carcinoma was also evaluated. Subsequently, two renal cancer cell lines, including769-P and 786-O, were selected for functional experiments *in vitro*. Eukaryotic initiation factor 5A2 (pcDNA-EIF5A2) or microRNA-588 mimics was transfected into 769-P cells, respectively. Meanwhile, si-EIF5A2 or microRNA-588 inhibitor was transfected into 786-O cells. After that, the mRNA expression level of EIF5A2 was detected by qRT-PCR. The invasiveness and metastasis abilities of the two cell lines were evaluated via transwell assay. Furthermore, the levels of EIF5A2 and epithelial-mesenchymal transition (EMT)-related proteins were analyzed using Western blot. Luciferase reporter gene assay was used to confirm that microRNA-588 could directly regulate EIF5A2 expression. QRT-PCR and Western blot were performed to explore the mRNA and protein expressions of EIF5A2 in patients with highly or lowly-expressed microRNA-588. The correlation between the two molecules was evaluated using linear analysis. Through the above experiments, it was verified whether microRNA-588 could enhance the invasiveness and metastasis of renal cancer by targeting EIF5A2.

RESULTS: MicroRNA-588 expression in tumor tissues of patients with renal carcinoma was significantly decreased with the increase of tumor diameter and stage. A higher level of microRNA-588 indicated significantly longer overall survival of patients. This suggested that microRNA-588 expression was negatively correlated with the prognosis of patients. Overexpression of microRNA-588 remarkably reduced the invasion and metastasis abilities of 769-P cells, as well as the expressions of EMT-related proteins. However, opposite results were observed in 786-O cells after knockdown of microRNA-588. Reporter gene assay confirmed that microRNA-588 could target bind to EIF5A2. In 769-P cells, up-regulated microRNA-588 significantly inhibited the mRNA and protein expressions of EIF5A2. However, down-regulated microRNA-588 in 786-O cells significantly enhanced the expressions of EIF5A2 at both mRNA and protein levels. Linear analysis verified that microRNA-588 was negatively correlated with EIF5A2 at the mRNA level. Additionally, the up-regulation of EIF5A2 in 769-P cells enhanced the malignancy of cancer cells and the expressions of EMT-related proteins. However, in 786-O cells, opposite results were observed after knockdown of EIF5A2.

CONCLUSIONS: MicroRNA-588 was lowly expressed in renal cancer tissues and cell lines. This might lead to an increase in the protein level of EIF5A2, eventually promoting tumor invasion and metastasis.

Key Words:
MicroRNA-588, EIF5A2, Invasion, Metastasis.

Introduction

Renal cell carcinoma, also known as renal adenocarcinoma or clear cell carcinoma, is a malignant tumor in the urinary system[1]. It is a common malignancy originated from the renal tubular urinary tubular epithelial system, accounting for 80% to 90% of all renal malignant tumors[2]. MicroRNAs (miRNAs) are a type of

Corresponding Authors: Zhenlei Zha, MM; e-mail: zhazhenlei728@163.com

small non-coding RNAs. MiRNAs are involved in post-transcriptional gene regulation, which have become potential biomarkers and molecular targets for cancer therapy. They also participate in various biological processes, such as cell proliferation, apoptosis and invasion and metastasis[3], acting as tumor suppressors or oncogenes[4]. Therefore, up-regulated or down-regulated miRNAs are able to promote or inhibit tumorigenesis. Different miRNA profiles can be found in different renal cell tumor histology[5]. Furthermore, differentially expression of miRNAs in tumor tissues plays a vital regulatory role in the process of carcinogenesis. Previous reports[5] have confirmed that the expression of microRNA-203 and microRNA-424 is significantly different between clear cell and papillary renal cell carcinoma. In addition, miR-210 and let-7 can be used to distinguish between type 1 and type 2 renal cell carcinoma[6]. Although miRNAs play an important role in promoting the initiation and progression of renal cell carcinoma (RCC), the molecular mechanisms remain unclear. One notable feature of cell epithelial-mesenchymal transition (EMT) is loss of homotypic adhesion and acquisition of mesenchymal characteristics[7]. EMT plays a catalytic role in regulating the metastasis and invasion of renal cancer cells. This can be verified by a decrease in E-cadherin level and an increase in N-cadherin and vimentin levels. However, whether it is associated with microRNA-588 has not been fully elucidated. Eukaryotic initiation factor 5A2 (EIF5A2) is recognized as an oncogenic protein that can promote cancer growth and metastasis. It has been proved that EIF5A2 is a downstream target of microRNA-588[8]. In this study, microRNA-588 inhibited cell migration and EMT proliferation through inhibiting EIF5A2 expression. In this study, we examined the expression of microRNA-588 in tumor tissues and adjacent normal tissues of renal cancer patients. We found that microRNA-588 was lowly expressed in tumor tissues or cells. However, up-regulation of microRNA-588 in renal cancer cells significantly inhibited the migration and invasion abilities of cells. Further studies indicated that EIF5A2 was a target gene for microRNA-588 in renal cancer cells. Therefore, this study revealed the role and specific molecular mechanism of microRNA-588 in renal cancer. Our findings might provide a basis for molecular diagnosis and medical targeted therapy of renal cell carcinoma in the future.

Patients and Methods

Patients

Tumor tissues and adjacent normal tissues were obtained from patients with renal cell carcinoma. All patients received no treatment of adjuvant chemotherapy such as radiotherapy and chemotherapy. Post-operative specimens were confirmed as renal tumor by pathology. Control specimens were collected from para-cancerous tissues of the same patients (at least 3 cm away from the surgical margin). Meanwhile, no tumor cells were found after pathological examination. All specimens were frozen in liquid nitrogen and then stored in a -80°C refrigerator for use. Our study was approved by the Ethics Committee of Lianshui County People's Hospital.

RNA Extraction and Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR)

Total RNA was extracted from cells and tissues by TRIzol reagent (Invitrogen, Carlsbad, CA, USA), chloroform and isopropanol. The concentration of extracted RNA was measured using a micronuclear quantifier, followed by storage at -80°C. Subsequently, RNA samples were reverse transcribed into complementary deoxyribose nucleic acid (cDNA), and SYBR Green (Invitrogen, Carlsbad, CA, USA) method was used for PCR detection. Specific PCR amplification conditions were as follows: pre-denaturation at 94°C for 5 min, followed by 40 cycles at 94°C for 30 s, 55°C for 30 s, and 72°C for 1 min and 30 s. Primer sequences used in this study were as follows: EIF5A2, F: 5'-CTACGGAACCAATCCTTACC-3', R: 5'-CTCCGATGTGTAAGACTGGA-3'; microRNA-588, F: 5'-GGATGTAAACATCCTCGACTG-3', R: 5'-ATTGCGTGTCAGTGGAGGCG-3'; U6: F: 5'-GCTTCGACAGCACACTACCT-3', R: 5'-CGCTTCAGAATTTGCGTGTCAT-3'; GAPDH: F: 5'-CGCTCTCTGCTCCTCCTGTTC-3', R: 5'-ATCCGTTGACTCCGACCTTCAC-3'.

Cell Culture and Transfection

Renal cancer cell lines, including HK-2, 786-O and 769-P, were purchased from American Type Culture Collection (ATCC) (Manassas, VA, USA). All cells were cultured in RPMI-1640 complete medium (HyClone, South Logan, UT, USA) containing 10% fetal bovine serum (FBS) (Gibco, Rockville, MD, USA) at 37°C with 5% CO_2. Well-developed renal cancer cells were se-

lected and counted. Next, cells were seeded into 6-well plates at a density of about 10^4/well. After cell density reached about 75-85%, cell transfection was performed according to the instructions of Lipofectamine™ 2000 (Invitrogen, Carlsbad, CA, USA). Briefly, the mixture was prepared, and 1.5 mL of serum-free medium and 500 μL of the mixture were added to cells. After 4-6 h of culture in a 37°C incubator, complete medium was added. After transfection of mimics or inhibitor of microRNA-588, pcDNA- EIF5A2 or si-EIF5A2 of EIF5A2 for 24-48 h, the cells were selected for subsequent experiments.

Cell Migration

24 h before transwell assay, stable transfected cells were seeded into 24-well transwell chamber at a density of 3×10^4 cells/well. 100 μL of serum-free medium was added to the lower chamber. Meanwhile, 500 μL of serum-containing medium was added to the upper chamber. After the 24-well chamber plate was placed in a well-regulated 37°C thermostat closed incubator for 12 h, 3 mL of 0.1% crystal violet staining solution was added to the chamber. After that, the plate was incubated for 30 min at room temperature to be fully stained. After rinsing twice with pre-warmed phosphate-buffered saline (PBS) solution, the cells in the upper layer of the chamber were wiped with a cotton swab. The chamber was then placed under a 10×20 microscope. Finally, migrated cells of each group were observed, photographed and counted.

Cell Invasiveness

Fibronectin (FN) was diluted to a final concentration of 100 μg/mL. Matrigel (BD Biosciences, Franklin Lakes, NJ, USA) was diluted 1:9 with serum-free medium. The bottom of each chamber was coated with 50 μL of FN and placed in a clean bench for 2 h to air dry. The inside of the chamber was coated with 100 μL of Matrigel and placed in an incubator overnight. Cell density was then adjusted to 1×10^6 cells/ml. Subsequently, 100 μL of cell suspension was seeded into the upper chamber. Meanwhile, 600 μL of medium containing 10% fetal bovine serum (FBS) was added to the lower chamber. After incubation for 24 h, the cells were fixed with methanol, stained with trypan blue, and washed 3 times with PBS. After that, the cells in the upper chamber were wiped with a cotton swab. Finally, invading cells were photographed under a microscope, and the number of cells was calculated.

Western Blot

Transfected cells were first seeded into 6-well plates containing 2.5 mL of medium, which were collected after 72 h of culture. Total protein in cells of each group was extracted, and the concentration of protein samples was determined using the bicinchoninic acid (BCA) protein quantification kit (Pierce, Rockford, IL, USA). After separated by sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE), the protein samples were transferred onto polyvinylidene difluoride (PVDF) membranes (Millipore, Billerica, MA, USA). After blocking for 2 h at room temperature, the membranes were incubated with specific primary antibodies overnight. On the next day, the membranes were incubated with corresponding secondary antibody at room temperature for 2 h. Finally, immuno-reactive bands were exposed by enhanced chemiluminescence method.

Luciferase Reporter Gene Assay

Renal cancer cells (3×10^5) were first seeded into 24-well plates. Cells in each well were co-transfected with microRNA-588 mimics and wild-type or mutant psiCHECK-2 vector using Lipofectamine 2000 (Sigma-Aldrich, St. Louis, MO, USA). 24 h after transfection, the cells were harvested. Luciferase activity was measured using a dual luciferase reporter assay system.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 19.0 statistical software (IBM, Armonk, NY, USA) was used for all statistical analysis. Measurement data were expressed as mean ± standard deviation. *t*-test was used to compare the difference between two groups. Chi-square test was used to analyze the correlation between clinical information and NKILA expression. $p<0.05$ was considered statistically significant.

Results

MicroRNA-588 Expression was Significantly Reduced in Renal Tumor Tissues

To investigate whether microRNA-588 was differentially expressed in tumor tissues of patients with renal cell carcinoma, we selected paired tumor tissues and adjacent normal tissues for experiments. The results revealed that the level of microRNA-588 in renal tumor tissues was significantly lower than of normal tissues (Figure 1A).

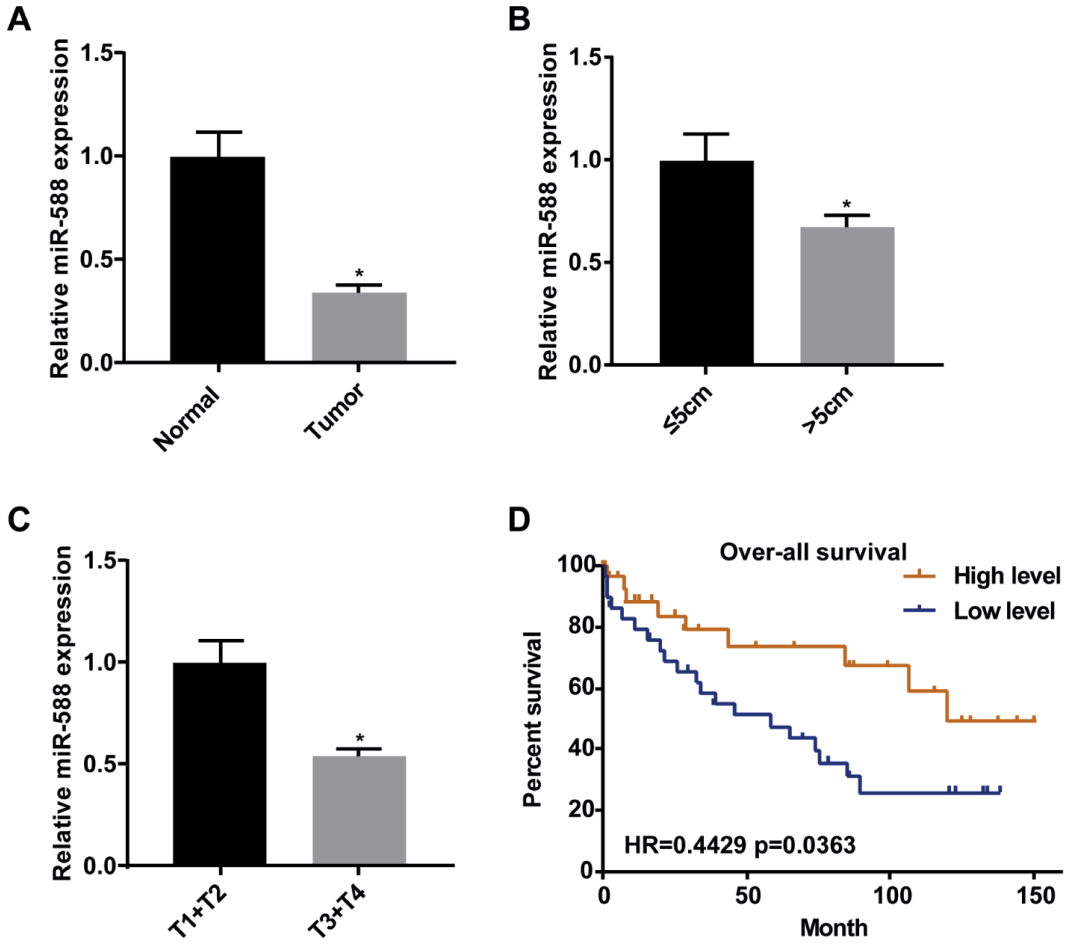

Figure 1. MiR-588 is lowly expressed in renal cell carcinoma tissues. **A,** MiR-588 expression in renal cell carcinoma tissues was significantly lower than of normal kidney tissues. **B,** MiR-588 expression in tumor tissues that were larger than 5 cm in diameter was significantly lower than those with a diameter less than or equal to 5 cm. **C,** MiR-588 expression in tumor tissues of patients with T3+T4 stage was notably lower than those with T1+T2 stage. **D,** The overall survival rate of patients with higher microRNA-588 level was obviously longer than that of patients with lower microRNA-588 level.

Meanwhile, the expression of microRNA-588 in tumor tissues that were larger than 5 cm in diameter was obviously lower than those with a diameter less than or equal to 5 cm (Figure 1B). In addition, microRNA-588 level in tumor tissues of patients with T3+T4 stage was notably lower than those with T1+T2 stage (Figure 1C). Overall survival analysis showed that the overall survival rate of patients with higher microRNA-588 level was obviously longer than that of patients with lower microRNA-588 level (Figure 1D).

Knock-Down of microRNA-588 Promoted Migration Capacity and Invasiveness of Renal Cancer Cells

To test whether microRNA-588 was involved in promoting the migration capacity and invasiveness of renal cancer cells, normal renal epithelial cells (HK-2) and renal cancer cells (including 786-O and 769-P) were selected for experiments. The results suggested that microRNA-588 expression in two renal cancer cell lines was conspicuously lower than that of normal renal epithelial cells (Figure 2A). Over-expression of microRNA-588 in renal cancer cells significantly increased microRNA-588 level (Figure 2B). However, knocking down microRNA-588 remarkably reduced microRNA-588 expression (Figure 2C). Over-expression of microRNA-588 in 769-P cells significantly inhibited cell invasion and metastasis. The opposite results were observed after knock-down of microRNA-588 (Figure 2D). Meanwhile, up-regulation of microRNA-588 in 769-P cells obviously increased the protein expression of E-Ca, while decreased the expressions of N-Ca and Vimentin (Figure 2E). However, opposite

results were observed after microRNA-588 was down-regulated. The above results indicated that knockdown of microRNA-588 could promote the migration and invasiveness of renal cancer cells, as well as increase the expression of EMT-related proteins. This might eventually increase the malignancy of renal cancer cells.

MicroRNA-588 Could Target EIF5A2 to Regulate its Expression

Luciferase reporter gene assay confirmed that microRNA-588 could target bind to EIF5A2 (Figure 3A). In renal cancer cells, up-regulation of microRNA-588 inhibited the mRNA and protein expressions of EIF5A2 (Figure 3B), while knockdown of microRNA-588 increased EIF5A2 expressions at both mRNA and protein levels (Figure 3C, 3D). These results demonstrated that microRNA-588 could bind to EIF5A2 and regulate its expression.

A Negative Correlation Between microRNA-588 and EIF5A2 Expression in Renal Cell Carcinoma

A certain number of patients with renal cell carcinoma were selected. These patients were divided into two groups according to the expression of microRNA-588 in tumor tissues, including: high microRNA-588 expression group and low microRNA-588 expression group. The results

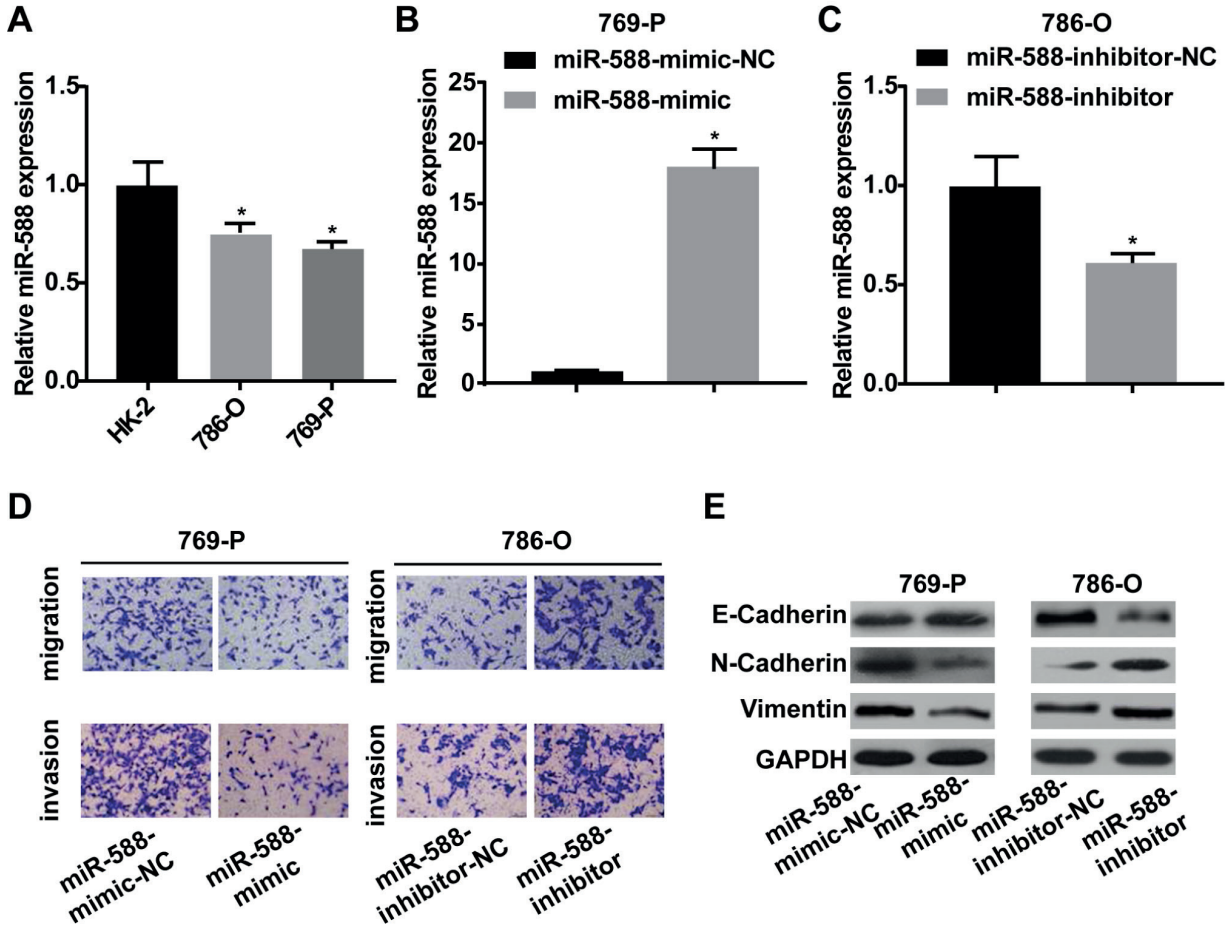

Figure 2. Low expression of miR-588 promotes migration and invasion of renal cancer cells. **A,** MiR-588 expression in renal cancer cell lines (including 786-O and 769-P) was significantly lower than of normal renal epithelial cells HK-2. **B,** MiR-588 was overexpressed in 769-P cells. **C,** After knockdown of miR-588 in 786-O cells, the expression of miR-588 significantly decreased. **D,** After overexpression of miR-588 in 769-P cells, the migration and invasion abilities of cells significantly decreased. After miR-588 knockdown in 786-O cells, the migration and invasion abilities of cells were significantly enhanced (magnification: 40×). **E,** After overexpression of miR-588 in 769-P cells, the protein expression of E-Cadherin was elevated, whereas N-Cadherin and Vimentin was reduced. After miR-588 knockdown in 786-O cells, the protein level of E-Cadherin decreased, while the protein levels of N-Cadherin and Vimentin were significantly elevated.

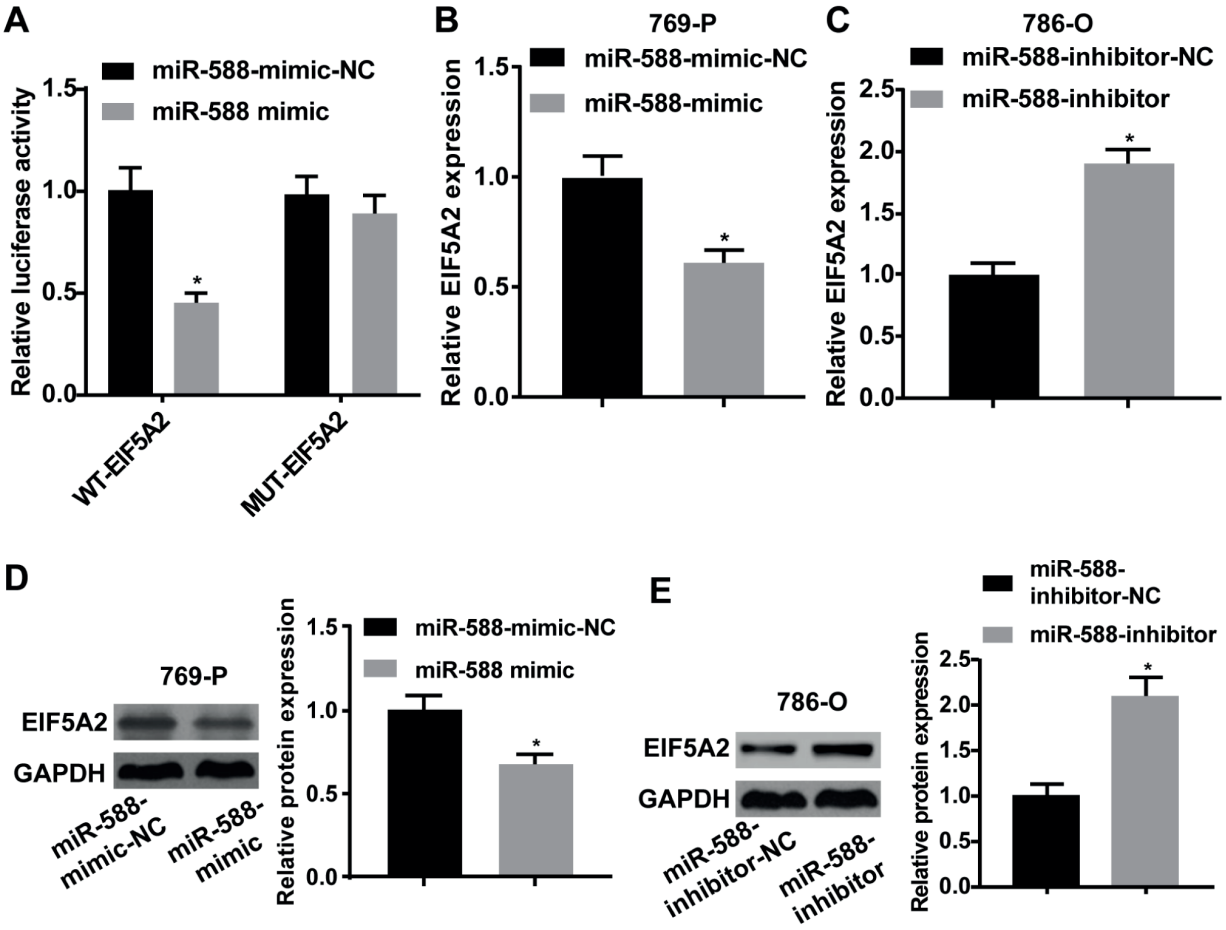

Figure 3. MiR-588 can target bind to EIF5A2. **A,** Luciferase reporter gene assay detected that after overexpression of miR-588, wild-type EIF5A2 could be quenched by fluorescence. **B,** After overexpression of miR-588 in 769-P cells, the expression of EIF5A2 decreased significantly. **C,** After knockdown of miR-588 in 786-O cells, the mRNA expression of EIF5A2 significantly increased. **D,** After overexpression of miR-588 in 769-P cells, the protein expression of EIF5A2 decreased significantly. **E,** After knocking down miR-588 in 786-O cells, the protein expression of EIF5A2 remarkably increased.

revealed that the mRNA (Figure 4A) and protein expressions (Figure 4B and 4C) of EIF5A2 were conspicuously lower in tumor tissues of patients with higher microRNA-588 level than those with lower level. Linear analysis revealed a negative correlation between microRNA-588 and EIF5A2 expression in tumor tissues of renal cancer patients (Figure 4D). These results indicated that microRNA-588 was negatively correlated with the expression of EIF5A2 in renal cancer tumor tissues.

High Expression of EIF5A2 Could Promote the Migration Capacity and Invasiveness of Renal Cancer Cells

To investigate whether EIF5A2 was involved in the migration capacity and invasiveness of renal cancer cells, 769-P and 786-O cell lines were treated with high expressed-plasmid and siRNA of EIF5A2, respectively. Over-expression of EIF5A2 in 769-P cells significantly increased the expression of EIF5A2 and EMT-related proteins. Meanwhile, it significantly promoted cell invasiveness and metastasis. However, the opposite results were observed after EIF5A2 was silenced (Figure 5A-5D). The above results indicated that up-regulation of EIF5A2 could promote the migration capacity and invasiveness of renal cancer cells.

Discussion

Renal cell carcinoma is one of the most invasive human tumors in the world, accounting for

about 2-3% of adult malignancies[9]. The typical "triple syndrome" of renal cancer is characterized by hematuria, back pain and renal mass[10]. Statistical analysis indicated that renal cancer ranks second in urogenital tumors in China, second only to bladder tumors. MicroRNAs, also known as miRNAs, are a small group of non-coding RNAs. They have also been identified as important components of non-coding RNAs, which are involved in cancer development and progression. MiRNAs have the property of regulating gene expression by altering the 3'-UTR region of target gene that causes mRNA degradation[11]. More and more evidences have demonstrated that miRNAs are associated with the development of human cancers. Meanwhile, various miRNAs are involved in the progression of oxidative stress, cell proliferation, cell cycle and renal cancer[12]. In addition, the expression profiles of miRNAs are considered to be more accurate in classifying different cancer types[13,14]. Studies have indicated that miRNA can inhibit carcinogenesis by inhibiting tumor suppressor genes. They can also act as tumor suppressors by down-regulating oncogenes[15]. It is worth noting that miRNAs have been found to be abnormally expressed in several tumors, including renal cell carcinoma[16]. A recent study has revealed that microRNA-588 is down-regulated in lung cancer[17]

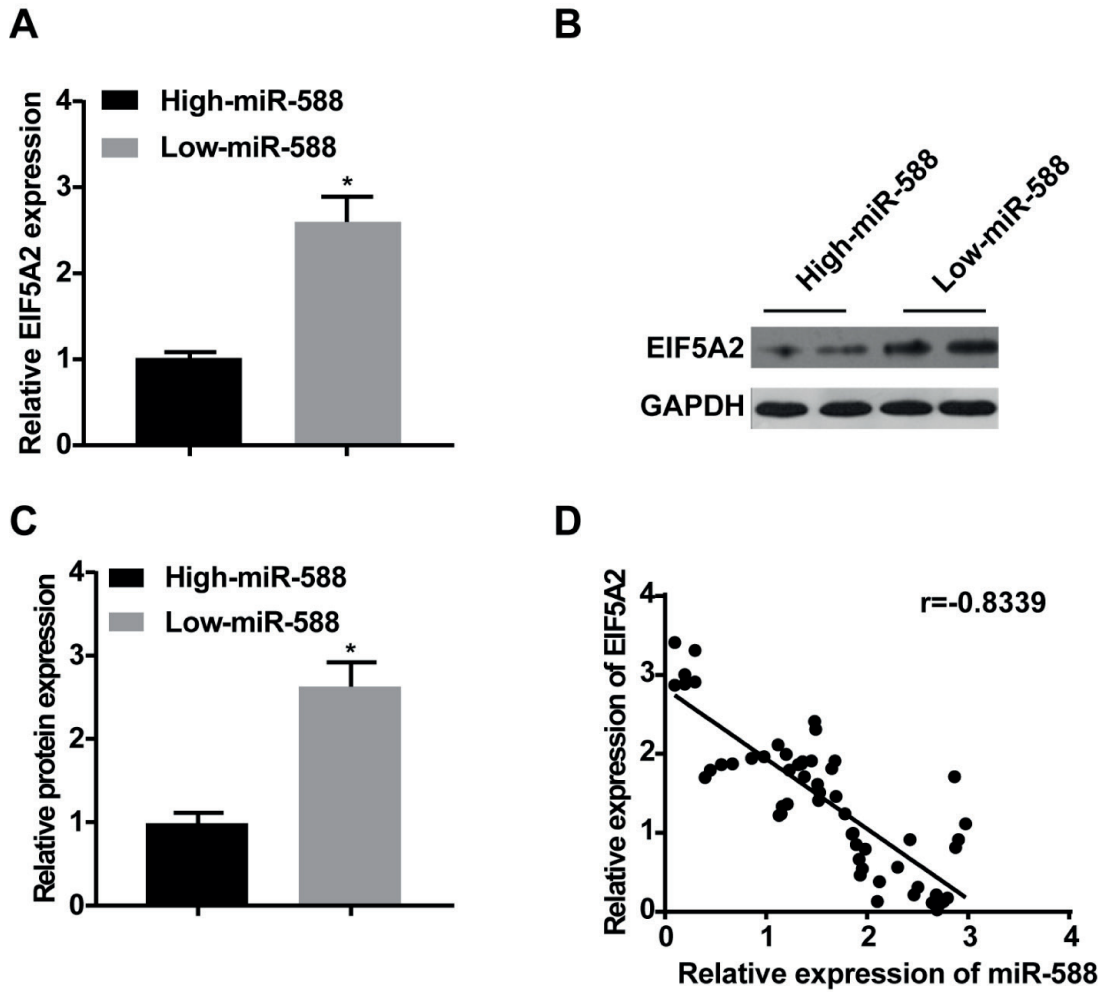

Figure 4. A Negative correlation between miR-588 and EIF5A2 expression in renal cell carcinoma**. A,** QRT-PCR detected low mRNA expression of EIF5A2 in tumor tissues with high level of miR-588, and high mRNA expression of EIF5A2 in tumor tissues with low expression of miR-588. **B-C**, Western blot result showed that the protein expression of EIF5A2 was significantly lower in tumor tissues with higher expression of miR-588. However, the protein expression of EIF5A2 was remarkably higher in tumor tissues with lower expression of miR-588. **D,** There was a negative correlation between miR-588 and EIF5A2 expression in renal cell carcinoma.

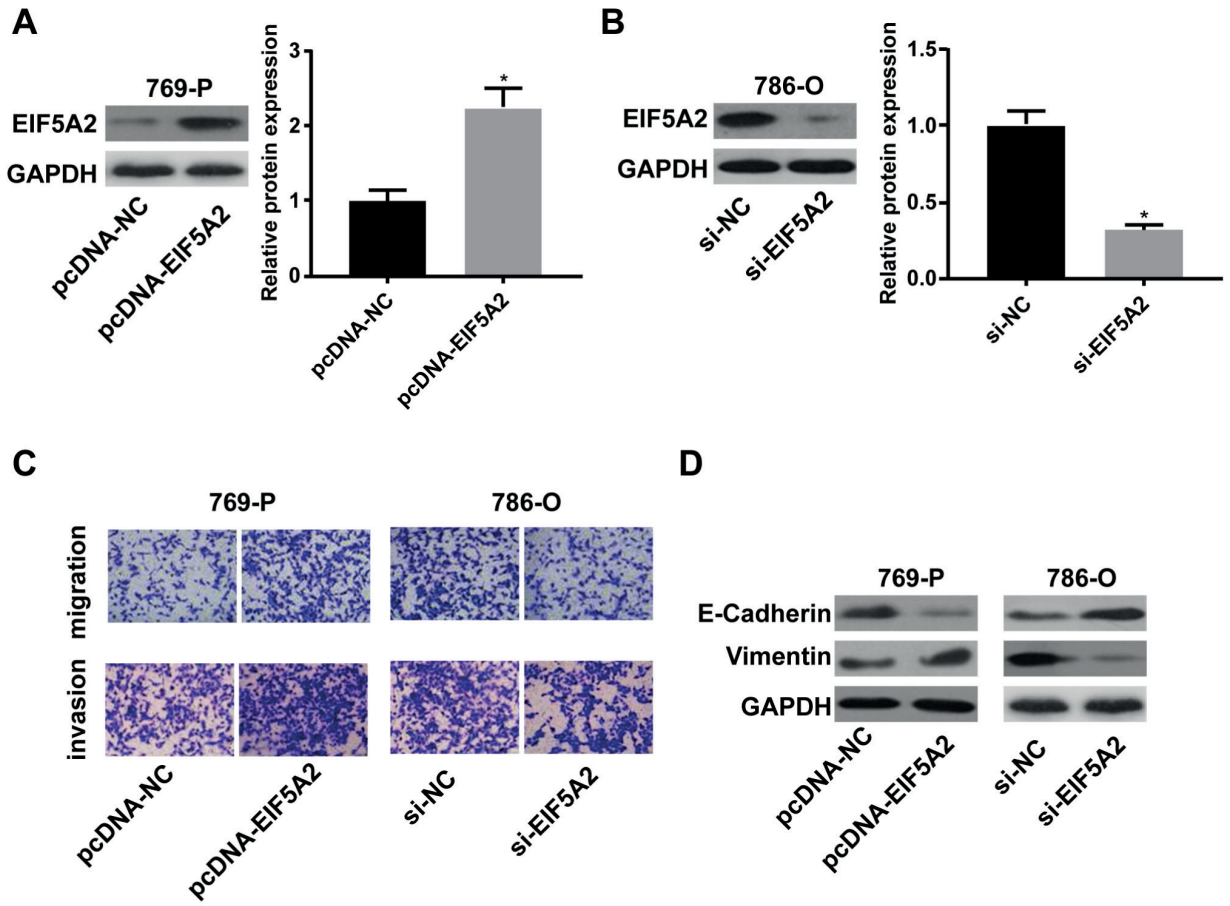

Figure 5. High expression of EIF5A2 promotes migration and invasion of renal cancer cells. **A,** After overexpression of EIF5A2 in 769-P cells, the protein expression of EIF5A2 significantly increased. **B,** After knocking down EIF5A2 in 786-O cells, the protein expression of EIF5A2 significantly decreased. **C,** After overexpression of EIF5A2 in 769-P cells, the migration and invasion abilities of cells were significantly enhanced. After knocking down EIF5A2 in 786-O cells, the migration and invasion abilities of cells significantly decreased (magnification: 40×). **D,** After overexpression of EIF5A2 in 769-P cells, the level of E-Cadherin protein decreased, whereas the levels of Vimentin protein increased. After knocking down EIF5A2 in 786-O cells, the level of E-Cadherin protein increased, while Vimentin protein level reduced.

and breast cancer[18]. Moreover, microRNA-588 acts as a tumor suppressor by regulating its target gene (the precursor of granulin protein), thus participating in the inhibition of cancer progression. EMT is a key process in the progression and metastasis of renal cell carcinoma. In this process, epithelial cancer cells in primary tumors lose cell-cell adhesion, which also obtain mesenchymal phenotype after inhibition of E-cadherin. This enhances the ability of cancer cells to metastasize and invade to distant locations. EIF5A2, which is located on chromosome 3q26, has also been described as involving in a variety of cancers, including colorectal cancer and hepatocellular carcinoma[19]. It can participate in promoting the proliferation, invasion and metastasis of cancer cells by inducing EMT. Overexpression of EIF5A2 is associated with the development of different human malignancies[20]. This can initiate tumor formation and promote cancer cell growth and metastasis as well[21]. At the same time, knockdown of EIF5A2 inhibits the proliferation, migration capacity and invasiveness of renal cancer cells by inhibiting EMT. All these findings suggest the carcinogenic effects of EIF5A2. Early studies have demonstrated that the role of microRNA-588 as a tumor suppressor in inhibiting tumor progression is associated with cancer type. In this study, microRNA-588 levels were lowly expressed in renal tumor tissues or cells. The protein expression of EIF5A2, the downstream gene of microRNA-58, increased significantly. Additionally, microRNA-588 could negatively regulate EIF5A2 expression in renal cell carcinoma cells, eventually inhibiting progression of EMT and cell invasive-

ness or metastasis. In addition, our results also revealed that overexpression of EIF5A2 abolished the inhibitory effect of microRNA-588 on the invasion and migration of renal cancer cells. Therefore, the above results demonstrated that EIF5A2 acted as a medium for microRNA-588 in renal cell carcinoma. Meanwhile, lowly expressed microRNA-588 could lead to an increased expression of EIF5A2 protein. This subsequently enhanced the migratory and invasive abilities of cancer cells and the malignancy of renal cancer, resulting in a significant decrease in patients' survival rate.

Conclusions

MicroRNA-588 expression was significantly reduced in renal tumor tissues and cells, and decreased with the increase tumor diameter. In addition, microRNA-588 could bind to EIF5A2 to regulate its expression. Lowly expressed microRNA-588 lead to increased expression of EIF5A2 protein, thus enhancing the invasion and migration abilities of renal cancer cells.

Conflict of Interests

The Authors declare that they have no conflict of interests.

References

1) Cohen HT, McGovern FJ. Renal-cell carcinoma. N Engl J Med 2005; 353: 2477-2490.
2) Clague J, Lin J, Cassidy A, Matin S, Tannir NM, Tamboli P, Wood CG, Wu X. Family history and risk of renal cell carcinoma: results from a case-control study and systematic meta-analysis. Cancer Epidemiol Biomarkers Prev 2009; 18: 801-807.
3) Szabo Z, Szegedi K, Gombos K, Mahua C, Flasko T, Harda K, Halmos G. Expression of miRNA-21 and miRNA-221 in clear cell renal cell carcinoma (ccRCC) and their possible role in the development of ccRCC. Urol Oncol 2016; 34: 533e21-e27.
4) Kiselev FL. [MicroRNA and cancer]. Mol Biol (Mosk) 2014; 48: 232-242.
5) Petillo D, Kort EJ, Anema J, Furge KA, Yang XJ, Teh BT. MicroRNA profiling of human kidney cancer subtypes. Int J Oncol 2009; 35: 109-114.
6) Wach S, Nolte E, Theil A, Stohr C, T TR, Hartmann A, Ekici A, Keck B, Taubert H, Wullich B. MicroRNA profiles classify papillary renal cell carcinoma subtypes. Br J Cancer 2013; 109: 714-722.
7) Valastyan S, Weinberg RA. Tumor metastasis: molecular insights and evolving paradigms. Cell 2011; 147: 275-292.
8) Zhou X, Xu M, Guo Y, Ye L, Long L, Wang H, Tan P, Xu M. MicroRNA-588 regulates invasion, migration and epithelial-mesenchymal transition via targeting EIF5A2 pathway in gastric cancer. Cancer Manag Res 2018; 10: 5187-5197.
9) Xu XW, Li S, Yin F, Qin LL. Expression of miR-205 in renal cell carcinoma and its association with clinicopathological features and prognosis. Eur Rev Med Pharmacol Sci 2018; 22: 662-670.
10) Ball MW, Singer EA, Srinivasan R. Renal cell carcinoma: molecular characterization and evolving treatment paradigms. Curr Opin Oncol 2017; 29: 201-209.
11) Ying SY, Chang DC, Lin SL. The microRNA (miRNA): overview of the RNA genes that modulate gene function. Mol Biotechnol 2008; 38: 257-268.
12) He Y, Liu J, Wang Y, Zhu X, Fan Z, Li C, Yin H, Liu Y. Role of miR-486-5p in regulating renal cell carcinoma cell proliferation and apoptosis via TGF-beta-activated kinase 1. J Cell Biochem 2019; 120: 2954-2963.
13) Catto JW, Alcaraz A, Bjartell AS, De Vere White R, Evans CP, Fussel S, Hamdy FC, Kallioniemi O, Mengual L, Schlomm T, Visakorpi T. MicroRNA in prostate, bladder, and kidney cancer: a systematic review. Eur Urol 2011; 59: 671-681.
14) Spector Y, Fridman E, Rosenwald S, Zilber S, Huang Y, Barshack I, Zion O, Mitchell H, Sanden M, Meiri E. Development and validation of a microRNA-based diagnostic assay for classification of renal cell carcinomas. Mol Oncol 2013; 7: 732-738.
15) Guo H, Ingolia NT, Weissman JS, Bartel DP. Mammalian microRNAs predominantly act to decrease target mRNA levels. Nature 2010; 466: 835-840.
16) Hayes J, Peruzzi PP, Lawler S. MicroRNAs in cancer: biomarkers, functions and therapy. Trends Mol Med 2014; 20: 460-469.
17) Qian L, Lin L, Du Y, Hao X, Zhao Y, Liu X. MicroRNA-588 suppresses tumor cell migration and invasion by targeting GRN in lung squamous cell carcinoma. Mol Med Rep 2016; 14: 3021-3028.
18) Yu M, Zhang X, Li H, Zhang P, Dong W. MicroRNA-588 is downregulated and may have prognostic and functional roles in human breast cancer. Med Sci Monit 2017; 23: 5690-5696.
19) Deng B, Wang B, Fang J, Zhu X, Cao Z, Lin Q, Zhou L, Sun X. MiRNA-203 suppresses cell proliferation, migration and invasion in colorectal cancer via targeting of EIF5A2. Sci Rep 2016; 6: 28301.
20) Yang SS, Gao Y, Wang DY, Xia BR, Liu YD, Qin Y, Ning XM, Li GY, Hao LX, Xiao M, Zhang YY. Overexpression of eukaryotic initiation factor 5A2 (EIF5A2) is associated with cancer progression and poor prognosis in patients with early-stage cervical cancer. Histopathology 2016; 69: 276-287.
21) Tian SB, Yu JC, Liu YQ, Kang WM, Ma ZQ, Ye X, Yan C. MiR-30b suppresses tumor migration and invasion by targeting EIF5A2 in gastric cancer. World J Gastroenterol 2015; 21: 9337-9347.