European Review for Medical and Pharmacological Sciences 2017; 21: 4050-4057

MicroRNA-217 functions as a prognosis predictor and inhibits pancreatic cancer cell proliferation and invasion via targeting E2F3

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Abstract. – OBJECTIVE: Pancreatic cancer (PC) is the most malignant tumor among all the tumors in the digestive system. MiR-217 has been reported to take a critical part in various malignant tumors. The aim of this study was to explore the function of MiR-217 in pancreatic cancer and its target genes.

PATIENTS AND METHODS: Twenty pairs of PC tissues and matched normal adjacent pancreatic tissues were collected. The expression of miR-217 in PC tissues and normal pancreatic tissues was detected by Real-time polymerase chain reaction (PCR). PC cells were transfected with miR-217 mimics, inhibitors and negative control, respectively. Cell Counting Kit-8 (CCK-8) assay was used to detect cell viability. Cell apoptosis was checked via Annexin V-FITC/PI apoptosis kit. The protein expression of E2F3 was detected by Western blot. To detect repression by miR-217, HEK293T cells were co-transfected with the indicated E2F3 3′-UTR luciferase reporter.

RESULTS: The expression of miR-217 was reduced in PC tissues comparing to normal pancreatic tissues. Meantime, the in-vitro study revealed that miR-217 suppressed PC cell growth, invasion but promoted apoptosis. Next, we proved that E2F3 was the target of miR-217 on PC cell function.

CONCLUSIONS: miR-217 suppresses PC cell growth, invasion but promotes apoptosis *in vitro* through targeting E2F3. The miR-217-E2F3 axis may be used for PC therapy.

Key Words:
Pancreatic cancer, miR-217, E2F3, Proliferation, Invasion, Apoptosis.

Introduction

Pancreatic cancer (PC) is the most malignant tumor in the digestive system. No clear clinical symptoms can been detected in early stage of pancreatic cancer, and about 80% of patients are in late stage when they are diagnosed with pancreatic cancer[1]. For patients with pancreatic cancer, 5-year survival rate is less than 5%, and the median survival time of late stage patients is only 9-10 months[2]. In the recent years, along with the changes of dietary patterns and living habits, the incidence rate of pancreatic cancer is on the rise[3]. Therefore, seeking for new anti-cancer drugs or molecular targets is of great significance[4]. The occurrence of tumor invasion and migration is a multi-factor, multi-step and complicated process, and it is related to various factors such as genomic instability, change in epigenetics and tumor microenvironment. In the past, researches mainly focused on gene study, which can encode proteins. In recent years, none-coding RNA (ncRNA) has drawn more and more attention in tumor invasion and migration. None-coding RNA takes an important part in various pathophysiological processes of human body, including the occurrence and development of malignant tumors. Among these, microRNA (miRNA) is one of the biggest concerns of scholars, as miRNA takes an important part in various processes including the occurrence and development of tumor[5]. The E2F3 family, a transcription factor family, plays an important role in cellular proliferation, apoptosis and

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differentiation[6]. When E2F3 was ablated in mouse embryonic fibroblasts (MEFs), E2F3 target gene expression was markedly reduced[7], and the proliferation of MEFs was significantly inhibited[8], suggesting that E2F3 has an important role in regulating cell proliferation. MiR-217 is located at 2p16, and it has been reported to serve as a critical role in various malignant tumors. In endothelial cells, miR-217 can inhibit the expression of oncogene silent information regulator 1 (SIRT1), suggesting that miR-217 can inhibiting cancer via regulating SIRT1[9]. Moreover, in glomerular mesangial cells, miR-217 can regulate the expression of tumor suppressor gene phosphatase and tensin homolog deleted on chromosome ten (PTEN)[10]. These reports suggest that miR-217 not only serves as a tumor suppressor via targeting oncogene, but also can promoting cancer via targeting tumor suppressors. According to published research[11,12], miR-217 was downregulated in PC tissues compared with normal tissues. However, further study is needed to explore the function of MiR-217 in pancreatic cancer and its target genes.

Patients and Methods

Patients and Cells

Twenty pairs of PC tissues and matched normal adjacent pancreatic tissues were from Beijing Chao-Yang Hospital with written informed consent. This research was undertaken with the approval of the Ethic Committee of Beijing Chao-Yang Hospital. All pathologic diagnosis of tissues were made by two pathologists. Pancreatic cancer cells (PANC-1, AsPC-1 and SW1990), as well as normal pancreatic cells (HPNE), were obtained from ATCC (Manassas, VA, USA) and they were incubated at 37°C, with 5% CO_2.

Real-time PCR

After whole RNA extraction, a PrimeScript RT kit purchased from TaKaRa was used to reverse transcription. The reversed cDNA were ready for RT-PCR. These following primers were used: miR-217 (forward: 5′-TAC TCA ACT CAC TAC TGC ATC AGG A-3′, reverse: 5′-TAT GGT TGT TCT GCT CTC TGT GTC-3′); U6 (forward: 5′-AGA GAA GAT TAG CAT GGC CCC TG-3′, reverse: 5′-ATC CAG TGC AGG GTC CGA GG-3′); E2F3 (forward: 5′- GTA TGA TAC GTC TCT TGG TCT GC -3′, reverse: 5′- CAA ATC CAA TAC CCC ATC GGG -3′); β-actin (forward: 5′-TCC TGT GGC ATC CAC GAA ACT-3′, reverse: 5′-GAA GCA TTT GCG GTG GAC GAT-3′). U6 and β-actin served as internal reference. The relative expression levels were determined by $2^{-\Delta\Delta Ct}$ equation.

Western Blot Analysis

PIPA buffer (Beyotime, Shanghai, China) was used to obtain total proteins of cells. Afterwards, we determined protein concentration with a protein assay kit. 10% sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) was used to separate protein. Next, it was shifted to polyvinylidene fluoride (PVDF) membranes purchased from Millipore (Billerica, MA, USA). 5% fat-free milk was used to block non-specific protein interactions in tris buffered saline tween (TBST) buffer. The membrane was then incubated with primary antibody at 4°C overnight, following with secondary antibody for 1 h at room temperature. After washing these membranes in TBST buffer, we developed the membranes using chemiluminescence to detect antibodies concentration and took GAPDH as our internal control. The antibodies, anti-E2F3 and anti-GAPDH were purchased from Abcam (Cambridge, MA, USA).

Cell Transfection

MiR-217 mimic, inhibitor, and a negative control (miR-NC) with fluorescent tags, were synthesized by Shanghai GenePharma (Shanghai, China). PC cells were transfected with miR-217 mimics, inhibitors and negative control, respectively with lipo2000 (Invitrogen, Carlsbad, CA, USA) according to the protocol of manufacturers. 4-6 h post-transfection, cell culture media was changed with normal medium with 10% fetal bovine serum (FBS). Moreover, we purchased pcDNA3/E2F3 from Shanghai GenePharma (Shanghai, China).

Cell Proliferation Assay

After cells were seeded into 96-well plates for 24 h, CCK-8 solution (10 μL per well; Dojindo, Kumamoto, Japan) was added and incubated for additional 1 h. Optical density was determined with a spectrophotometer by measuring the absorption of the excitation wave at 450 nm.

Cell Invasion Assay

The transwell chamber (BD Biosciences, Franklin Lakes, NJ, USA) coated with 60 μL Matrigel (BD, Franklin Lakes, NJ, USA) was put into a 24-well plate. The lower chamber was filled with 600 uL Dulbecco's Modified Eagle Medium (DMEM)

with 20% fetal bovine serum (FBS). $1*10^5$ cells in 200 uL DMEM without FBS were seeded into the upper chamber. After incubation of 24 h, cells were fixed with 4% paraformaldehyde and a cotton swab was used to remove cells on the upper side of chamber. Afterwards, cells on the lower side of chamber were stained with 0.1% crystal violet for 15 min and finally, cells that crossed the chamber were counted under a microscope. Five random images were selected for each chamber.

Apoptosis Assay

Annexin V-FITC/PI fluorescein isothiocyanate/propidium iodide apoptosis kit, obtaining from BD (Franklin Lakes, NJ, USA), was used for apoptosis assay. It was performed according to the standard procedure of manufactures on flow cytometer (Beckman Coulter, Brea, CA, USA).

Luciferase Assay

The luciferase reporter vector of E2F3 3'-UTR was ordered from Shanghai Genechem (Shanghai, China). To detect repression by miR-217, HEK293T cells were co-transfected with the indicated E2F3 3′-UTR luciferase reporter (with either wild-type or mutant-type miR-217 binding sites). The Renilla luciferase was transfected as an efficiency control. We got luciferase assay system (Promega, Madison, WI, USA) to measure the luciferase activity according to the instructions of the manufacturers.

Statistical Analysis

SPSS11.0 (SPSS Inc. Chicago, IL, USA) was used to analyze our data. Quantitative data was expressed as mean ± SEM. Non-paired *t*-test was used to analyze data between groups. $p<0.05$ was supposed to be statistically significant.

Results

MiR-217 is Down-Regulated in PC Tissues and Cells

We employed RT-qPCR to examine the level of miR-217 in pancreatic cancer tissues and normal pancreatic tissues. We found the expression of miR-217 was significantly down-regulated in the tumor tissues than normal pancreatic tissues ($p<0.01$, 1A). Next, RT-qPCR was applied to examine the expression level of miR-217 in pancreatic cells: SW1990, PANC-1, PsAC-1 and normal pancreatic cell: HPNE. Results revealed that miR-217 level was lower in pancreatic cells than normal pancreatic cell ($p<0.05$, Figure 1B). In short, miR-217 may be related to the carcinogenesis of pancreatic carcinoma.

MiR-217 Mimic Inhibits Viability of PC Cells

Since miR-217 is considered to be involved in the carcinogenesis of pancreatic carcinoma, we wanted to explore whether miR-217 can affect cell viability. The expression of miR-217 in cells (PANC-1 and AsPC-1 cells) transfected with miR-217 mimic, miR-217 inhibitor or negative controls was confirmed by RT-PCR. Results revealed that miR-217 mimic could increase the expression of miR-217 in both PANC-1 and PsAC-1 cells, whereas miR-217 inhibitor decreased miR-217 expression in both PC cells ($p<0.01$, Figure 2A-B). Next, CCK-8 assay was used to detect cell viability, and results indicated that the viability of miR-217 mimic group was significant decreased whereas the viability of miR-217 inhibitor group was significantly increased in both PC cells ($p<0.01$, Figure 2C-D). All these data support the role of miR-217 in inhibiting cell viability *in vitro*.

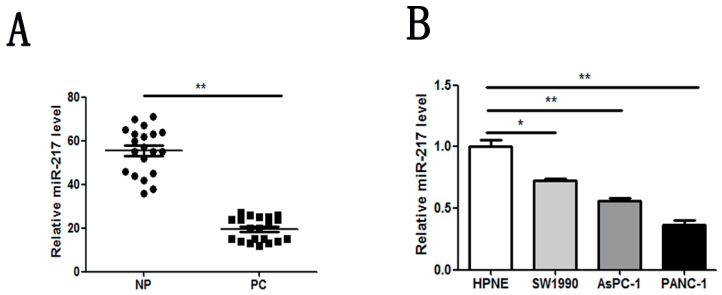

Figure 1. The expression level of miR-217 in pancreatic cancer tissues and cell lines. ***(A)*** The expression level of miR-217 in pancreatic cancer tissues and normal pancreatic tissues as determined by Real-time PCR. ***(B)*** The expression level of miR-217 in pancreatic cancer cell lines PANC-1, AsPC-1, and SW1990 by Real-time PCR. *$p<0.05$, **$p<0.01$.

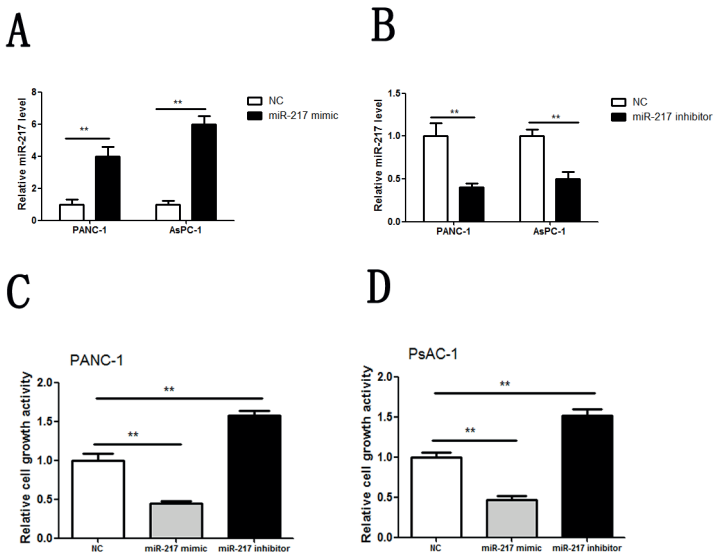

Figure 2. The effect of miR-217 on cell viability. ***(A)*** The expression of miR-217 in PANC-1 and AsPC-1 cells transfected with miR-217mimic or miR-NC. (B) The expression of miR-217 in PANC-1 and AsPC-1 cells transfected with miR-217 inhibitor or miR-NC. The cell viability in PANC-1 ***(C)*** and AsPC-1 cells ***(D)*** transfected with miR-217 mimic, miR-217 inhibitor and miR-NC. $^{**}p<0.01$.

MiR-217 Promotes Apoptosis of PC Cells

We further employed Annexine VFITC/PI apoptosis assay to identify the effect of miR-217 on the cell apoptosis in PC cells. As shown in Figure 3, miR-217 mimic promoted cell apoptosis, while miR-217 inhibitor decreased cell apoptosis comparing to the negative control group ($p<0.01$).

MiR-217 Inhibits the Invasion of PC Cells

Transwell assay was used to examine whether miR-217 could affect invasive ability of PC cells. From Figure 4 we can see that miR-217 mimic reduced the number of cells across the membrane, while miR-217 inhibitor increased the number of cells across the membrane, comparing to the negative control group ($p<0.01$). These data represented that miR-217 decreased the invasive ability of pancreatic cancer cells.

E2F3 Is the Direct Target of miR-217 in PC Cells

To explore the potential molecular mechanism of miR-217 in inhibiting cell viability and invasion of PC cells, we used TargetScan release 6.2 as wells as miRanda to search the target genes with an established function of tumor suppressor. Afterwards, we had the prediction that E2F3 could be a direct target of miR-217. In the two databases, MiR-217 was predicted as highly conserved. We constructed luciferase reporter plasmids of wild type, which contained the complete 3′UTR of E2F3, and luciferase reporter plasmids of muted type, which contained a muted binding site at the 3′UTR to verify that prediction. Firstly, HEK293T cells were transfected with a miR-217 mimic. Then, we co-transfected the wild group and muted group with WT E2F3 plasmid and MT E2F3 plasmid, respectively. As a result, the normalized luciferase activity declined in the WT cells and with the miR-217 mimic ($p<0.05$). However, we did not detect any significant difference in MT plasmid group. Furthermore, we performed RT-qPCR as well as Western blotting to validate the effect of miR-217 on the expression of E2F3 in PANC-1 cells (Figure 5 C-D). We concluded that protein expression of E2F3 was dramatically attenuated with the miR-217 mimic but up-regulated with the transfection of a miR-217 inhibitor, while no changes were seen in the mRNA level of E2F3.

The Effect of miR-217 Can Be Rescued by Overexpression of E2F3

To further identify whether miR-217 regulating cell invasion and proliferation was mediated by E2F3, we cotransfected pcDNA3/E2F3 and miR-217 mimic or miR-NC into PANC-1 and PsAC cells. The results revealed that miR-217 mimic inhibited cell viability and invasion of PANC-1 and PsAC-1 cells, which could be rescued by overexpression of E2F3 (pcDNA3/E2F3 + miR-217

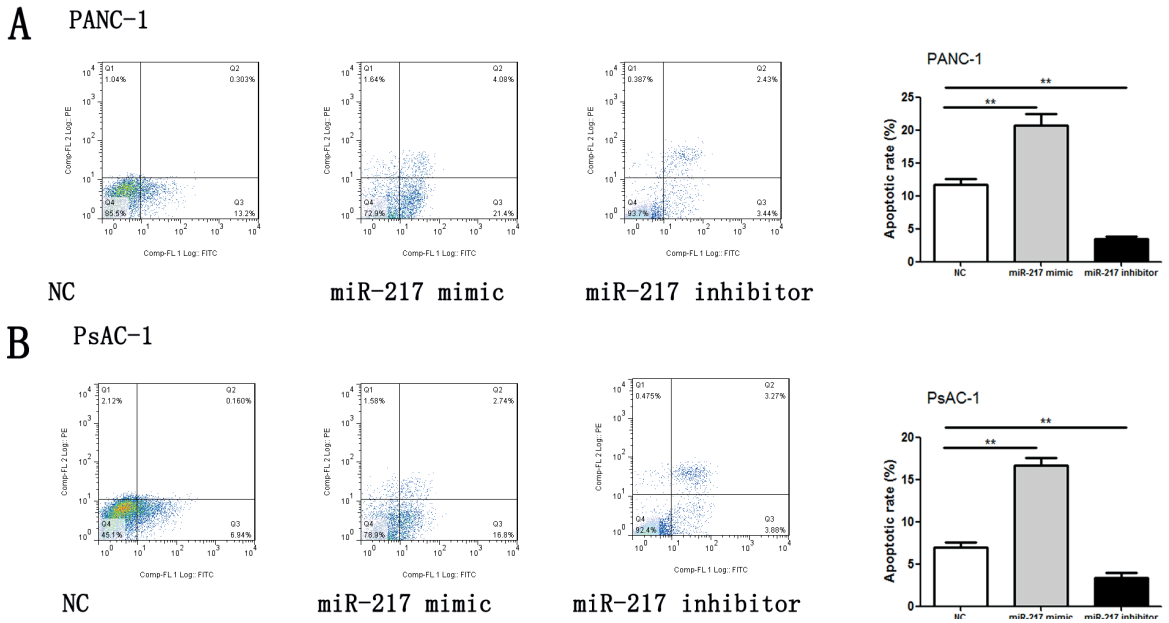

Figure 3. The effect of miR-217 on cell apoptosis. The cell apoptosis in PANC-1 ***(A)*** and AsPC-1 cells ***(B)*** transfected with miR-217 mimic, miR-217 inhibitor or miR-NC. **$p<0.01$.

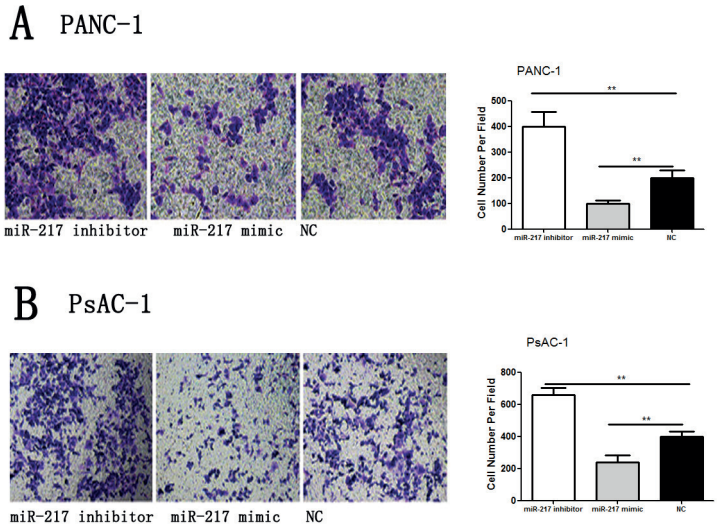

Figure 4. The effect of miR-217 on cell invasion. The cells across the membrane of chamber in PANC-1 ***(A)*** and AsPC-1 cells ***(B)*** transfected with miR-217 mimic, miR-217 inhibitor or miR-NC (200x magnifications). **$p<0.01$.

mimic group) ($p<0.01$, Figure 6). These results indicated miR-217 regulated pancreatic tumor cells viability and invasion via E2F3.

Discussion

MiRNAs is a kind of non-coding RNAs, which has about 22 nucleotides. It can target mRNAs for cleavage or translational repression[13]. It has been reported that more than 1/3 human genes can be regulated by conserved miRNA targets[14]. Moreover, it has been reported that various diseases are related to miRNA changes. MiRNAs can regulate numerous cellular activities, include cell proliferation, thus, resulting in taking an important part in senescence of cells and organisms, as well as human disease[15]. Mammalian E2F3 is a well-characterized transcrip-

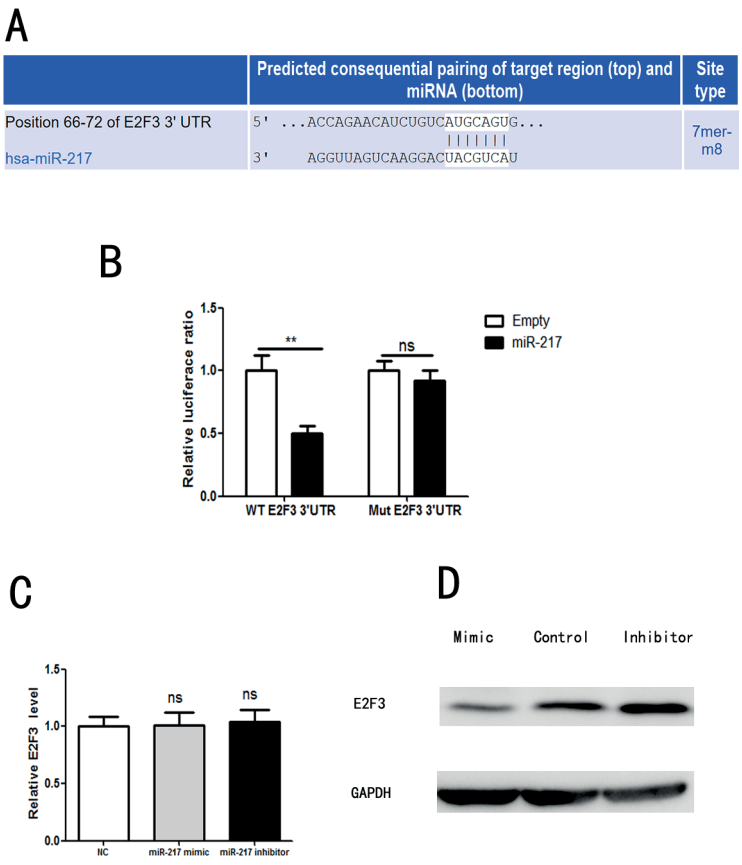

Figure 5. E2F3 is a direct target of miR-217. ***(A)*** Biological prediction revealed that E2F3 could be a direct target of miR-217. ***(B)*** Luciferase reporter assays in HEK293Ts, with co-transfection of WT or Mut DC-E2F3 and miR-217 as indicated. Transfection of miR-217 mimic markedly weakened luciferase activity of WT-DC-E2F3 3'-UTR. ***(C)*** Inhibition or overexpression of miR-217 in PANC-1 did not alter E2F3 mRNA level. ***(D)*** Overexpression of miR-217 significantly inhibited E2F3 protein expression. $^{**}p<0.01$.

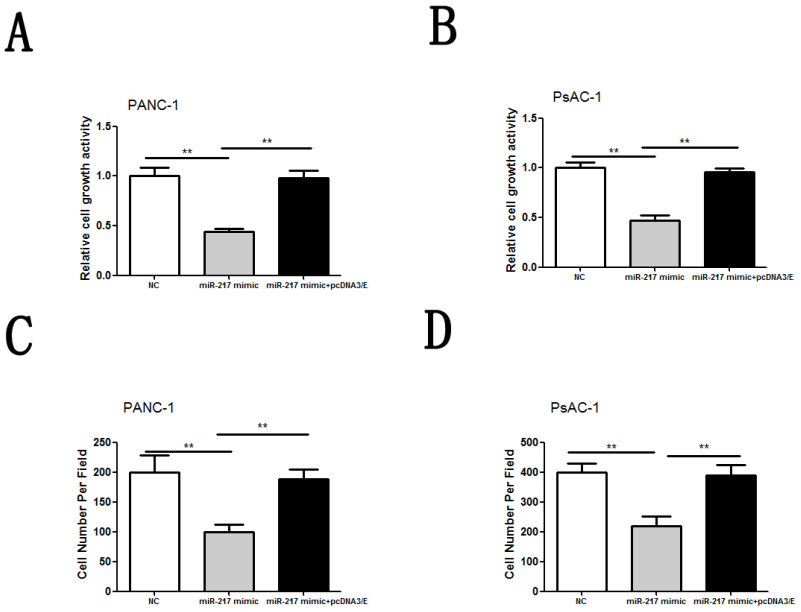

Figure 6. MiR-217 rescue experiments in PANC-1 and PsAC-1 cells. The cell viability of PANC-1 cells ***(A)*** and PsAC-1 cells ***(B)*** co-transfected with pcDNA3/E2F3 and miR-217/miR-NC. The invasive cell number of PANC-1 cells ***(C)*** and PsAC-1 cells ***(D)*** co-transfected with pcDNA3/E2F3 and miR-217/miR-NC. $^{**}p<0.01$.

tion factor, functioning depends on cell cycle. It can work out via specific binding to pRB, linking cell cycle proteins as CDKs and cyclins[16]. It has been reported that E2F3 can regulate numerous human genes, which play an important role in transcription, DNA synthesis, and signal transduction; E2F3 could also display apoptosis and drug resistance by initiating the downstream genes[17]. With strong oncogenic potential, the expression of E2F3 is always increased in different cancers. For example, in ovarian cancer, E2F3a was found to boost the proliferation of cancer cells via the EGFR-driven mitogenic cell signal[18]. According to what Martinez et al[19] reported, E2F3 can regulate DNA damage response, and it is involved with DNA damage-induced apoptosis. Moreover, in lung cancer, miR-200b can reduce cell sensitivity to docetaxel via targeting E2F3[20]. Additionally, E2F3 may serve as an independent factor for prostate cancer in predicting overall survival, as well as cause-specific survival[21]. In the current study, we found that miR-217 could inhibit cell viability, invasion, but promote cell apoptosis via reducing the expression of E2F3. The miR-217-E2F3 axis might serve as a new target for pancreatic cancer therapy. MicroRNA could function as either a tumor suppressor or promoter in different cancers in a context-dependent manner because it targets numerous different target genes. In human aggressive B-cell lymphomas, miR-217 is overexpressed and increases lymphomagenesis mature B-cell[22]; however, in most cancers, miR-217 has been reported to serve as a tumor suppressor. In breast cancer, Zhou et al[23] reported that miR-217 attenuates the ability of cell viability, migration, and invasion via targeting KLF5. In esophageal squamous cell carcinoma, miR-217 exhibits a inhibiting effect of cell proliferation, migration, as well as invasion via long noncoding RNA MALAT1 and kallikrein 7 (KLK7)[24]. Moreover, miR-217 inhibits ovarian cancer via IGF1R[25]. In pancreatic ductal adenocarcinoma, miR-217 has been reported to inhibit cell growth via targeting KRAS and SIRT1[26]. These studies suggest the tumor suppression function of miR-217 in pancreatic cancer. In the current research, we found miR-217 suppressed cell growth and invasion via targeting E2F3 in both PANC-1 and AsPC-1 cell lines. Therefore, miR-217 may act as a tumor suppressor in pancreatic cancer via different targets.

Conclusions

miR-217 suppresses PC cell growth and invasion, but promotes apoptosis *in vitro* through targeting E2F3. The miR-217-E2F3 axis may be used for PC therapy.

Acknowledgments

This study was supported by Natural Science Foundation of China (No.81541155).

Conflict of interest

The authors declare no conflicts of interest.

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