European Review for Medical and Pharmacological Sciences 2020; 24: 9915-9923

MiR-4282 contributes to inhibit pancreatic cancer metastasis by negatively interacting with ABCB5

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Abstract. – OBJECTIVE: To explore the regulatory mechanism of microRNA-4282 (miR-4282) on influencing pancreatic cancer progression by targeting ABCB5.

PATIENTS AND METHODS: MiR-4282 and ABCB5 levels in 58 cases of pancreatic cancer and paracancerous tissues were detected by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR). The influences of miR-4282 on pathological indicators and prognosis in pancreatic cancer patients were analyzed. MiR-4282 overexpression model was established in PANC-1 and BxPC-3 cells by transfection of miR-4282 mimic. Transwell and wound healing assay were conducted to illustrate the role of miR-4282 in influencing cell functions of pancreatic cancer. Bioinformatics analysis and Dual-Luciferase reporter assay were carried out to ascertain the interaction between miR-4282 and ABCB5.

RESULTS: MiR-4282 was downregulated in pancreatic cancer samples. Low level of miR-4282 predicted high incidences of lymphatic metastasis and distant metastasis, as well as poor prognosis in pancreatic cancer patients. Overexpression of miR-4282 remarkably inhibited migratory ability in PANC-1 and BxPC-3 cells. MiR-4282 was targeted by ABCB5 through specific binding sites. In pancreatic cancer tissues, ABCB5 level was negatively correlated to that of miR-4282. Overexpression of ABCB5 could abolish the inhibitory effects of overexpressed miR-4282 on the malignant progression of pancreatic cancer.

CONCLUSIONS: MiR-4282 is able to inhibit the migratory ability in pancreatic cancer cells by negatively targeting ABCB5, which may become a promising pancreatic cancer biomarker.

Key Words:
MiR-4282, ABCB5, Pancreatic cancer, Metastasis.

Introduction

Pancreatic cancer is a highly malignant tumor in the digestive system. Its median survival ranges 3-6 months and the 5-year survival is lower than 5%[1,2]. Although therapeutic outcomes of surgery resection and adjuvant medication have been progressed, the survival of pancreatic cancer has not been greatly improved in the past decades[3,4]. The latest epidemiological survey has reported that pancreatic cancer is the 12th most-common tumor and the 4th tumor killer throughout the world[5,6]. In China, the incidence of pancreatic cancer seriously increases each year[7,8]. Atypical symptoms in the early phase and lack of sensitive tumor biomarkers for pancreatic cancer result in the loss of the most optimal opportunity for surgery[9]. It is super urgent to identify highly specific and effective biomarkers for pancreatic cancer, thus enhancing the surgical resection rate[10,11].

In addition to clinical and pathological predictive factors, molecular subtypes of pancreatic cancer are increasingly valued[10,12]. Molecular profiling techniques have revealed the influences of oncogenes and tumor-suppressor genes on cancer development, metastasis patterns, treatment response and prognosis[12]. MicroRNAs (miRNAs) have been emerged as a novel type of tumor biomarkers[13,14]. These non-coding genes exert biological functions by silencing mRNAs and post-transcriptional regulation[15]. MiRNAs induce mRNA degradation and thereafter inhibit protein translation in a manner of complementary base pairing[16]. Deficiency in the normal functions of miRNAs triggers expression changes in oncogenes and/or tumor suppressors[13,14]. A relevant study detected 72 dysregulated miRNAs (23 upregulated and 49 downregulated miRNAs) in pancreatic cancer profiling, which are proven to be linked to its survival[17]. Previous studies[18,19] have shown the lowly expressed miR-4282 in oral squamous cell carcinoma and breast cancer, which is associated to pathological grade, tumor staging and prognosis. The potential role of miR-4282 in pancreatic cancer progression is rarely reported.

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Bioinformatics analysis suggested the interaction between miR-4282 and ABCB5. ABCB5, as a major member of the ATP-binding cassette (ABC) transporters, can maintain the dormant state of stem cells and decrease cell sensitivity to external physical and chemical stimuli. It has been identified as a molecular marker of malignant melanoma-derived cells[20,21]. Cells with abundantly expressed ABCB5 have a high tumorigenic rate. The knockdown of ABCB5 remarkably reduces tumor volume in tumor-bearing mice[22,23].

We collected pancreatic cancer samples to uncover the role of miR-4282 in influencing its clinical features. The molecular mechanism of miR-4282 on regulating malignant progression of pancreatic cancer with the involvement of ABCB5 provides experimental evidence for its clinical application.

Patients and Methods

Pancreatic Cancer Samples

Cancer tissues and normal ones were surgically resected from 58 pancreatic cancer patients operated in the Affiliated Yantai Yuhuangding Hospital of Qingdao University. Samples were confirmed by two experienced pathologists independently and stored at -80°C for experimental use. Tumor node metastasis (TNM) staging and histological classification of pancreatic cancer were defined according to the criteria proposed by UICC/AJCC. Inclusion criteria: patients with no severe diseases in other organs, and none of patients had preoperative chemotherapy or molecular targeted therapy. Exclusion criteria: patients complicated with other malignancies, those with mental disease, those complicated with myocardial infarction, heart failure or other chronic diseases, or those previously exposed to radioactive rays. This study was approved by the Ethics Committee of the Affiliated Yantai Yuhuangding Hospital of Qingdao University and it was conducted after informed consent of each subject.

Cell Lines and Reagents

Pancreatic cancer cell lines (AsPC-1, PANC-1, MIA PaCa-2, CFPAC-1, BxPC-3) and the pancreatic duct epithelial cell line (HPNE) were provided by American Type Culture Collection (ATCC; Manassas, VA, USA). Cells were cultured in Roswell Park Memorial Institute-1640 (RPMI-1640; HyClone, South Logan, UT, USA) with 10% fetal bovine serum (FBS; HyClone, South Logan, UT, USA) in a 5% CO_2 incubator at 37°C. Cell passage was performed at the confluence of 80-90% using 1 × trypsin + EDTA (ethylenediaminetetraacetic acid).

Transfection

MiR-4282 mimic, NC mimic, pcDNA3.1-NC or pcDNA3.1-ABCB5 were purchased from GenePharma (Shanghai, China). Cells in 6-well plates were cultured to 40-60% confluence and transfected using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). They were collected for use after 48 h.

Transwell Migration Assay

Transwell chambers (Millipore, Billerica, MA, USA) were inserted in each well of a 24-well plate. 200 μL of suspension (5×10^5 cells/ml) was applied in the upper layer of the chamber with 700 μL of medium containing 20% FBS in the bottom. After 48-h incubation, migratory cells in the bottom were reacted with 15-min methanol, 20-min crystal violet and captured using a microscope. Migratory cells were counted in 10 random selected fields per sample.

Wound Healing Assay

Cells were prepared into suspension with 5×10^5 cells/mL, and implanted in 6-well plates. Until 90% of cell attachment, an artificial wound was made using a sterilized pipette tip. The cells were washed in phosphate-buffered saline (PBS) for 2-3 times and cultured in the medium containing 1% FBS. 24 hours later, wound closure was captured for calculating the percentage of wound healing.

Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR)

TRIzol reagent (Invitrogen, Carlsbad, CA, USA) was used for isolating total cellular RNAs, which were reversely transcribed into complementary deoxyribose nucleic acids (cDNAs; PrimeScript RT Reagent; TaKaRa, Otsu, Shiga, Japan). Using the SYBR® Premix Ex Taq™ kit (TaKaRa, Otsu, Shiga, Japan) and StepOne Plus Real-time PCR system (Applied Biosystems, Foster City, CA, USA), qRT-PCR was carried out. Relative level was calculated by $2^{-\Delta\Delta Ct}$ and normalized to that of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) or β-actin. MiR-4282: forward: 5'-ATGTGGCAGATCCCACAGGAGTTT-3', reverse: 5'-ACTGGGTTTGACTTCGTAGCCCTT-3'; U6: forward: 5'-CCTGGCACCCAGCACAAT-3', reverse: 5'-TGCCGTAGGTGTCCCTTTG-3'; ABCB5: forward: 5'-TCAGAGAAATGGAACTGCAGAAGA-3', reverse: 5'-AAGGAAGGCAGGCTCCATTG-3';

β-actin: forward: 5'-CCTGGCACCCAGCACAAT-3', reverse: 5'-TGCCGTAGGTGTCCCTTTG-3'.

Western Blot

Cells were lysed in radioimmunoprecipitation assay (RIPA) buffer (Beyotime, Shanghai, China) on ice for 30 min. Cell lysate was centrifuged at 4°C, 14000×g for 15 min. Extracted protein samples were quantified by bicinchoninic acid (BCA) method (Pierce, Rockford, IL, USA). Protein samples were electrophoresed in 10% Sodium Dodecyl Sulphate-Polyacrylamide Gel Electrophoresis (SDS-PAGE), and loaded on polyvinylidene difluoride (PVDF) membranes. Subsequently, non-specific antigens were blocked in 5% skim milk for 2 hours. The membranes were reacted with primary (anti-ABCB5, GAPDH) and secondary antibodies (anti-mouse, anti-rabbit) for indicated time. Band exposure and analyses of grey values were finally conducted.

Dual-Luciferase Reporter Assay

Wild-type and mutant-type ABCB5 vectors were constructed based on the predicted consequential pairing of the seed sequence in the 3'untranslated region (3'UTR) of ABCB5 and miR-4282. PANC-1 and BxPC-3 cells were inoculated in 24-well plates. They were co-transfected with NC mimic/miR-4282 mimic and ABCB5-WT/ABCB5-MUT using Lipofectamine 2000. After culturing for 48 h, the Luciferase activity was measured.

Statistical Analysis

Data were expressed as mean ± standard deviation and analyzed by GraphPad Prism 5 V5.01 (La Jolla, CA, USA). Differences between groups were analyzed by the *t*-test. Chi-square analysis was conducted for analyzing the influences of miR-4282 on pathological indicators in pancreatic cancer patients. Pearson correlation test was applied for evaluating the correlation between relative expressions of two genes. Each experiment was conducted in triplicate. A significant difference was set at $p<0.05$.

Results

MiR-4282 Was Lowly Expressed in Pancreatic Cancer Tissues and Cell Lines

MiR-4282 was detected to be downregulated in pancreatic cancer cell lines than that of the pancreatic duct epithelial cell line (Figure 1A). PANC-1 and BxPC-3 cell lines were selected for the subsequent experiments because they expressed the lowest level of miR-4282 among the tested pancreatic cancer cell lines. Similarly, miR-4282 was downregulated in pancreatic cancer tissues compared with that in normal ones (Figure 1B). It is suggested that miR-4282 may exert the anti-cancer role in the progression of pancreatic cancer.

MiR-4282 Expression Was Correlated with Metastasis and Overall Survival in Pancreatic Cancer Patients

We recruited pancreatic cancer tissues from 58 patients, and they were classified into two groups according to the median level of miR-4282 in their cancer tissues. Chi-square test was conducted for assessing the relationship between miR-4282 and pathological indicators in pancreatic cancer patients. As the data revealed, low level of miR-4282 was related to high incidences of lymphatic metastasis and distant metastasis in pancreatic cancer (Table I). Lower abundance of miR-4282 was identically detected in pancreatic cancer patients accompanied lymphatic or distant metastasis than those without metastases (Figure 1C). Poor prognosis was observed in pancreatic cancer patients expressing low level of miR-4282 (Figure 1D).

Overexpression of MiR-4282 Inhibited Metastasis in Pancreatic Cancer

MiR-4282 overexpression model was constructed in PANC-1 and BxPC-3 cells by transfection of miR-4282 mimic (Figure 2A). Overexpression of miR-4282 largely decreased migratory cell number in PANC-1 and BxPC-3 cells (Figure 2B). Meanwhile, wound closure percentage was lower in pancreatic cancer cells overexpressing miR-4282 than those of controls (Figure 2C). It is concluded that overexpression of miR-4282 inhibited migratory ability in pancreatic cancer.

MiR-4282 Bound to ABCB5

Using online bioinformatics tools, we predicted consequential pairing of target region in the seed sequence of ABCB5 and miR-4282 was identified. Dual-luciferase reporter assay was conducted by co-transfection of Luciferase vectors and miR-4282 mimic. Luciferase activity markedly decreased in PANC-1 and BxPC-3 cells co-transfected with miR-4282 mimic and ABCB5-WT vector, confirming that miR-4282 could be bound by ABCB5 (Figure 3A). Protein and mRNA levels of ABCB5 were downregulated in

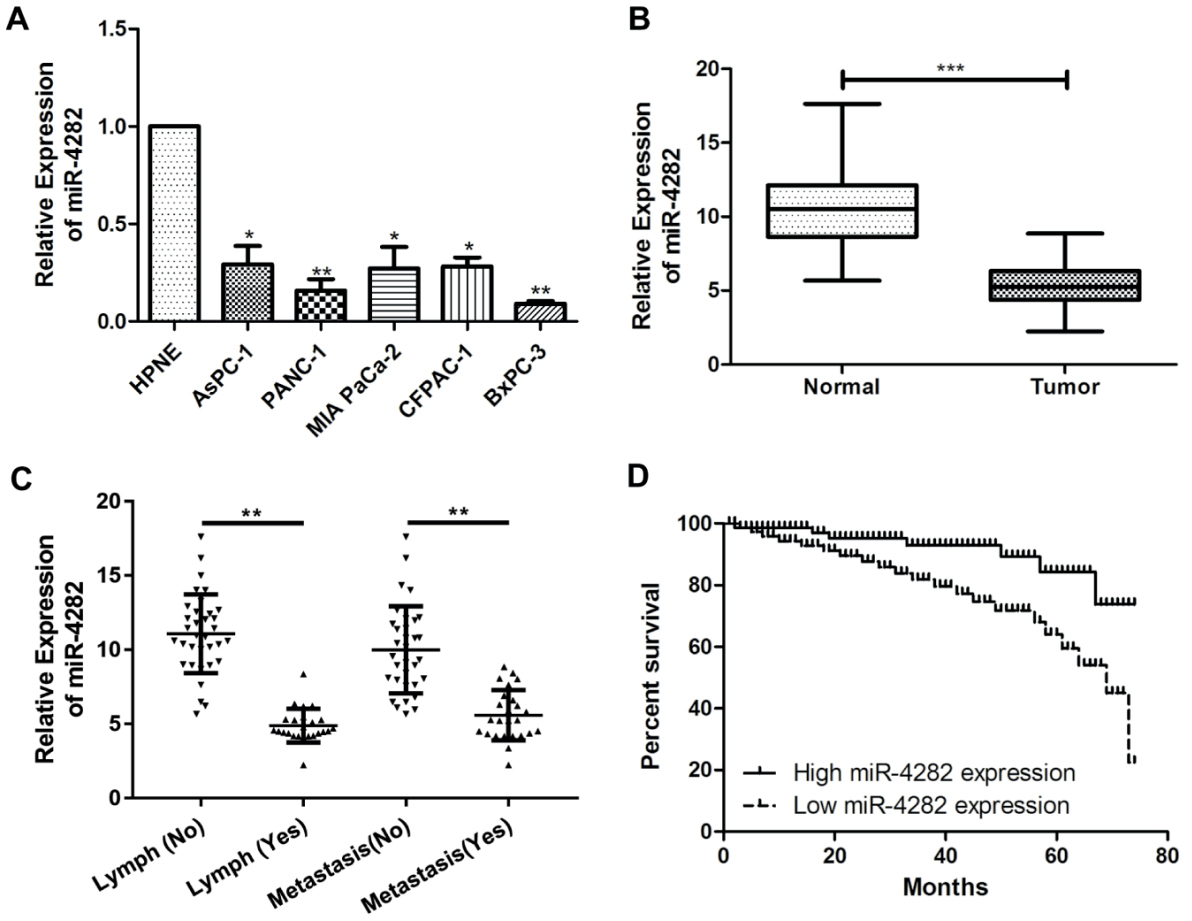

Figure 1. MiR-4282 was lowly expressed in pancreatic cancer tissues and cell lines. **A,** MiR-4282 levels in pancreatic cancer cell lines. **B,** MiR-4282 levels in pancreatic cancer tissues and normal ones. **C,** MiR-4282 levels in pancreatic cancer patients either with lymphatic metastasis, distant metastasis or not. **D,** Overall survival in pancreatic cancer patients with high or low expression of miR-4282. Data were expressed as mean±SD. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Table I. Association of miR-4282 expression with clinicopathologic characteristics of pancreatic cancer.

Parameters	Number of cases	miR-4282 expression		p
		High (%)	Low (%)	
Age (years)				0.778
<60	23	14	9	
≥60	35	20	15	
Gender				0.863
Male	21	12	9	
Female	37	22	15	
T stage				0.419
T1-T2	35	22	13	
T3-T4	23	12	11	
Lymph node metastasis				0.028
No	34	24	10	
Yes	24	10	14	
Distance metastasis				0.012
No	33	24	9	
Yes	25	10	15	

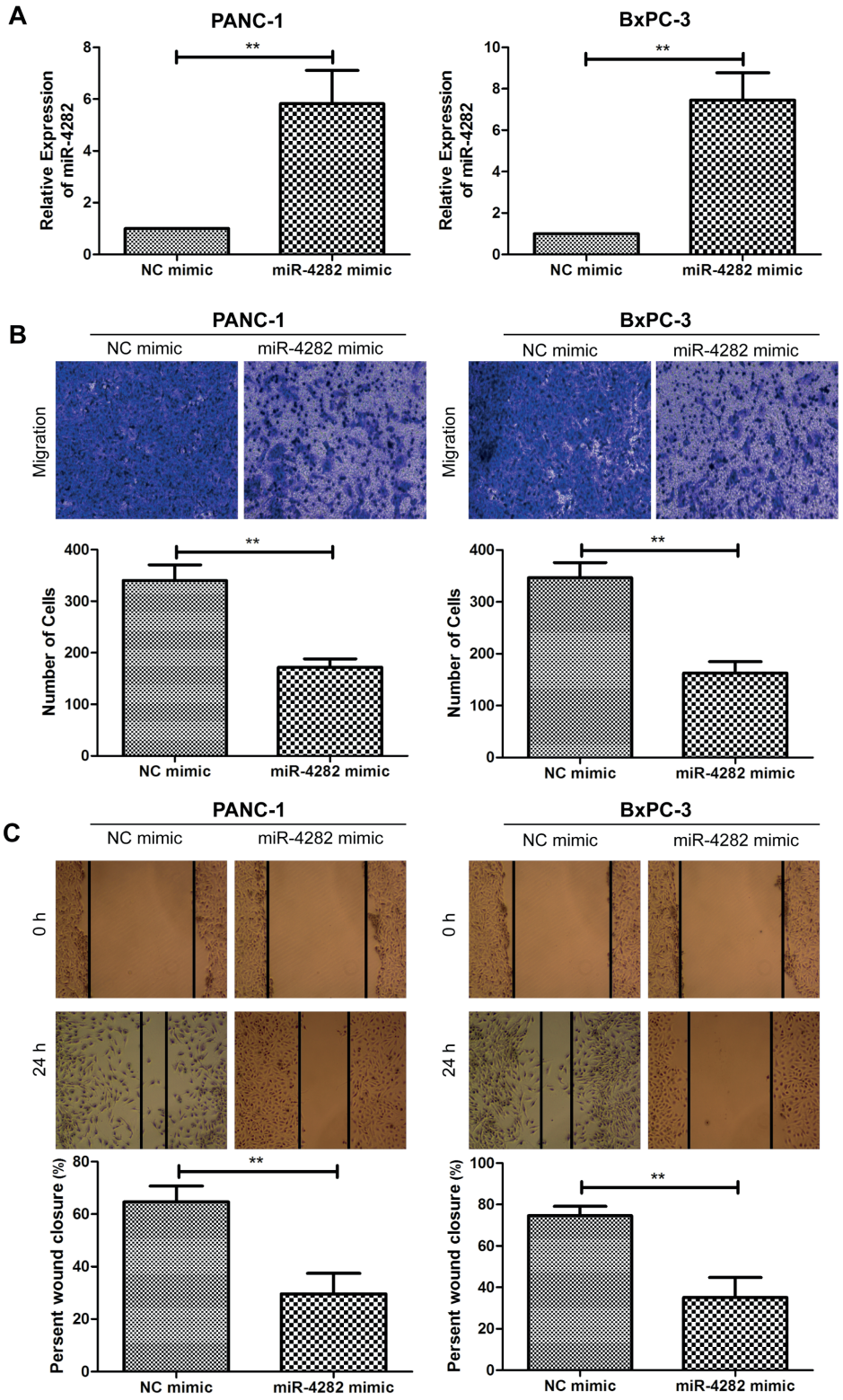

Figure 2. Overexpression of miR-4282 inhibited metastasis in pancreatic cancer. **A,** MiR-4282 level in PANC-1 and BxPC-3 cells transfected with NC mimic or miR-4282 mimic. **B,** Migration in PANC-1 and BxPC-3 cells transfected with NC mimic or miR-4282 mimic (magnification: 40×). **C,** Wound closure percentage in PANC-1 and BxPC-3 cells transfected with NC mimic or miR-4282 mimic (magnification: 40×). Data were expressed as mean±SD. $^{**}p < 0.01$.

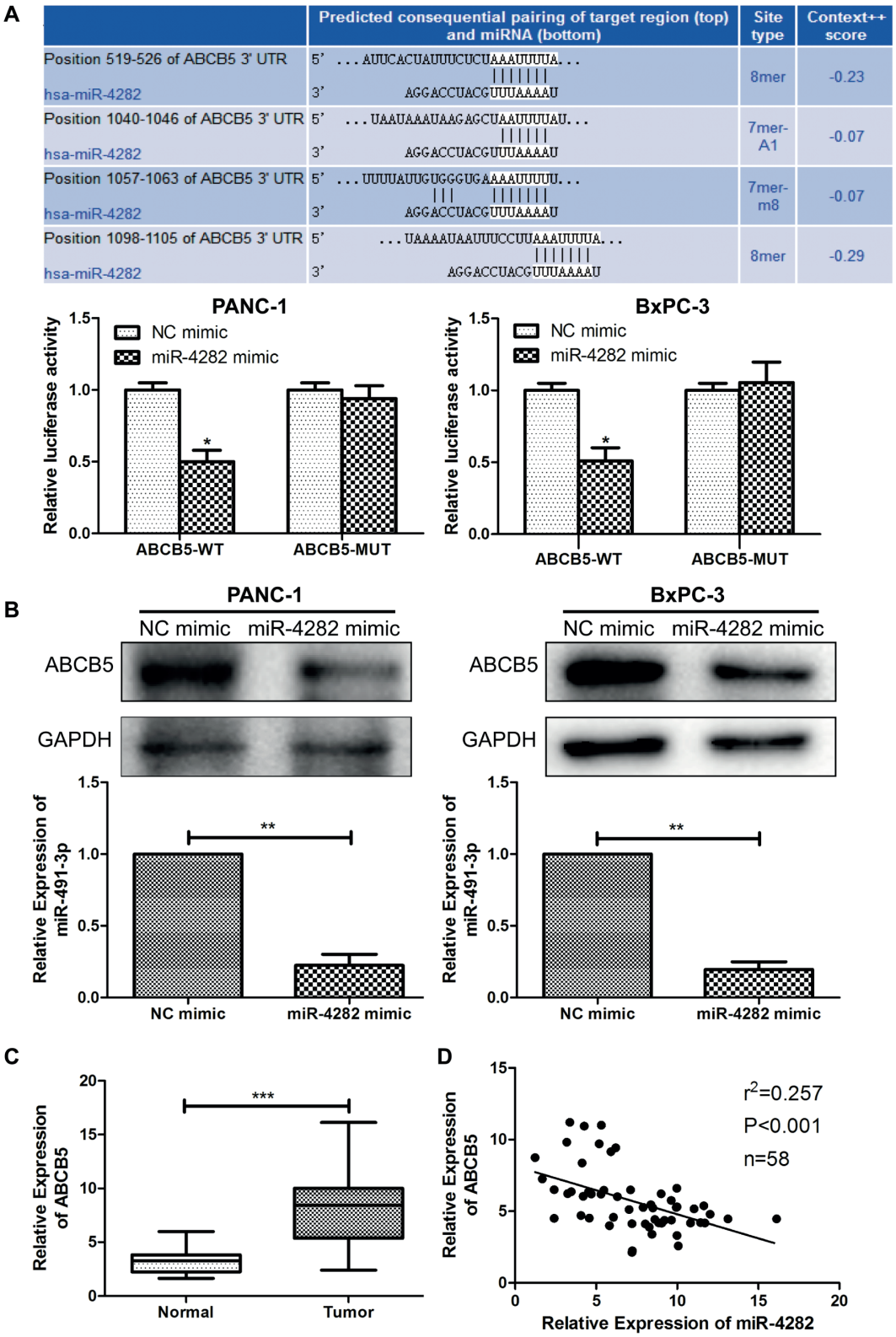

Figure 3. MiR-4282 bound to ABCB5. **A,** Luciferase activity in PANC-1 and BxPC-3 cells co-transfected with NC mimic/miR-4282 mimic and ABCB5-WT/ABCB5-MUT. **B,** Protein and mRNA levels of ABCB5 in PANC-1 and BxPC-3 cells transfected with NC mimic or miR-4282 mimic. **C,** ABCB5 levels in pancreatic cancer tissues and normal ones. **D,** A negative correlation between expression levels of miR-4282 and ABCB5. Data were expressed as mean±SD. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

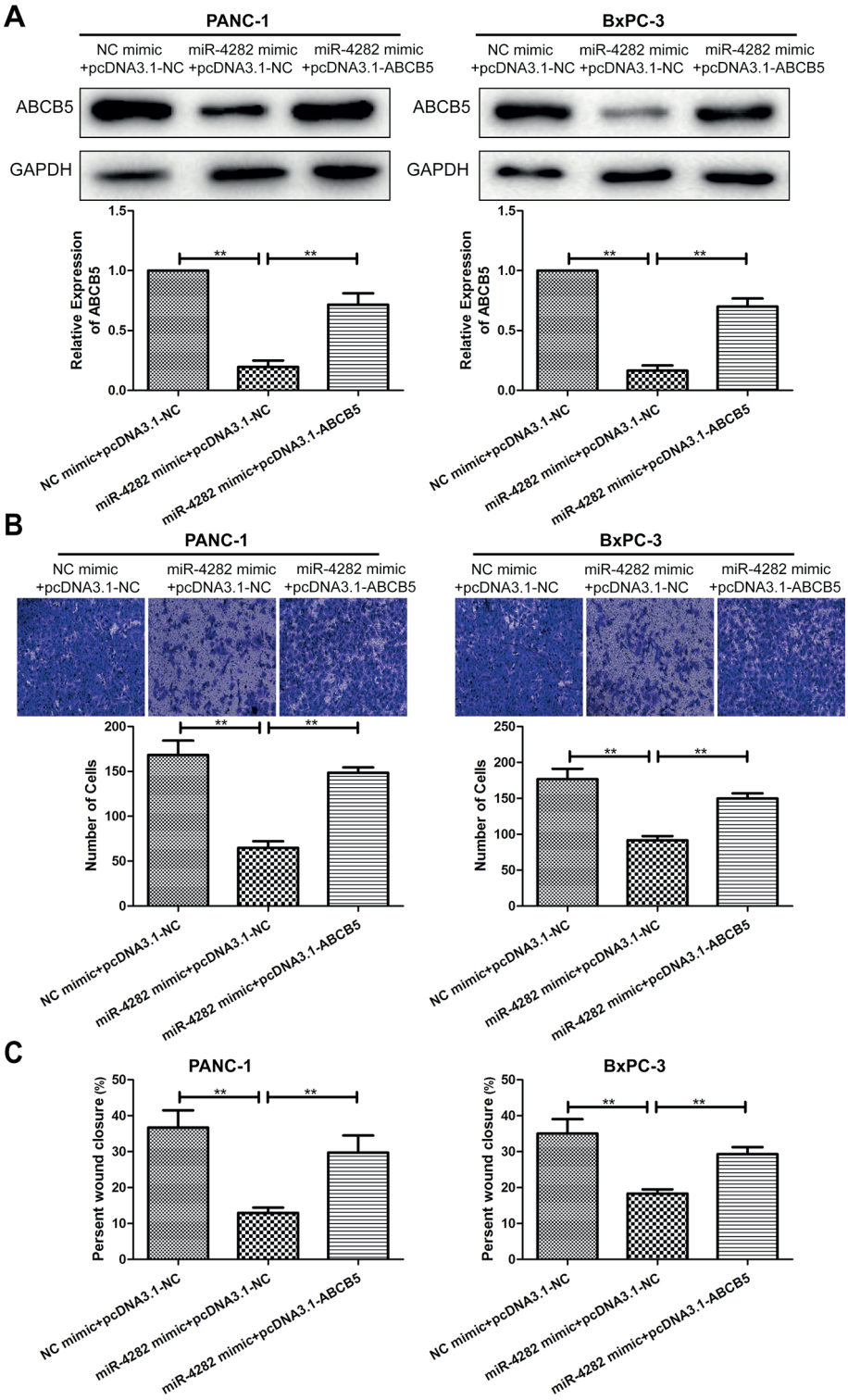

Figure 4. ABCB5 was involved in miR-4282-regulated phenotypes of pancreatic cancer cells. **A,** Protein and mRNA levels of ABCB5 in PANC-1 and BxPC-3 cells transfected with NC mimic+pcDNA3.1-NC, miR-4282 mimic+pcDNA3.1-NC or miR-4282 mimic+pcDNA3.1-ABCB5. **B,** Migration in PANC-1 and BxPC-3 cells transfected with NC mimic+pcDNA3.1-NC, miR-4282 mimic+pcDNA3.1-NC or miR-4282 mimic+pcDNA3.1-ABCB5 (magnification: 40×). **C,** Wound closure percentage in PANC-1 and BxPC-3 cells transfected with NC mimic+pcDNA3.1-NC, miR-4282 mimic+pcDNA3.1-NC or miR-4282 mimic+pcDNA3.1-ABCB5 (magnification: 40×). Data were expressed as mean±SD. $^{**}p < 0.01$.

pancreatic cancer cells overexpressing miR-4282 (Figure 3B). Differential expressions of ABCB5 were examined between pancreatic cancer tissues and normal ones. As qRT-PCR data uncovered, ABCB5 was upregulated in pancreatic cancer tissues (Figure 3C), and notably, displayed a negative correlation to miR-4282 level (Figure 3D).

ABCB5 Was Involved in MiR-4282-Regulated Phenotypes of Pancreatic Cancer Cells

We next explored the biological function of ABCB5 in pancreatic cancer progression. Transfection of pcDNA3.1-ABCB5 markedly increased the downregulated level of ABCB5 in PANC-1 and BxPC-3 cells overexpressing miR-4282 (Figure 4A). Subsequently, migration changes in pancreatic cancer cells influenced by both miR-4282 and ABCB5 were assessed by transwell and wound healing assay. Co-overexpression of miR-4282 and ABCB5 markedly reversed migratory characteristic in pancreatic cancer cells induced by overexpression of miR-4282 (Figure 4B, 4C).

Discussion

Pancreatic cancer is a digestive system solid tumor featured by an extremely high mortality. The medical burden on pancreatic cancer is the greatest in Asia owing to the large population and increased incidence[1-4]. In our country, the morbidity to mortality ratio of pancreatic cancer is approximately 1:0.99, and it has become a malignant tumor that severely affects human health[4-6]. Pancreatic cancer has a strong ability to promote the growth of fibrous connective tissues. Such an ability is beneficial to the rapid development of local invasion through infiltration to the surrounding organs and blood vessels, and distant metastasis by extensive lymph node involvement[7,8]. Surgical resection is an effective strategy only preferred to early stage pancreatic cancer patients[8,9]. Pancreatoduodenectomy is also optional in a small number of advanced pancreatic cancer patients. Most of these patients are treated by palliative care aiming to relieve the pain. However, surgery cannot remarkably improve their prognosis. More than 80% of operated pancreatic cancer patients may develop relapse. Therefore, comprehensive treatment for pancreatic cancer, such as radiotherapy and chemotherapy, is needed[7-9]. It is believed that early diagnosis of pancreatic cancer is the best way to improve the survival[9-11].

MiRNAs are non-coding RNAs containing 18-24 nucleotides. They are highly stable and tissue-specific. Their expressions in the blood are not affected by an extreme pH value and body temperature[14,17]. MiRNAs are functional in life activities, which are responsible for regulating development, differentiation, metabolism and other aspects[16,17]. In addition, they are key regulators in many human diseases. Serving as oncogenes or tumor suppressors, miRNAs are involved in tumor progression[13,14]. For lowly expressed miRNAs in tumor samples with the anti-cancer characteristics, they can be utilized as therapeutic targets for tumor diseases[13,14,17]. The literature on the miR-4282 is scarce; and its association and pancreatic cancer is unclear. Our findings showed that miR-4282 was downregulated in pancreatic cancer tissues than that of normal ones. Its level was closely related to metastasis incidence and poor prognosis in pancreatic cancer patients, indicating the potential anti-cancer role of miR-4282 in pancreatic cancer progression. *In vitro* experiments were conducted in PANC-1 and BxPC-3 cells transfected with miR-4282 mimic or NC mimic. Overexpression of miR-4282 remarkably weakened migratory ability in pancreatic cancer cells.

MiRNAs negatively regulate gene expressions by inhibiting transcriptional pathway or post-transcriptionally degrading target mRNAs[15,16]. Over 60% of protein-encoding genes can be regulated by miRNAs[16]. Our results verified the direct binding between miR-4282 and ABCB5. The behavior of ABCB5 was better known in the oncology by contrast to miR-4282. Moreover, miR-4282 overexpression failed to enrich mutant-type ABCB5 vector, further supporting our conclusion. ABCB5 level was found to be negatively regulated by miR-4282 in pancreatic cancer cells. At last, rescue experiments illustrated that ABCB5 abolished the regulatory effects of miR-4282 on pancreatic cancer migration. Collectively, the anti-cancer effect of miR-4282 on the malignant progression of pancreatic cancer cells required the involvement of ABCB5. To sum up, as a novel tumor suppressor gene, miR-4282 could inhibit the malignant development of pancreatic cancer, which became a promising biomarker for diagnosis and treatment for pancreatic cancer.

Conclusions

Summarily, miR-4282 is able to inhibit the migratory ability in pancreatic cancer cells by neg-

atively targeting ABCB5, which may become a promising pancreatic cancer biomarker.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Ilic M, Ilic I. Epidemiology of pancreatic cancer. World J Gastroenterol 2016; 22: 9694-9705.
2) McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: a review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol 2018; 24: 4846-4861.
3) Mohammed S, Van Buren GN, Fisher WE. Pancreatic cancer: advances in treatment. World J Gastroenterol 2014; 20: 9354-9360.
4) Chiorean EG, Coveler AL. Pancreatic cancer: optimizing treatment options, new, and emerging targeted therapies. Drug Des Devel Ther 2015; 9: 3529-3545.
5) Yabar CS, Winter JM. Pancreatic cancer: a review. Gastroenterol Clin North Am 2016; 45: 429-445.
6) Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology 2013; 144: 1252-1261.
7) Lin QJ, Yang F, Jin C, Fu DL. Current status and progress of pancreatic cancer in China. World J Gastroenterol 2015; 21: 7988-8003.
8) Jia X, Du P, Wu K, Xu Z, Fang J, Xu X, Lin K. Pancreatic cancer mortality in China: characteristics and prediction. Pancreas 2018; 47: 233-237.
9) Raman P, Maddipati R, Lim KH, Tozeren A. Pancreatic cancer survival analysis defines a signature that predicts outcome. PLoS One 2018; 13: e201751.
10) Collisson EA, Bailey P, Chang DK, Biankin AV. Molecular subtypes of pancreatic cancer. Nat Rev Gastroenterol Hepatol 2019; 16: 207-220.
11) Gilliland TM, Villafane-Ferriol N, Shah KP, Shah RM, Tran CH, Massarweh NN, Silberfein EJ, Choi EA, Hsu C, McElhany AL, Barakat O, Fisher W, Van Buren G. Nutritional and metabolic derangements in pancreatic cancer and pancreatic resection. Nutrients 2017; 9: 243.
12) Torres C, Grippo PJ. Pancreatic cancer subtypes: a roadmap for precision medicine. Ann Med 2018; 50: 277-287.
13) Tutar Y. MiRNA and cancer; computational and experimental approaches. Curr Pharm Biotechnol 2014; 15: 429.
14) Rupaimoole R, Slack FJ. MicroRNA therapeutics: towards a new era for the management of cancer and other diseases. Nat Rev Drug Discov 2017; 16: 203-222.
15) Afonso-Grunz F, Muller S. Principles of miRNA-mRNA interactions: beyond sequence complementarity. Cell Mol Life Sci 2015; 72: 3127-3141.
16) Sun B, Liu C, Li H, Zhang L, Luo G, Liang S, Lu M. Research progress on the interactions between long non-coding RNAs and microRNAs in human cancer. Oncol Lett 2020; 19: 595-605.
17) Abreu FB, Liu X, Tsongalis GJ. miRNA analysis in pancreatic cancer: the Dartmouth experience. Clin Chem Lab Med 2017; 55: 755-762.
18) Zhang Y, Zhang Z, Huang W, Zeng J. MiR-4282 inhibits tumor progression through down-regulation of ZBTB2 by targeting LIN28B in oral squamous cell carcinoma. J Cell Physiol 2020. Doi: 10.1002/jcp.29458. Online ahead of print.
19) Zhao J, Jiang GQ. MiR-4282 inhibits proliferation, invasion and metastasis of human breast cancer by targeting Myc. Eur Rev Med Pharmacol Sci 2018; 22: 8763-8771.
20) Louphrasitthiphol P, Chauhan J, Goding CR. ABCB5 is activated by MITF and beta-catenin and is associated with melanoma differentiation. Pigment Cell Melanoma Res 2020; 33: 112-118.
21) Sasamoto Y, Sasamoto N, Tran J, Mishra A, Ksander BR, Frank MH, Frank NY. Investigation of factors associated with ABCB5-positive limbal stem cell isolation yields from human donors. Ocul Surf 2020; 18: 114-120.
22) Guo Q, Grimmig T, Gonzalez G, Giobbie-Hurder A, Berg G, Carr N, Wilson BJ, Banerjee P, Ma J, Gold JS, Nandi B, Huang Q, Waaga-Gasser AM, Lian CG, Murphy GF, Frank MH, Gasser M, Frank NY. ATP-binding cassette member B5 (ABCB5) promotes tumor cell invasiveness in human colorectal cancer. J Biol Chem 2018; 293: 11166-11178.
23) Yao J, Yao X, Tian T, Fu X, Wang W, Li S, Shi T, Suo A, Ruan Z, Guo H, Nan K, Huo X. ABCB5-ZEB1 axis promotes invasion and metastasis in breast cancer cells. Oncol Res 2017; 25: 305-316.