Knockdown EIF3C Suppresses Cell Proliferation and Increases Apoptosis in Pancreatic Cancer Cell

Heng Jiao¹, Lingxiao Zeng¹, Shengsheng Yang², Jianpeng Zhang², and Wenhui Lou¹

Abstract
Increasing evidence shows that eukaryotic initiation factor subunit (EIF3C) plays a crucial role in development of tumors. However, the underlying roles of EIF3C in the development of pancreatic cancer (PC) remain unknown. In this study, we examined the expression of EIF3C in PC tissues, their adjacent normal tissues and 3 cell lines (SW1990, PANC-1 and AsPC-1). Moreover, the EIF3C-shRNA lentivirus was constructed to suppress EIF3C expression. Following this, the cell colony formation assay was employed to evaluate proliferation ability of PC cells. Meanwhile, the cell cycle and apoptotic assays were also performed by flow cytometry. We found that level of EIF3C in PC tissues was significantly increased compared with that in adjacent normal tissues. Furthermore, the knockdown of EIF3C can significantly reduce cell proliferation, block cell cycle in G2/M and induce apoptosis in both SW1990 and PANC-1 cells. Our findings suggest that EIF3C plays a crucial role in the progression of PC and may be a potential target in the treatment of PC.

Keywords
eukaryotic initiation factor subunit, pancreatic adenocarcinoma, SW1990 cells, PANC-1 cells

Introduction
Pancreatic cancer (PC) is a lethal disorder for people around the world, which is characterized by high metastasis and recurrence.¹,² Some studies have shown that smoking, obesity, diabetes and pancreatitis are risk factors for PC, and approximately 10% of PC patients have a family background.³-⁶ The prevalence of obesity is high in Chinese population.⁷-⁹ Delineating obesity could be a beneficial strategy to combat PC. Moreover, the incidence of PC in China has been gradually increasing over the recent decades.¹⁰ According to a recent report, the 5-year survival rate is still less than <5% for patients suffering from PC.¹¹ Numerous studies have reported that more than half of the patients diagnosed with PC were often in the stage of tumor progression, or even had metastasis with poor treatment effect.¹²,¹³ Unfortunately, the molecular mechanisms of PC progression have not been completely clarified. Eukaryotic translation initiation factor (EIF) played essential roles in regulating the translation initiation process in eukaryotes and a total of 12 kinds of EIF have been found.¹⁴ In particular, increasing research groups have suggested that EIF3 is one of the largest and most complex EIF. In mammalian cells, EIF3 is composed of 13 subunits such as EIF3A, EIF3B, EIF3C, EIF3E and EIF3F.¹⁵ Protein translation initiation plays an important role in protein synthesis and regulating various cellular activities. EIF3 is also an important regulatory factor involved in various physiological processes of cells. Studies have shown that the abnormal expression EIF3 may be closely related to cell growth, cell cycle and tumorigenesis.¹⁶ Furthermore, several research groups have found that several EIF3 subunits such as EIF3D and EIF3G were abnormally expressed in melanoma and colorectal cancer.¹⁷,¹⁸ These findings suggest that EIF3 may play a vital role in the treatment of PC.

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role in the process of human carcinogenesis. However, the underlying pathogenesis of EIF3C in PC development and progression has not been fully explored.

In the current study, we examined the expression levels of EIF3C in PC tissue and adjacent normal tissues. In addition, loss-function experiments of EIF3C were conducted to investigate the biological roles of EIF3C in PC cell proliferation, growth and apoptosis, which will contribute to understanding the molecular mechanisms of EIF3C for PC development.

**Materials and Methods**

**Immunohistochemical Staining**

The PC and adjacent normal tissues were obtained from PC patients. The clinical information of these patients including TNM, clinical stage and pathological grade was also collected (Table 1). The tissue chip (PA807) was purchased from Xi’an Alina biotechnology co., LTD., which is a combination chip of PC, cancer perianth and necrotic tissue with a total of 80 cases/80 points. Immunohistochemistry (IHC) staining was performed according to the standard protocol. Briefly, the tissue chip was firstly placed in an Oven (Shanghai Precision Instrument Manufacturing Co., Ltd) at 64% and then dewaxed. Subsequently, the tissue chip was removed from the dyeing machine and rinsed 3 times with pure water followed by antigen retrieval by microwave exposure in the citric acid repair solution. Afterward, the tissue chip was blocked with 10% bovine serum albumin for 30 min and incubated overnight with primary Rabbit anti(EIF3CIgG (1:400), followed by biotinylation with secondary anti-goat antibodies IgG for 60 min. Then, the tissue chip was treated with diaminobenzidine (DAB) according to the manufacturer’s instructions. Finally, the tissue chip was counterstained with hematoxylin and examined using a microscope (Olympus, Japan).

**Cell Culture**

The 293 T cells and 3 human PC cell lines (SW1990, PANC-1 and AsPC-1) were purchased from the cell bank of the Chinese Academy of Sciences. The cells were maintained in DMEM supplemented with 10% FBS, 100 U/mL penicillin, and 100 mg/mL streptomycin in a humidified atmosphere of 5% CO2 at 37°C.

**Table 1.** The clinical information of pancreatic cancer patients.

| Characteristic        | Pancreatic cancer (n = 80) |
|-----------------------|----------------------------|
| Sex                   |                            |
| Male                  | 42                         |
| Female                | 38                         |
| Race                  |                            |
| Asian                 | 80                         |
| Age, years            | 56.3 ± 4.7                 |
| Smoking history       |                            |
| NO                    | 65                         |
| YES                   | 15                         |
| Disease stage         |                            |
| I (13)                |                            |
| II (36)               |                            |
| III (31)              |                            |

**Figure 1.** Immunohistochemical staining of EIF3C in PC tissue chips and 3 PC cell lines. (A) Immunohistochemical staining of EIF3C in PC tissue chips. (B) The EIF3C protein levels were detected by immunohistochemistry in tumor and paratumor. (C) the expression levels of EIF3C in 3 pancreatic cancer cell lines. (D) Relative expression level of EIF3C in patients of different tumor stages.
academy of sciences in Shanghai and stored in the biochemistry teaching and research office of the second military medical university. The cells were cultured in RPMI1640 medium supplemented with 10% fetal bovine serum (FBS) and penicillin/streptomycin (100 μg/mL) at 37% in a humidified atmosphere of 5% CO₂. When cell growth approached 80% confluence, 0.25% trypsin was used for digestion and passage.

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

Total RNA was extracted from adherent cells cultured in 25 cm² culture flasks and used to synthesize the cDNA using the Promega M-MLV cDNA synthesis kit according to the manufacturer’s instructions. The expression level of EIF3C was examined using TAKARA SYBR qPCR Mix kit. The semi-quantitative RT-PCR was carried out with initial denaturation at 95°C for 60 s, followed by 40 cycles of 95°C for 15 s, and 60°C for 60 s. The glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as an internal reference. The primers used were as followed: EIF3C, forward primer 5’-AGATGAGGAT-GAGGATGAGGAC-3’ and reverse primer 5’-GGAATCG-GAAGATGTGGAACC-3’; GAPDH, forward primer 5’-TGACTTCAACAGCGACACCCA-3’ and reverse primer 5’-CACCCCTGGTGTGCTAGCCAAA-3’.

Western Blot Analysis

Briefly, the cells were washed 2 times with cold phosphate buffered saline (PBS), lysed with 200μL radio-immune precipitation assay (RIPA) and placed on ice for 30 min. The mixture was fully blown and centrifuged at 12000 r/min for 10 min. Then,
the protein concentration was determined by BCA protein quantitative kit using standard procedures. The 15 μL of collected protein was loaded onto a 12% sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) gel and electrophoresed at 120 V. After that, the gel was transferred to polyvinylidene difluoride membrane and the proteins were detected by respective. Millipore’s western blot enhanced chemiluminescence Reagent (ECL Reagent A&B) was used for imaging.

Construction and Transfection of the eIF3c-shRNA Lentivirus

The eIF3C-shRNA nucleotide sequence (5’-GTCAGTTTTAAAGGTCTGTGTTTA-3’) was inserted into the plasmid using the vector pGV115 and lentivirus packing eIF3C-shRNA Lentivector Expression Systems (Jikai biotechnology co., LTD, China). Then, the generated eIF3C-shRNA lentiviral was confirmed by DNA sequencing. The SW1990 and PANC-1 cells were infected with eIF3C-shRNA lentivirus and control shRNA (shCtrl), respectively. After 3 days of infection, GFP expression was observed by fluorescence microscopy. Moreover, the cells were harvested to determine knockdown efficiency by real-time quantitative PCR and western blot after transfection for 5 days.

The Detection of Cell Proliferation and Growth

The SW1990 and PANC-1 cells with eIF3C-shRNA or control shRNA lentivirus transfection was collected during logarithmic phase and dispersed with trypsin digestive method. Then these cells were re-suspended, plated and maintained in incubators at 37% in a humidified atmosphere of 5% CO2. After 2 days, the Celigo image cytometer was utilized to examine the cell growth and computed the number of cells. Finally, the curve of cell proliferation was constructed.

Cell Apoptosis and Cell Cycle Detection

When the confluence rate reached 70%, cells were cultured in 6-well plates and infected with eIF3C-shRNA or control shRNA lentivirus. Fresh culture medium was replaced after transfection for 12 h, digested with 0.25% trypsin after transfection for 48 h, and collected in 1.5 ml micro-tube for cell apoptosis and cell cycle detection. Furthermore, we examined

Figure 3. The effect of shIF3c lentivirus on proliferation of SW1990 cells. (A) Colony-forming growth assay was performed to determine the proliferation of shCtrl or shEIF3C transfected SW1990 and PANC-1 cells. (B) The clone number of control and shEIF3C group of SW1990 cells are 148 ± 11.36 and 56 ± 14.32, respectively. The clone number of control and shEIF3C group of PANC-1 cells are 139 ± 14.23 and 47 ± 9.72, respectively. (C) Cell proliferation of SW1990 cells were examined by CCK-8 after transfection with shEIF3C and shCtrl from day 1 to 3. (C) Cell proliferation of PANC-1 cells were examined by CCK-8 after transfection with shEIF3C and shCtrl from day 1 to 3.
the apoptosis-related proteins (caspase-e3/7) by Aspase-glo® 3/7 assay. Multifunctional enzyme marker was used to determine signal strength. Additionally, for the detection of cell cycle, cells with EIF3C-shRNA or control shRNA lentivirus transfection were washed twice with PBS solution and fixed using 70% ethanol overnight. Subsequently, these cells were re-suspended and 1mg/ml RNase A and 50µg/mL PI (propidium iodide) solution was added. After staining for 30 min, the cell cycle DNA content was analyzed using flow cytometry to determine the distribution of cell cycle.

Statistical Analysis

All data was statistically analyzed using SPSS 11.7 software and expressed as mean ± standard deviation (SD) in this study. The paired t test and ANOVA was also used for comparison analysis between groups. The significant differences between the groups were analyzed by a Chi-square test and Fisher’s exact test. All figures were constructed by Prism 5 software.

Results

The expression of EIF3C protein in PC microarray and 3 PC cell lines The expression of EIF3C protein in PC tissues was analyzed by immunohistochemistry. The results showed that EIF3C protein was located in the cytoplasm and was not observed in the nucleus or envelope (Figure 1A and B). Moreover, the staining intensity of EIF3C protein in PC tissues was 2.55 times higher than that in adjacent normal tissues ($P < 0.001$), suggesting that there was a higher level of EIF3C in PC tissues than adjacent normal tissues. Furthermore, the expression level of EIF3C in patients of different tumor stages were evaluated, we observed significantly increased expression level of EIF3C in late stages of PC (stage II and III) than early stage (stage I, Figure 1D). In addition, the expression levels of EIF3C in PC cell lines (SW1990, PANC-1 and AsPC-1) were detected by qRT-PCR. The ΔCt values of EIF3C expression level in SW1990, PANC-1 and AsPC-1 cells were 4.71, 3.64 and 2.98, respectively (Figure 1C), showing that the EIF3C gene was highly expressed in these 3 PC cells. Herein, we chose the SW1990 and PANC-1 cell line in the following analysis.

Effect of EIF3C Silencing on Proliferation of SW1990 and PANC-1 Cells

As shown in Figure 2A, the establishment of lentivirus vector with EIF3C-shRNA was confirmed by colony PCR identification. Furthermore, the positive clones were
cultured and sequenced, confirming the accuracy of the interference gene sequence inserted by EIF3C (Figure 2B). In addition, the efficiency of EIF3C knockdown of SW1990 and PANC-1 cells transfected with EIF3C shRNA and control shRNA was confirmed by real-time PCR and western blot analysis (Figure 2C-F). The results indicated that EIF3C was markedly decreased in those cells with EIF3C-shRNA transfection compared with that transfected with control shRNA.

We further evaluated the impact of on the cell proliferation for SW1990 cell with EIF3C-shRNA or control shRNA. After EIF3C knockdown, colonies formation was significantly inhibited compared with control cells in both SW1990 and PANC-1 cells (Figure 3A and B). The number of cells decreased significantly on day2 and 3 after transfection with EIF3C-shRNA compared with those cells transfected with control (Figure 3C and D). These results indicated that the EIF3C knockdown could significantly suppressed the proliferation of SW1990 and PANC-1 cells.

**Effects of EIF3C Silencing on the Apoptosis of SW1990 and PANC-1 Cells**

In order to investigate the influence of EIF3C on cell apoptosis. We therefore performed PI and Annexin V staining followed by flow cytometry. As shown in Figure 4A and B,

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**Figure 5.** The effect of shEIF3C lentivirus on SW1990 and PANC-1 cell cycle (A) Cell cycle of SW1990 cells transfected with EIF3C shRNA and control shRNA were analyzed by flow cytometry analysis. (B) The percentage of G1, S and G2/M phase after transfection with EIF3C shRNA and control shRNA of SW1990 cells. (C) Cell cycle of PANC-1 cells transfected with EIF3C shRNA and control shRNA were analyzed by flow cytometry analysis. (D) The percentage of G1, S and G2/M phase after transfection with EIF3C shRNA and control shRNA of PANC-1 cells.
the apoptotic rates in cells transfected with EIF3C-shRNA group and control group (shCtrl) were 12.13% and 4.57%, respectively, in SW1990 cells; 15.32% and 6.52%, respectively, in PANC-1 cells (Figure 4A and B). Meanwhile, the number of apoptotic cells in EIF3C-shRNA group was significantly increased compared with control group ($P < 0.05$). In addition, the caspase3/7 activity was also significantly increased in the EIF3C-shRNA group compared with the control group in SW1990 cells (Figure 4C). Therefore, these results showed that inhibition of EIF3C expression in SW1990 and PANC-1 cells could significantly induce the cell apoptosis.

**Effects of EIF3C Silencing on Cell Cycle, Migration and Invasion of SW1990 and PANC-1 Cells**

Flow cytometry was used to detect the role of EIF3C in SW1990 and PANC-1 cell cycle progression. As shown in Figure 5, the cell group with EIF3C-shRNA transfection had fewer cells in G1 phase ($P < 0.05$), no significant changes in S phase, and more cells in G2/M phase compared with the control group. The results showed that inhibition of EIF3C expression resulted in G2/M phase arrest in SW1990 and PANC-1 cells. What’s more, EIF3C knockdown could significantly inhibit the migrative and invasive abilities of SW1990
and PANC-1 cells compared with the control, as detected by transwell assays (Figure 6A-D). Western blot analysis of epithelial mesenchymal transition (EMT) markers showed that EIF3C knockdown enhance EMT in both SW1990 and PANC-1 cells (Figure 6E and F).

**Discussion**

Existing evidence has showed that EIF3C, a key subunit in the EIF3 complex, plays an important role in the initiation of protein translation. In addition, previous studies have demonstrated that inhibition of EIF3C expression can lead to inhibit cell proliferation and apoptosis. However, the potential roles of EIF3C in PC have not been fully understood.

To our knowledge, we firstly explored the effects of this gene on the molecular mechanisms of PC in this work. Our results found that there was a higher expression level of EIF3C in PC tissues than adjacent normal tissues. Doldan et al. previously investigated the association between EIF3 and PC progression and they noted that EIF3 was remarkably reduced in PC patients, which provided the direct support for our finding. Furthermore, we measured the expression levels of EIF3C in 3 PC cell lines (SW1990, PANC-1 and AsPC-1) and found that there was a higher EIF3C level in SW1990 cell line than other cell lines. Therefore, the SW1990 cell line was used to investigate the potential roles of EIF3C in PC initiation and development. Notably, the overwhelming evidence has indicated that aberrant expression of EIF3C is closely associated with several cell biological processes such as cell proliferation, growth and apoptosis. For example, a study reported that the inhibition of EIF3C in the glioma cells significantly suppressed cell proliferation and increased apoptosis. Moreover, it was found that the introduction of EIF3C-shRNAs into melanoma cells could inhibit their growth. In addition, Song et al. also used shRNA technology to knock down EIF3C in RKO colon cancer cells, and found that it could significantly inhibit the proliferation and clone formation of RKO cells and induced apoptosis. In this research, we examined the effects of EIF3C knockdown on the SW1990 and PANC-1 cell activities. Our results revealed that EIF3C silence markedly suppressed cell proliferation, resulted in cell cycle arrest in G2/M phase, and promotes cell apoptosis and EMT, which implying that EIF3C might be a promising therapeutic target for PC treatment.

Although our study reported the roles of EIF3C in 2 of PC cell lines (SW1990 and PANC-1), there still were some limitations. Firstly, the effects of EIF3C on the PC development still need to be explored by other PC cell lines and animal model experiments. Moreover, the detailed mechanisms of EIF3C in cell processes also require to be illuminated in the following investigation.

In conclusion, our study showed that there was a high expression of EIF3C in PC tissues and 3 PC cell lines (SW1990, PANC-1 and AsPC-1). Furthermore, the inhibition of EIF3C can significantly blocked cell proliferation, retarded cell cycle and induced apoptosis, migration and invasion of tumor cells which provided deeper understanding of the influence of EIF3C on PC occurrence and development.

**Author Contribution**

Heng Jiao and Lingxiao Zeng have contributed equally to this article.

**Declaration of Conflicting Interests**

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