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# Long noncoding RNA negative regulator of antiviral response contributes to pancreatic ductal adenocarcinoma progression *via* targeting miR-299-3p

Wang HQ *et al*. NRAV promotes progression of pancreatic ductal adenocarcinoma

Hai-Quan Wang, Chun-Hua Qian, Zeng-Ya Guo, Pei-Ming Li, Zheng-Jun Qiu

BACKGROUND

Pancreatic ductal cancer (PDAC) has high malignancy and poor prognosis. Long coding RNAs (lncRNAs) are associated with high levels of malignancies, including PDAC. However, the biological and clinical significance of negative regulator of antiviral response (NRAV) in PDAC is unclear.

AIM

To study the regulatory role of lncRNA NRAV in PDAC.

METHODS

"GEPIA" analyzed lncRNA NRAV and microRNA (miR)-299-3p expression levels in PDAC tissues and measured them in PDAC cells by quantitative measurements in real-time. The specific role of NRAV and miR-299-3p in cell proliferation and transfer potential was evaluated by cell formation analysis, cell counting kit-8 and Transwell analysis. The relationship between NRAV and miR-299-3p was studied by predictive bioinformatics, RNA immunoassay, and fluorescence enzyme analysis. *In vivo* experiments included transplantation of simulated tumor cells under naked mice.

RESULTS

The expression level of lncRNA NRAV was higher in both tumor tissues and cell lines of PDAC and was negatively associated with the clinical survival of PDAC patients. Functionally, overexpression of NRAV promoted cell proliferation and metastasis of PDAC cells, while knockdown of NRAV reversed these effects. Finally, NRAV was

performed as a molecular sponge of miR-299-3p. Moreover, overexpression of miR-299-3p could reverse the promoting effects of NRAV on cell proliferation and metastasis of PDAC cells.

CONCLUSION

NRAV facilitates the progression of PDAC as a molecular sponge of miR-299-3p and may be indicated as a potential molecular marker for the diagnosis and treatment of PDAC.

**Key Words:** Long noncoding RNA; Negative regulator of antiviral response; miR-299-3p; Proliferation; Migration; Invasion; Pancreatic cancer

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**Core Tip:** In the present research, the expression level of long noncoding RNA negative regulator of antiviral response (NRAV) in pancreatic ductal adenocarcinoma (PDAC) was detected, and the clinicopathological relationship between NRAV and PDAC was demonstrated. Moreover, cell and animal tests were conducted to assess the concrete roles of NRAV in the progression of PDAC. Finally, the existence of potential specific molecular mechanisms that can provide new ideas for finding new molecular markers for the diagnosis and treatment of PDAC is demonstrated.

## INTRODUCTION

As an extremely malignant tumor, pancreatic ductal adenocarcinoma (PDAC) has shown a rapidly increasing incidence rate in recent years worldwide[1]. According to the latest cancer report in 2021, there are 495773 new cases reported globally every year and about 466003 people die of PDAC annually[2]. Due to insufficient means of early

diagnosis and effective treatment, the 5-year survival rate of PDAC patients is only about 8% and will drop to about 3% in patients with advanced PDAC[1]. Therefore, it is urgent to establish a comprehensive pathological mechanism of PDAC and explore a more effective PDAC diagnosis and treatment center.

Long noncoding RNAs (lncRNAs) is a new non-coding RNAs that are composed of more than 200 nucleotides, accounting for the largest proportion of the entire human gene transcriptome[3,4]. LncRNAs mainly regulates gene expression in a variety of manners, including chromatin remodeling and transcriptional and post-transcriptional processing, and participate in regulating a variety of biological process[5,6]. Recently, a large number of researches showed that lncRNAs are dysregulated in most tumors and function as key regulators in the process of tumor growth, metastasis, drug tolerance, and angiogenesis[7,8]. The lncRNA negative regulator of antiviral response (NRAV) is a newly identified lncRNA and is mainly related to immunity[9]. Xu *et al*[10] found that NRAV is highly expressed in the cell system of hepatocytes and regulates the course of hepatocellular carcinoma. However, the statements and specific role of NRAV in PDAC are still unclear.

lncRNAs play an important regulatory role in the occurrence and development of various cancers and may be considered a potential molecular marker. Many studies have shown that RNA plays its biological function of competing with endogenous RNAs[11,12]. Hsa-miR-299-3p plays an important role in the development of many cancers. Many studies describe the regulation of the relationship between miR-299-3p and lncRNAs[13,14]. Many experts conducted in-depth research on the regulation of the relationship between the two and stated that miR-299-3p increased the volume and cellular system and prevented proliferation and metastasis of Pancreatic Cancer Cells with exposure to Notch1[15]. The relationship between NRAV and miR-299-3p in PDAC has not yet been investigated.

In this study, we tested the expression of NRAV in PDAC and studied its function, and found that NRAV and PDAC have obvious overlaps. The results of functional experiments showed that the level of NRAV expression was directly associated with

cell proliferation and metastasis and was closely related to the growth of tumors in naked mice. In addition, we found that NRAV, as a molecular sponge of miR-299-3p, contributes to PDAC progress. Therefore, the results of this study may provide new insights into the role of NRAV in PDAC. It can be a biomarker for the diagnosis and treatment of PDAC.

## MATERIALS AND METHODS

### *Cell lines*

PDAC cell lines (PANC-1, AsPC-1, Mia Paca-2, and BxPC-3) and Human immortalized normal pancreatic duct epithelial cell HPDE are obtained from the US ATCC agency (Manassas, United States). The cell lines were cultured at an appropriate concentration in a specific environment in a moistened cell incubator with a CO2 content of 5% at 37 °C. Percentage of 10 fetal serum and 1% penicillin-streptomycin were added to the cellular environment, including RPMI-1640 and DMEM.

### *RNA isolation and quantitative real-time-PCR*

The introduction in the instructions shows that total cellular RNA is extracted from cultured cells using Trizol reagent (Invitrogen, United States). For lncRNA, FastKing gDNA Dispeeling RT Supermix (TIANGEN, China) was selected for reverse transclncRNAn. The specific cDNAs of microRNAs were obtained with a specific kit (miDETECT A Track RT Reagent Kit) (RiboBio, China). According to the manufacturer's plan, the QRT PCR system uses ABI 7300 PCR (Foster City, United States). *U6* and *ACTB* were respectively deemed as standardized internal controls of microRNA and lncRNA. The specific sequences of the primers were designed as follows. For NRAV , 5′-GGAGTTGATGCCTCCGAACA-3′ (forward) and 5′-ATGACCGGAGCTGAAAGGTG-3′ (reverse); for β-actin, 5′-TCCCTGGAGAAGAGCTACGA-3′ (forward) and 5′-AGCACTGTGTTGGCGTACAG-3′ (reverse); for miR-299-3p, 5′-ACACTCCAGCTGGGTATGTGGGATGGTAAAC-3′ (forward) and 5′-GTGCAGGGTCCGAGGT-3′ (reverse); and for U6, 5′-

CTCGCTTCGGCAGCACA-3′ (forward) and 5′-AACGCTTCACGAATTTGCGT-3′ (reverse). The relative expression level of each gene was calculated with the $2^{-\Delta\Delta}$Ct method.

### *Cell transfection*

Lipofectamine 2000 kit (Invitrogen) was used to conduct cell transfection. Short hairpin RNAs (shRNAs) targeting NRAV were designed by Genepharma (Shanghai, China). The specific sequences targeting NRAV were designed as follows: For sh-NRAV #1, 5′-CACCTCATCCACAAGTAGGAC-3′; for sh-NRAV #2, 5′-TTGGAGCCAAGGACTGTACTG-3′; and negative control: 5′-TTCTCCGAACGTGTCACGT-3′. NRAV overexpression plasmid and shRNAs against NRAV were inserted into the pcDNA3.1 vector and pGpU6/GFP/Neo vector, respectively. The miR-299-3p mimic was purchased from RiboBio. The quantitative real-time-PCR (qRT-PCR) was performed to examine the transfecting efficiency.

### *Cell counting kit-8 assay*

First, a 96-well plate was selected, where 2000 tumor cells were cultured in each well; then they were transfected with different vectors and waited 48 h; 10 μL cell counting kit-8 (CCK-8) solution (Mashiki, Japan) was then added to each well, and incubated for 2 h; finally, a microplate reader (Winooski, United States) was used to check cell viability.

### *Colony formation assay*

The specific PDAC cells transfected with different plasmids were inoculated into 6-well plates at a certain concentration and incubated at 37 °C for 10 d. Then, tumor cells were fixed for 20 min in methanol after being washed with phosphate-buffered saline in triplicate. Cell colonies were stained and counted.

### *Transwell assay*

In migration and invasion assays, PDAC cells were added to resuspension after setting a concentration of $10^5$ mL in a serum-free environment. Two hundred μL of cell suspension was added to the upper layer of each Transwell chamber and 600 μL of complete media containing 10% fetal serum was added to the lower layer. To set up the invasion analysis phase, the Matrigel layer (BD Biosciences, United States) was first applied to the chamber membrane, the cell suspension was then placed on top of the transition chamber. A 24-h incubation was followed and the invasive cells were finally fixed and monitored and compared in five random fields.

***Tumor xenograft experiments***

All animal studies were approved by the Ethics Committee for Animal Studies at Shanghai 10th People's Hospital. Specific PANC-1 cells (2 × $10^6$, 200/L) were transplanted subcutaneously to the right side of naked male mice aged 4 wk. The condition of the mice was monitored daily and the size of the tumor was measured every five days. Tumor volume was calculated according to tumor length and length formula volume = length through × wide$^2$/2, tumour volume was estimated by combining the length and width of a specific tumor. Twenty days after vaccination, naked mice in humans were sacrificed and the entire tumor removed as much as possible and weighed.

***Immunohistochemical analysis***

Mouse tumors were removed and removed for immunohistochemical staining to visualize Ki-67 expression. Briefly, paraffin-bound sections were prepared and wax removed in 100% xylene, followed by rehydration with various gradients of ethanol and distilled water. The fabric is dyed with a protractor for 60 min at room temperature and removed during washing with distilled water. Subsequently, tissue sections were incubated with secondary antibodies bound to horseradish peroxidase for 20 min. To facilitate visualization, 3,3′-diaminobenzidine tetrahydrochloride Ki-67 was selected for positive staining.

### *Nuclear/cytoplasmic fractionation assay*

According to the manufacturer's instruction, PARIS Kit (Life Technologies, United States) was used to specifically isolate RNA from the nuclear and cytoplasm. Then, qRT-PCR assays were conducted as described.

### *RNA immunoprecipitation assay*

RIP assays were performed by EZ-Magna RNA Immunosuppression Kit (Millipore, United States). The cells were briefly collected and resuspended in an immuno-deposition buffer and kept on ice for 30 min. The cell suspension was then incubated with a separate RNA immunoprecipitation (RIP) buffer containing magnetic beads. Proteinase K was added to the bead state after buffering for further digestion of proteins. Finally, all RNA was extracted with Trizol and measured with qRT-PCR.

### *Dual-luciferase activity assay*

According to a special combination of software for network prediction starbes 3.0 and NRAV miR-299-3p (http://starbase.sysu.edu.cn/ b). Other matters according to the V2 specification (enzyme, China), it is a rapid mutation reagent for NRAV, and supplementary DNA and mutant miR-299-3p are added to psicheck2 (US Promega) (NRAV wild and music) satellite. Paycheck-2 and miR-229-3p plasmid samples or miR-229-3p negative control were transferred to PDAC cells. After 48 h of transplantation, the fluorescent enzyme activity of each well was examined by the Promega reporting system. The relative activity of luciferase is used for normalization.

### *Statistical analysis*

Use GraphPad Prism 8.2 (LA Jolla, United States) and SPSS 22.0 (International Trading Machine, United States). Student $t$ is used to compare the differences between the two groups and calculate the $P$ value. $P < 0.05$ was statistically significant.

## RESULTS

### *NRAV was significantly upregulated in PDAC and predicted a poor prognosis*

First, we used GEPIA to determine NRAV expression levels as an online bioinformatics tool for gene expression analysis based on the cancer genome database (TCGA)[16]. In Figure 1A and NRAV, the expression of PDAC in tissues was significantly higher than that in non-medical tissues. In addition, the survival curve showed that the total life cycle ($P$ = 0.034; Figure 1D) and disease-free life cycle ($P$ = 0.046; Figure 1E) of STD patients were decreasing. In addition, the data of the TGA database also showed that the level of emotional expression was negatively correlated with the level of clinical pathology (Figure 1C). Then the relative level of NRAV expression in HPDE and four PDAC systems was tested. The results showed that NRAV in the PDAC cell system was significantly higher than that in HPDE (Figure 1F). Based on these data, we believe that temper may be a potential carcinogen related to lncRNA.

### *Knockdown of NRAV inhibited proliferation, migration, and invasion of PDAC cells*

Next, we will study the biological role of the Qi spleen in the PDAC cell system. First, we used heterogeneous RNA transplantation to reduce NRAV expression in PANC-1 and AsPC-1 cells QRT-PCR analysis showed a significant decrease in the expression in the pot after NRAV (Figure 2A) After showing the results of CCK-8 tests and colony formation, there was a significant reduction after removal of signs of proliferation and abscision of PANC-1 and AsPC-1 cells (Figure 2B and C). Furthermore, we perform Transwell analysis to test whether temperament affects metastasis and damage to police cells. Similarly, the results showed that after the removal of punk-1 and asp-1 cells migration and invasion rates slowed down significantly (Figure 2D and E). In any case, in addition to physical inhibition of proliferation, movement, and invasion of PDAC cells, gaseous deposits also appear.

### *Overexpression of NRAV promoted PDAC cell proliferation, migration, and invasion*

In addition, the high expression of NRAV in BXPC-3 and Mia PaCa-2 cells used to display exogenous particles confirmed the effectiveness of the expression (Figure 3A). The results of the CCK-8 test and the product reduction test showed that NRAV overexpression significantly supported proliferation and formation of PDAC cells (Figure 3B and C). Moreover, transwell analysis found that NRAV overexpression significantly increased displacement and invasion of MIA cells PaCa-2 and BXPC-3 (Figure 3D and E). Overall, the results showed that NRAV promotes proliferation, metastasis, and invasion of PDAC cells.

**NRAV *ablation inhibited tumor growth in vivo***

To further investigate whether NRAV supports tumor growth *in vivo*, PANC-1 cells were injected into naked mice treated with sh-NRAV and internal control cells. As shown in Figure 4A and B, the tumor volume of the NRAV genotype was significantly lower than the negative control volume. Similarly, the mass of the tumor in the NRAV group (Figure 4C) was significantly reduced compared to the control group. In addition, Ki-67 was also analyzed for lignin content and staining immunochemistry. Data showed that reduction of NRAV led to a significant reduction of Ki-67 and inhibition of tumor growth (Figures 4D and E). Overall, these findings suggest that NRAV does not inhibit tumor growth *in vivo*.

***NRAV acted as a molecular sponge for miR-299-3p in PDAC***

To further study how NRAV plays a catalytic role in PDAC, we first used the nuclear/cell separation method to determine the location of NRAV cells in PDAC. The results show that spleen qi is mainly located in cells (Figure 5A), and it can play its biological function as a competitive endogenous RNA[17,18]. Then we use starbase V3.0 (http://starbase.sysu.edu.cn/) Interactive Bio information Analysis Software to identify potential microRNAs that may interact with genes. In Figure 5B, miR-299-3p is selected as the tempered target due to potential point complementarity. Rip analysis confirms this point[19]. As shown in Figure 5C, overexpression in PDAC cells resulted in

significant enrichment of miR-299-3p on ago2. In addition, the miR-299-3p simulator significantly reduced the fluorescence activity of the wild NRAV group, while this change did not occur in the modified NRAV group (Figure 5D). In addition, according to qRT-PCR analysis, the expression of miR-299-3p in PDAC cells was significantly enhanced after removing the traits (Figure 5E), Spearman's analysis showed that the expression of NRAV and miR-299-3p in PDAC tissue was opposite (Figure 5F). Therefore, these results suggest that temper may play the role of molecular sponge miR-299-3p.

***MiR-299-3p reversed the effect of NRAV on PDAC cells***

To validate whether NRAV affected proliferation and metastasis of PDAC cells through sponging miR-299-3p, specific miR-299-3p mimic and mimic NC vector was co-transfected into PDAC cells after overexpression of NRAV. Subsequently, we evaluated the cell proliferation, migration, and invasion of PDAC cells. As exhibited in Figure 6A and B, miR-299-3p mimic reversed the dramatic promotion by overexpression of NRAV on proliferation. Similarly, miR-299-3p mimic also inhibited the promoting effects of NRAV overexpression on cell migration and invasion in PDAC cells (Figure 6C and D). In conclusion, it indicated that miR-299-3p mediated the promoting effects of NRAV in PDAC cell proliferation, migration, and invasion.

## DISCUSSION

More and more studies have shown that lncRNAs play an important role in the development of various malignant tumors. Recent studies have shown that large amounts of lincRNAs are abnormally expressed in PDAC and participate in the tumor process[20,21]. Guo *et al*[22] found that under hypoxia, lncRNAs extract of PDAC *UCA1* cells increased to promote angiogenesis. First, we use the TGA database to identify NRAV in PDAC. This study confirms that the code of good conduct is a key element related to the program of action, and that significant progress has been made in the program of action. In addition, in PDAC patients, high levels of NRAV expression hurt

overall survival (OS) and disease-free survival (DFS). It is worth noting that temper may participate in the PDAC program.

The specific role of NRAV in oncology is not clear due to increased immunization. Recent studies have shown that sexual behavior is significantly increased due to liver cancer and myeloma and can play a key role in the development of these two tumors[10,23]. To verify the biological function of NRNA in PDAC, function loss and acquisition studies were carried out. Fortunately, the results of *in vitro* experiments show that temper has a great contribution to the movement, invasion, and reproduction of PDAC cells. In addition, ablation temperament significantly reduced the tumor of the nude mouse model overall, these results show that the NRAC plays an important role in promoting cancer and can be used as a new biometric index for diagnosis and prediction of diseases caused by PDAC.

To further study the potential mechanism of temper, nuclear/cell division experiments were carried out in PDAC, and it was found that temper was mainly in the cytoplasmic part. Further analysis of the rip report analysis shows that temper may play the role of the miR-299-3p molecular sponge. In addition, the stimulation effect of NRAV on malignant tumors in PDAC cells was also proved in the rescue experiment. In short, the role of NRA in promoting the progress of PDAC mainly depends on miR-299-3p.

Overall, at the beginning of the study, it was emphasized that the significant increase of lncRNA was negatively correlated with OS and DFS in PDAC patients. In addition, it also plays a carcinogenic role by promoting the proliferation and metastasis of cells in the sponge world. In short, our research shows that NRAV/miR-299-3p plays a key role in PDAC and can be used as a potential biomarker for PDAC diagnosis and treatment.

However, because no samples from patients with pancreatic cancer were collected, there was a lack of correlation analysis between temperament expression and PDAC clinicopathological features. In addition, it is also of great significance to study the significance of NRAV and miR-299-3p in PDAC organization.

## CONCLUSION

In our study, we concluded that NRAV can act as a molecule sponge of the miR-299-3p and significantly promote the proliferation and metastasis of PDAC cells.

## ARTICLE HIGHLIGHTS

### *Research background*

Pancreatic ductal adenocarcinoma (PDAC) is of high malignancy with a very poor prognosis, worldwide. Long noncoding RNAs (lnRNAs) are recognized as crucial factors and associated with the process of PDAC. However, the specific biological role and practical clinical significance of lnRNA, negative regulator of antiviral response (NRAV) in PDAC remain unclear.

### *Research motivation*

At present, the early and timely diagnosis and treatment of PDAC are still scarce. Therefore, it is a matter of urgency to comprehensively understand the pathogenesis of PDAC and explore more effective targets for the diagnosis and treatment of PDAC.

### *Research objectives*

To study the role of NRAV in the growth and metastasis of PDAC.

### *Research methods*

Real-time PCR detects the expressions of NRAV and miR-299-3p in PDAC cells. The temperament correction and miR-299-3p in the process of cell proliferation, metastasis, and invasion were verified by cell count package-8, precipitation test, and Transwell test. RNA and fluorescent enzyme immunoprecipitation test to test the interaction between NRAV and miR-299-3p. Verify the interaction between NRAV and miR-299-3p.

### *Research results*

According to our data, NRAV in PDAC is significantly increased, which is related to the functional negative survival rate of PDAC patients. NRAV overexpression is conducive to the proliferation and metastasis of PDAC cells, and NRAV knockout can reverse these functions. Finally, in terms of mechanism, NRAV acts as a miR-299-3p molecular sponge. In addition, overexpression of miR-299-3p significantly changed the catalytic role of NRAV in the proliferation, metastasis, and invasion of PDAC cells.

***Research conclusions***

In our study, we concluded that NRAV promotes proliferation and metastasis of PDAC by playing the molecule sponge function of miR-299-3p.

***Research perspectives***

NRAV facilitated the progression of PDAC, which might provide a potential biological marker for diagnosis and target for the treatment of PDAC.

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