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The Role and Mechanism of NCAPD2 in Regulating the P53 Signaling Pathway to Mediate the Proliferation and Invasion of Pancreatic Cancer Cells

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Abstract

Background: The relationship between non-structural maintenance of chromosomes condensin I complex subunit D2 (NCAPD2) and pancreatic cancer (PC) has never been explored, but NCAPD2 has been confirmed to play a role in a variety of tumors. This study aimed to study the anti-cancer effect of NCAPD2 in pancreatic cancer PaTu8988 cells in vitro and its mechanism.

Methods: NCAPD2 expression level within PC and the survival rate of patients was analyzed by making use the public database for bioinformatics analysis. Western blotting served to detect the expression level and knockdown level of NCAPD2 mRNA within PC. Cell Counting Kit-8 (CCK-8), colony formation, wound healing assays and Transwell assays were employed to examine the proliferation inhibition which induced by NCAPD2 knockdown. Furthermore, Western blotting was applied to analyze the influence of NCAPD2 knockdown on the p53 signaling pathway.

Results: NCAPD2 was upregulated in PC cells lines PaTu8988T and tissues and was involved in poor prognosis ($P < 0.05$). Down-regulation of NCAPD2 expression can effectively inhibited the proliferation, migration, and invasion processes of PC cells. Additionally, the expression levels of p53, phosphorylated p53 (p-p53), and p21 proteins were markedly reduced following NCAPD2 knockdown ($P < 0.05$).

Conclusion: NCAPD2 is highly expressed in PC and has poor prognosis. Its regulatory function in PC progression may be mediated through modulation of the p53 signaling pathway, thereby influencing, proliferation, apoptosis, and invasion in PaTu8988T cells.

Keywords: Cell Cycle Proteins, Non-SMC Condensin I Complex Subunit D2, Pancreatic Neoplasms, Tumor Suppressor Protein p53.

Introduction

Pancreatic carcinoma (PC) is truly one of the "number one killers" of cancer death. Due to its highly aggressive nature, the difficulty of treatment rises sharply, the survival rate is less than five years (1). Several factors contribute to its poor prognosis, including its deep-seated location in the retroperitoneum, which makes tissue biopsy challenging, its resistance to conventional radiotherapy and chemotherapy, and the lack of effective molecular diagnostic and screening strategies. Consequently, PC has a persistently low cure rate and a high five-year recurrence rate following treatment. Therefore, early detection of pancreatic lesions, identification of molecular therapeutic targets, and elucidation of their mechanisms of action are crucial for improving patient survival rates (2-3).

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Structural maintenance of chromosomes (SMC) proteins plays a pivotal role in preserving chromosomal stability during cell division. Among the extensively studied SMC subunits, Structural maintenance of chromosomes 2 (SMC2) and Structural maintenance of chromosomes 4 (SMC4) are integral components of the condensin I and condensin II complexes. These complexes localize along the chromosome axis, where their abundance is thought to regulate the width of metaphase chromosomes (4). Furthermore, mutations in condensin complex subunits have been implicated in microcephaly, highlighting their relevance to human disease pathogenesis.

Non-structural maintenance of chromosomes condensin I complex subunit D2 (NCAPD2) is one of the three core subunits of the condensin I complex. Existing studies have shown that NCAPD2 contributes to cell cycle progression, ensuring proper chromosome condensation and segregation during mitosis (5). Emerging oncological research has indicated that NCAPD2 is aberrantly expressed in multiple malignancies, including oral squamous cell carcinoma (6), ovarian cancer (7), hepatocellular carcinoma (HCC) (8), and lung cancer (9), suggesting its role as a potential oncogene. However, there is a lack of literature on NCAPD2 expression in PC and its regulatory effects on the proliferation and invasion of the PC cell line PaTu8988T. Building on prior investigations into NCAPD2, our bioinformatics analysis has revealed a strong association between NCAPD2 and cell cycle regulation. Given that the p53 signaling pathway has indispensable functions in cell cycle regulation, apoptosis, and autophagy, we hypothesize that p53 may be a potential downstream target of NCAPD2. After long-term exploration, the academic community is still in an unexplored state in the research field of the regulatory mechanism of the NCAPD2 and p53 signaling pathways, and no related research results have been published yet. Therefore, this study aims to examine NCAPD2 expression in PC tissues, assess the effects of NCAPD2 gene knockdown on the biological behavior of PC, and investigate its regulatory interaction with p53. The research results of this study are expected to open a brand-new perspective for targeted therapies in PC treatment.

Materials and Methods

Bioinformatics analysis

NCAPD2 expression across multiple cancer types, particularly in PC, was analyzed using the gene expression profiling interactive analysis (GEPIA2) database. The University of Alabama at Birmingham Cancer data analysis Portal (UALCAN) database was used to assess NCAPD2 protein expression in 137 PC cases and 74 normal pancreatic tissues. Human Protein Atlas (HPA) database was employed to evaluate negative, positive, and strongly positive NCAPD2 expression in PC tissues. The Kaplan-Meier Plotter database was used to generate overall survival curves for PC patients.

Cell culture and transfection

The PC cell lines PANC-1 (primary tumor of the pancreatic head), MIA PaCa-2, PaTu8988T (liver metastasis of pancreatic head cancer), and BxPC-3 were purchased from Qing Shi (Yanbian) Biotechnology Co., Ltd. All cell lines were cultured and preserved in the Central Laboratory of Hospital of Yanbian University (Yanbian Hospital).

PANC-1, MIA PaCa-2, PaTu8988T, and BxPC-3 cells were cultured in specialized media under standard conditions (37 °C, 5% CO_2). Cells were transfected with siNCAPD2#1, siNCAPD2#2, or siNCAPD2#3, along with the non-targeting negative control (siNC), using LipofectAMINE3000 (Thermo Fisher, America). Cells were cultured for 48 hours post-transfection before further experiments.

Western blotting

Total protein was extracted from PANC-1, MIA PaCa-2, PaTu8988T, and BxPC-3 cells, and NCAPD2 protein expression levels were assessed via western blotting. PaTu8988T cells were selected for further experiments. Cells

transfected with siNCAPD2#1, siNCAPD2#2, siNCAPD2#3, or siNC were collected after 48 hours and lysed using RIPA buffer (Thermo Fisher, America) containing protease inhibitors. After centrifugation, total protein concentration was quantified using the Bicinchoninic Acid Assay (BCA). Proteins were separated via SDS-PAGE and transferred onto a nitrocellulose membrane using a semi-dry transfer system. The membrane was blocked with 5% non-fat milk at room temperature for 1 hour and incubated overnight at 4 °C with primary antibodies including rabbit anti-NCAPD2 monoclonal antibody, 1:1000 and rabbit anti-GAPDH monoclonal antibody' 1:3000. After three TBST washes, the membrane was incubated with fluorescent secondary antibodies (1:20,000) at room temperature for 1.5 hours. Protein expression was visualized using a chemiluminescence imaging system, and ImageJ software was used for quantification.

CCK-8 assay

Exponentially growing PC cells were digested, centrifuged, and resuspended. Cells (2×10^3/well) were seeded into 96-well plates and allowed to adhere for 24 hours before transfection (0 hours). At 24-, 48-, and 72-hours post-transfection, 10 μL of CCK-8 solution was added to each well, and cells were incubated at 37 °C for 1.5 hours. Absorbance at 450 nm was measured, and cell viability was calculated to generate proliferation curves.

Colony formation assay

Following transfection, PaTu8988T cells were digested and centrifuged to prepare a single-cell suspension. Cells (2×10^3/well) were seeded into six-well plates and cultured for seven days. Colonies were washed with pre-cooled PBS, fixed with 4% paraformaldehyde for 20 minutes, and stained with crystal violet for 15 minutes. After three PBS washes and air drying at room temperature, images were captured, and colony numbers were counted based on three independent experiments.

Wound healing assay

PaTu8988T cells, at a density of 5×10^3 cells per well, were seeded into six-well plates and transfected upon reaching confluency. After 24 hours, a scratch was introduced using a sterile pipette tip (0 hours), and cells were cultured in serum-reduced medium (1% FBS) for 48 hours. Images were captured, and wound closure was analyzed using ImageJ software.

Transwell assay

At 24 hours post-transfection, 2×10^3 cells were seeded into the upper chamber of a Transwell insert in serum-free medium, while the lower chamber contained 10% FBS medium. After 48 hours, the upper chamber was removed, and cells were fixed with 4% paraformaldehyde for 30 minutes and stained with 0.1% crystal violet. Non-migrated cells were removed using a cotton swab. The migrated cells were imaged under a microscope.

Statistical analysis

All statistical analyses were performed using SPSS 26.0. Graphs were generated using GraphPad Prism 9.5, and image processing was performed using Photoshop. Data are presented as mean ± standard deviation (SD). Two-group comparisons were conducted using the t-test, while multiple-group comparisons were performed using one-way ANOVA. All experiments were repeated at least three times independently, and $P < 0.05$ was considered statistically significant.

Results

Expression of NCAPD2 in PC

To assess the expression of NCAPD2 in different cancer types, we conducted a pan-cancer analysis using the GEPIA online analysis tool, which can efficiently process complex data. The data for this analysis was sourced from The Cancer Genome Atlas (TCGA) database encompassing 33 different tumor types and adjacent normal tissues. The results demonstrated that NCAPD2 was significantly upregulated in multiple malignancies, including PC (Table 1 & Fig. 1A).

Further analysis revealed that both NCAPD2 mRNA and protein levels were significantly elevated in PC tissues ($P < 0.01$, Fig. 1B). Moreover, immunohistochemical staining results from The Human Protein Atlas (HPA) database showed that NCAPD2 was expressed in both the cell membrane and nucleus of PC cells. While NCAPD2 exhibited negative expression in normal pancreatic tissues, it demonstrated positive and strongly positive expression in PC tissues ($P < 0.01$, Fig. 1C). Collectively, these data indicate that NCAPD2 is highly expressed in PC tissues. Survival analysis using the Kaplan-Meier Plotter online tool revealed an association between NCAPD2 expression and patient prognosis in a cohort of 1,237 PC patients. Patients characterized by high NCAPD2 expression demonstrated a markedly reduced overall survival, significantly worse than that of individuals with low NCAPD2 expression ($P < 0.01$, Fig. 1D).

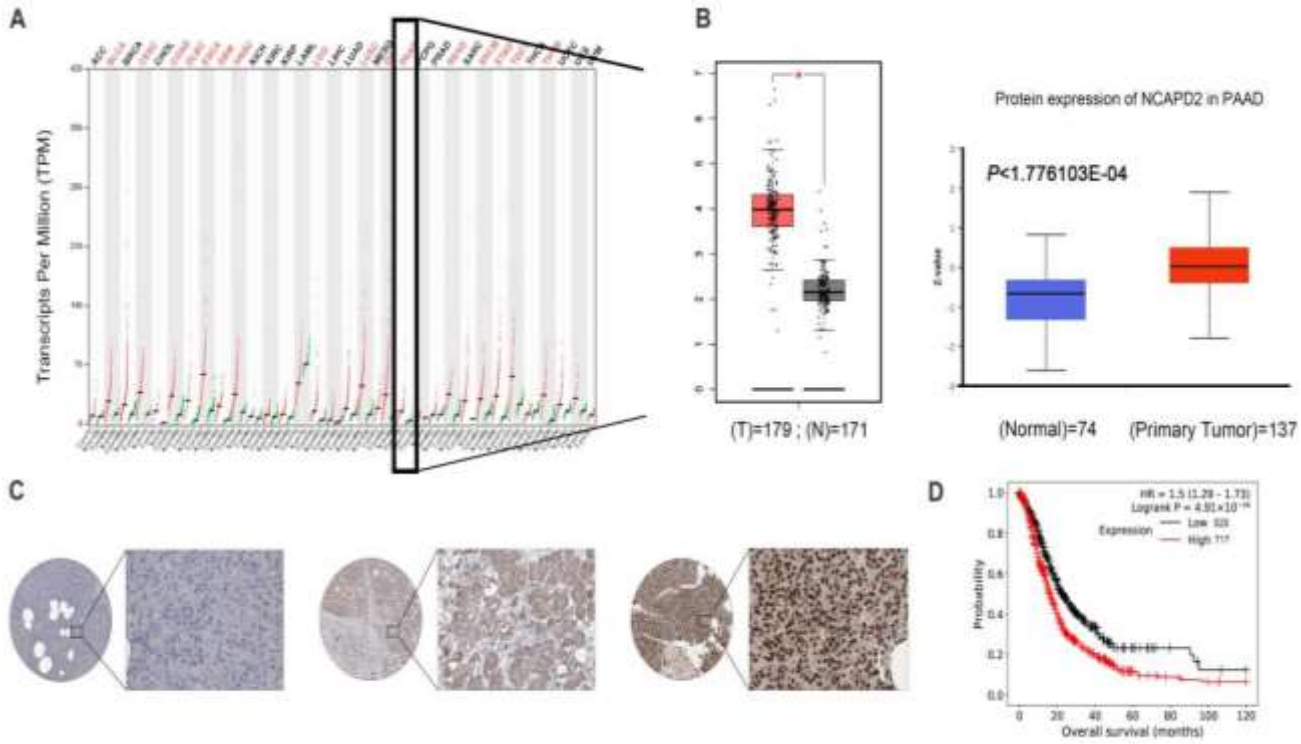


Fig. 1. Expression of NCAPD2 in PC. A. GEPIA database analysis of NCAPD2 high expression in PC. B. NCAPD2 mRNA and protein expression levels are higher in PC than in normal tissue. C. The Human Protein Atlas database analyses NCAPD2 protein expression in PC cell membranes and nuclei. D. Kaplan-Meier Plotter online analysis of NCAPD2 high expression in PC tissues.

Analysis of the biological process of NCAPD2

We conducted pathway enrichment analysis on the co-expressed gene of NCAPD2. The verification results show that the NCAPD2 co-expressed gene is significantly enriched in related pathways such as the cell cycle, apoptosis and senescence (Fig. 2A-B). To further verify the expression correlation between NCAPD2 and the core genes of the p53 pathway, CDKN1A/p21 and CDK1, in PC tissues and normal pancreatic tissues (Fig. 2C). The results showed that NCAPD2 was positively correlated with p53($R = 0.28$, $P = 0.00011$), CDKN1A/p21 ($R = 0.36$, $P < 0.001$), and CDK1 ($R = 0.4$, $P < 0.001$). This result suggests that both may be affected by the same regulatory mechanism or functionally involved in cellular life activities and predicts a high proliferation index and poor prognosis of cancer cells.

Table 1. Relationship between NCAPD2 expression level and clinicopathological characteristics of PC.

Clinicopathological Characteristics	Overall Survival (n=1237)			Disease Free Survival (n=278)		
	N	Hazard Ratio	*p*-Value	N	Hazard Ratio	*p*-Value
Histology						
all	1237	1.5(1.29-1.73)	$4.91\times10^{-08***}$	278	1.19(0.9-1.57)	0.226
PADC only	852	1.62(1.37-1.91)	$2.06\times10^{-08***}$	150	1.76(1.16-2.67)	0.00792^{***}
Gender						
male	401	1.57(1.21-2.03)	$5.84\times10^{-04***}$	141	1.42(0.96-2.11)	0.0829
female	320	1.49(1.04-2.14)	0.0278^{*}	126	0.76(0.52-1.11)	0.158
Stage						
I	82	1.64(0.78-3.45)	0.192	-	-	-
II	477	1.88(1.49-2.36)	$6.45\times10^{-08***}$	140	1.78(1.15-2.75)	0.00962^{***}
III	19	1.76(0.61-5.06)	0.293	-	-	-
IV	21	0.39(0.12-1.24)	0.11	-	-	-
Grade						
I	65	3.04(0.87-10.6)	0.081	-	-	-
II	294	1.69(1.25-2.27)	0.00668^{***}	120	2.14(1.32-3.46)	0.00209^{***}
III	200	1.15(0.83-1.58)	0.411	88	0.58(0.37-0.92)	0.0207^{*}
IV	14	3.84(0.63-23.37)	0.144	-	-	-
Node						
N0	199	1.56(1.05-2.31)	0.0261^{*}	-	-	-
N1	383	1.77(1.38-2.27)	$5.76\times10^{-06***}$	127	1.67(1.06-2.64)	0.0275^{*}
Metastatic						
M0	578	1.72(1.4-2.13)	$3.53\times10^{-07***}$	148	1.82(1.18-2.79)	0.00645^{***}
M1	21	0.39(0.12-1.24)	0.11	-	-	-

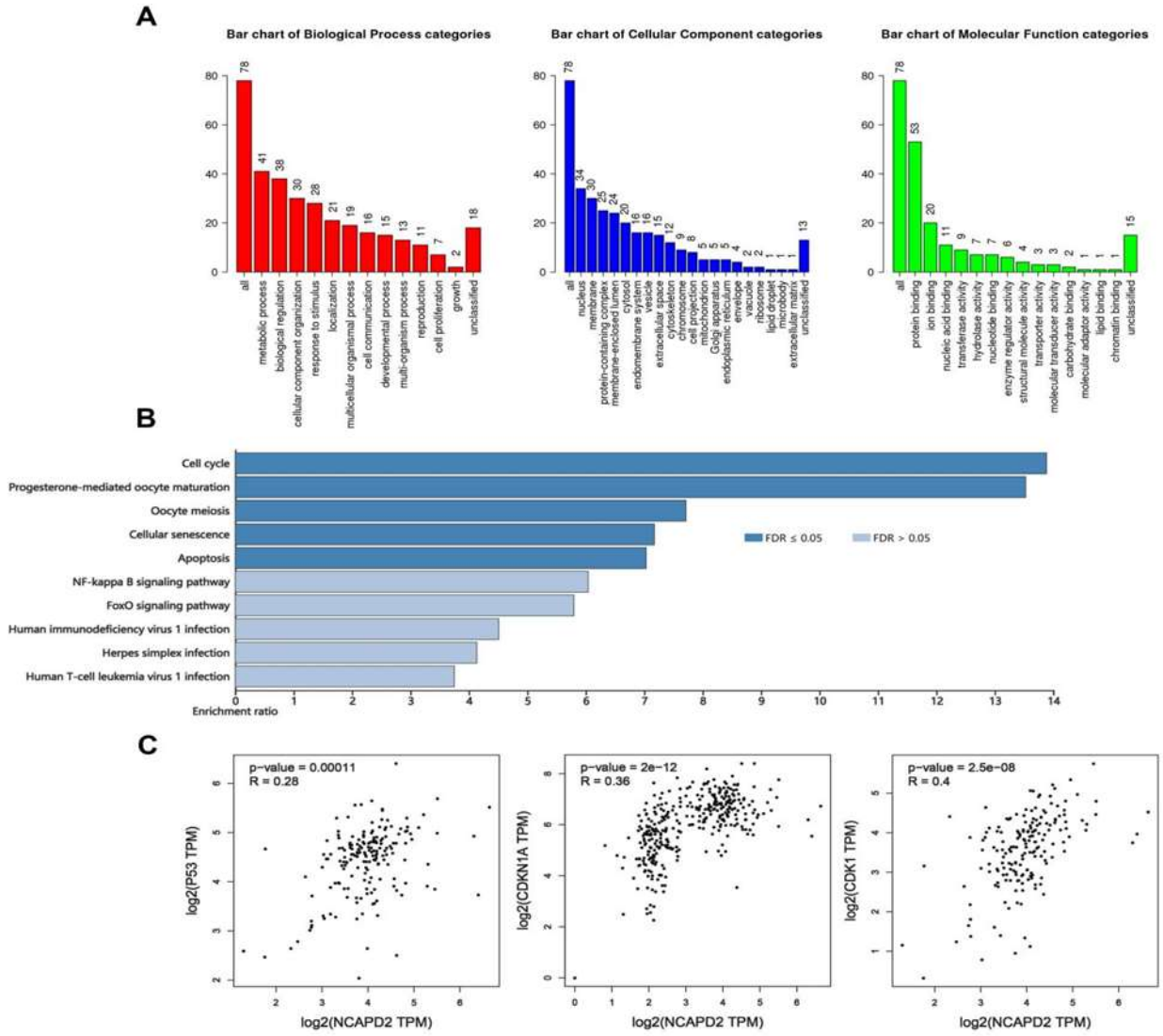


Fig. 2. Analysis of the biological process of NCAPD2. A-B. Enrichment analysis of NCAPD2 co-expressed genes. C. Correlation analysis of core genes in the NCAPD2 and p53 pathways.

Knockdown of NCAPD2 in the PC Cell Line

To determine NCAPD2 expression levels in PC, we used the Western blotting to detect four cell lines, namely PANC-1, MIA PaCa-2, PaTu8988T, and BxPC-3. The results indicated that NCAPD2 was expressed in all four PC cell lines, with the highest expression observed in PaTu8988T cells (Fig. 3A). Consequently, PaTu8988T cells were selected for subsequent experiments.

To investigate the functional role of NCAPD2, three small interfering RNA (siRNA) sequences targeting NCAPD2 (siNCAPD2#1, siNCAPD2#2, and siNCAPD2#3) were designed and transfected into PaTu8988T cells. The efficiency of NCAPD2 knockdown was evaluated via Western blotting. Researchers concluded that, compared to the control group, NCAPD2 mRNA expression was reduced in all siNCAPD2-transfected groups, confirming successful knockdown of NCAPD2 in PaTu8988T cells (Fig. 3B). Among the three siRNA constructs, siNCAPD2#1 (P= 0.0104) and siNCAPD2#3 (P= 0.0165) exhibited the most effective knockdown, while siNCAPD2#2 did not achieve statistical significance.

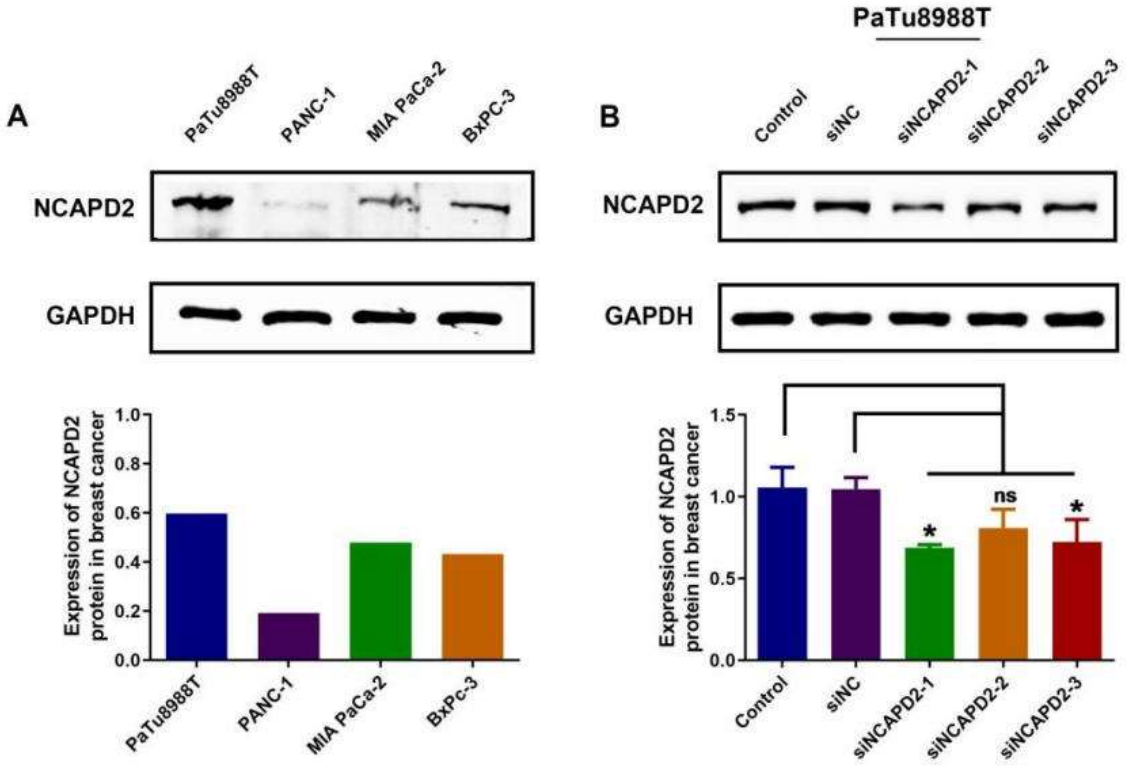


Fig. 3. Knockdown of NCAPD2 in the PC Cell Line. A. Western blotting method to detect NCAPD2 expression in PC cell lines PANC-1, MIA PaCa-2, PaTu8988T and BxPC-3. B. Western blotting method was used to detect the transfection and knockdown effects of different siRNAs.

Knockdown of NCAPD2 Inhibits PC Cell Proliferation and Migration

The CCK-8 assays were used to detect the proliferative ability of PaTu8988T cells after NCAPD2 knockdown, to explore the effect of NCAPD2 expression on the proliferation of PC cells. The results demonstrated that, compared to the control and siNC groups, the proliferation ability of PaTu8988T cells transfected with NCAPD2 siRNA (siNCAPD2#1 and siNCAPD2#3) was significantly reduced ($P < 0.001$, Fig. 4A).

We conducted colony formation assays to further validate the effect of NCAPD2 on the proliferation of PC cell. Our results showed that NCAPD2 knockdown significantly decreased the colony-forming ability of PaTu8988T cells ($P = 0.0002$, $P = 0.0008$, Fig. 4B). These findings indicate that NCAPD2 knockdown inhibits PC cell proliferation.

Furthermore, wound healing assays were executed to evaluate the effect of NCAPD2 knockdown on PC cell migration. The results demonstrated that the migration rate of PaTu8988T cells into the wound area was significantly reduced following NCAPD2 knockdown ($P = 0.0019$, $P = 0.0107$), with a statistically significant difference (Fig. 4C). These findings suggest that NCAPD2 knockdown suppresses PaTu8988T cells migration.

To assess the impact of NCAPD2 expression on PC cell invasion, transwell invasion assays were conducted using transfected PaTu8988T cells. The results showed that the number of cells that migrated through the membrane into the lower chamber was significantly lower in the NCAPD2 siRNA-transfected groups (siNCAPD2#1 and siNCAPD2#3) compared to the control and siNC groups ($P = 0.0002$, $P = 0.0001$). The differences were statistically significant (Fig. 4D). Based on the results presented above, NCAPD2 knockdown can potently inhibits the proliferation, migration, and invasion of PC cells.

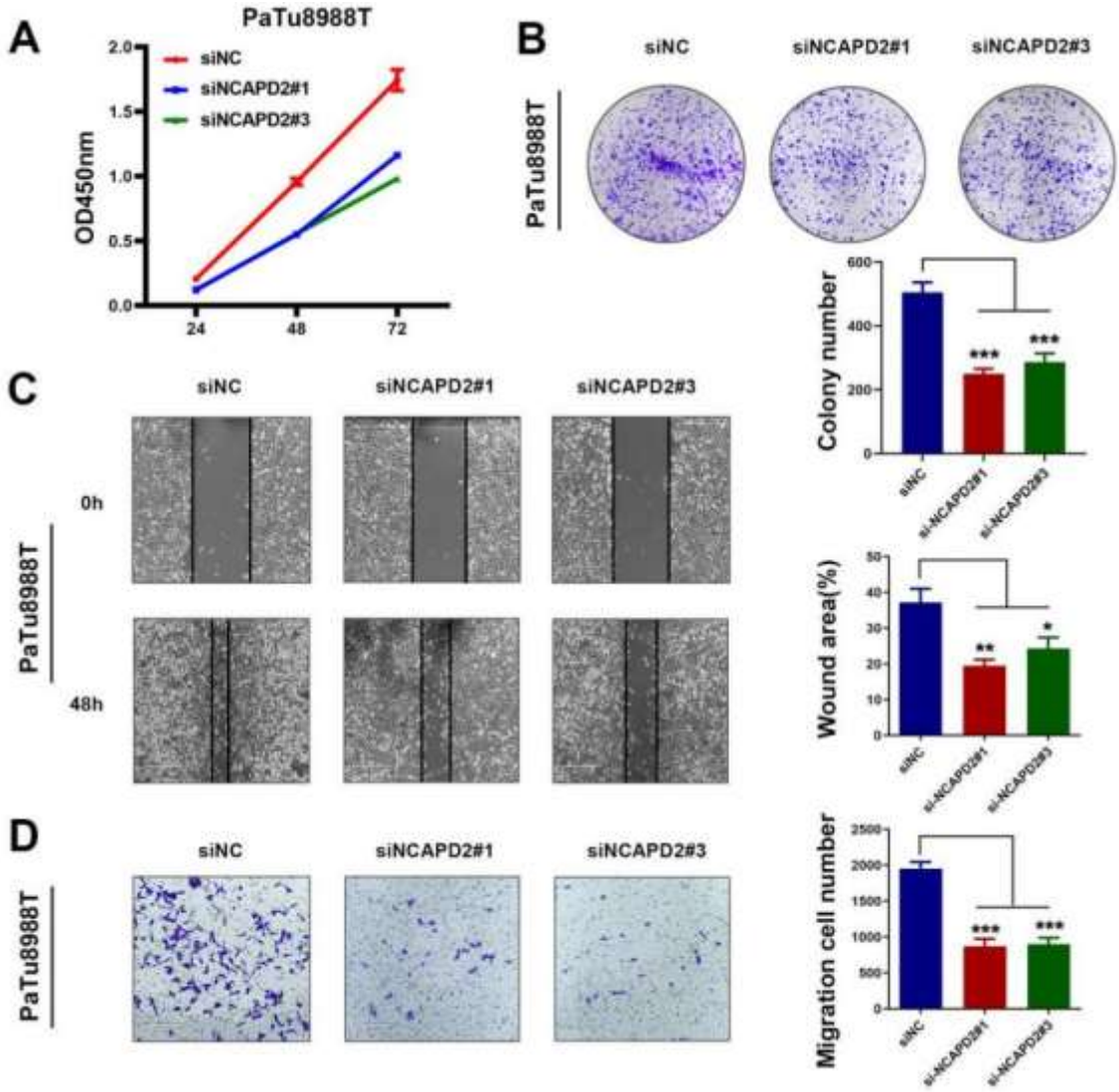


Fig. 4. Knockdown of NCAPD2 Inhibits PC Cell Proliferation and Migration. A. CCK-8 kit to detect the effect of knockdown of NCAPD2 on the proliferative capacity of PaTu8988T cells. B. Clone formation validates the effect of NCAPD2 expression on PC cell proliferation. C. Cell scratch assay to verify the effect of NCAPD2 expression on PC cell migration. D. Transwell assay experiments were performed to validate the effect of NCAPD2 expression on PC cell invasion.

NCAPD2 Regulates the Cell Cycle Pathway

Previous studies have explored the potential of NCAPD2 as a treatment for cancer and how it impacts the cell cycle. Upon this foundation, investigated the underlying mechanisms. p53, a well-established star molecule in the fight against cancer, which stops the growth cycle of cancer cells and then initiates the "suicide program" of cancer cells. (9). The p53-mediated cell cycle regulation primarily involves the classical p53-p21-RB signaling pathway. p21, the first transcriptional target downstream of p53, functions as a cyclin-dependent kinase (CDK) inhibitor, effectively regulating cell cycle progression.

To further investigate the potential mechanisms underlying NCAPD2-mediated regulation of PC cell migration, the expression levels of p53 pathway-related proteins were examined using Western blotting. The results revealed that in PaTu8988T cells transfected with NCAPD2 siRNA, the knockdown of NCAPD2 led to a significant reduction in key molecules of the p53 signaling pathway; p53, phosphorylated p53 (p-p53), and p21 ($P< 0.01$), (Fig. 5A).

These findings indicate that NCAPD2 knockdown regulates the p53 signaling pathway, suggesting a potential mechanism through which NCAPD2 influences PC progression.

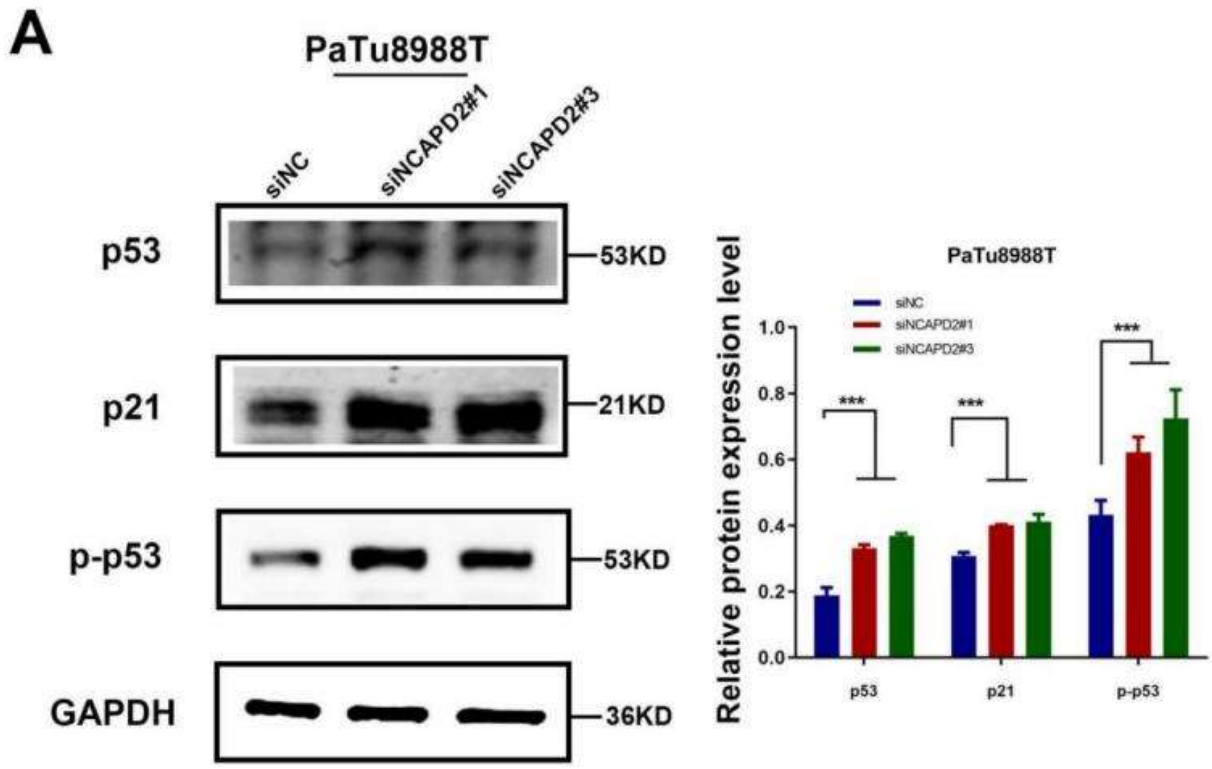


Fig. 5. NCAPD2 Regulates the Cell Cycle Pathway. A. Western blotting to detect the expression of experimental NCAPD2 and p53 pathway-related proteins.

Discussion

PC is an insidious malignancy characterized by the absence of obvious clinical symptoms and signs in its early stages, as well as a high propensity for systemic metastasis, making it a key factor causing cancer-related deaths. Despite continuous advancements in surgical techniques and chemoradiotherapy, the effectiveness of these treatments in improving patient prognosis remains limited. With the emergence of immunosuppressive therapies and molecular-targeted approaches, increasing attention has been directed toward improving the cure rate for cancer patients, yielding promising preliminary results (11-12). Therefore, this study delves deeply into one of the newly discovered genes - NCADP2. The obtained results show that both the NCAPD2 gene and protein are highly expressed in pancreatic cancer and lead to a poor prognosis for patients with pancreatic cancer. Whether one has PDAC, lymph node metastasis, gender, tumor stage, lymph node metastasis and distant metastasis are important prognostic indicators.

After knocking down NCAPD2 using small molecule interference technology, the expression was analyzed in PaTu8988T cells through Western blotting experiments. For the verification of cell proliferation and migration tests, experiments such as cck-8 were used. Compared with the control group, the number of pancreatic cancer cells proliferating after knockdown of NCAPD2 decreased, and the migration and invasion abilities also decreased. Recent studies have consistently demonstrated that NCAPD2 is implicated in tumorigenesis, invasion, and metastasis, although its underlying mechanisms vary across malignancies. According to several published studies, NCAPD2 has a potential regulatory role in mammalian target of rapamycin (mTOR) pathway. In colorectal cancer,

NCAPD2 has been shown to activate mTOR complex 1 (mTORC1), thereby promoting tumor cell growth via the Ca^{2+}/CaMKK2/AMPK/mTORC1 pathway and the PARP-1/SIRT1 axis, which regulate tumor cell autophagy (14). Similarly, another study demonstrated that NCAPD2 promotes epithelial–mesenchymal transition (EMT) in HCC through activation of the PI3K/Akt/mTOR signaling pathway (15).

Given its involvement in chromosomal organization, elucidating the specific mechanisms by which NCAPD2 participates in the cell cycle is essential for understanding its biological significance. Other scientists have confirmed that as a subunit of condensin I, NCAPD2 is dynamically localized throughout the cell cycle, playing a pivotal role in mitotic chromosome assembly and segregation, thereby influencing cellular biological functions (16). Our research has confirmed that NCAPD2 is involved in biological processes such as the cell cycle, cell senescence, and cell apoptosis. In this study, NCAPD2 knockdown in PaTu8988T cells led to a significant upregulation of p53, p21, and phosphorylated p53 (p-p53), which is the same as the research results of Zhang et al (17). NCAPD2 knockdown (siNCAPD2) resulted in G_2/M phase arrest in TNBC cells, leading to reduced cell proliferation, which was hypothesized to be associated with the p53 signaling pathway. To date, thousands of studies have focused on p53, which is widely recognized as a critical tumor suppressor gene. p53 regulates the transcription of hundreds of genes, modulating the expression of oncogenes to suppress tumor progression. When p53 is inactivated, tumorigenesis may occur. The p53 signaling pathway is one of the most crucial targets for anticancer drug development. The CDKN1A gene, which encodes p21, is a key target in the p53 pathway and a principal inducer of cell cycle arrest (18). When p21 is activated by reactive oxygen species (ROS), it can enhance the expression of apoptotic factors, thereby inducing cell apoptosis (19). Interestingly, some articles have confirmed that p21 is associated with the risk of developing PDAC (20).

In summary, our study demonstrated that NCAPD2 is particularly high in patients with PC. And the risk of recurrence is higher, and the survival period is shorter. In vitro experiments confirmed that NCAPD2 downregulation inhibits PC cell proliferation, migration, and invasion, with further evidence suggesting that NCAPD2 promotes PC progression through the p53 signaling pathway.

However, this study has certain limitations. First, the role of NCAPD2 was not validated in in vivo models, necessitating further animal studies to confirm its function. Second, the specific downstream target genes within the p53 pathway that mediate NCAPD2-induced tumor progression remain unclear. Future research will focus on refining our understanding of NCAPD2's role in PC pathogenesis, conducting in-depth molecular mechanism studies, and in vivo experiments to elucidate how NCAPD2 regulates the cell cycle at a mechanistic level. These efforts may offer new possibilities for improving patient outcomes.

Ethical Approval

This study does not involve ethical approval.

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Conflict of Interest

We hereby declare that the manuscript has not been previously published in any language anywhere and that it is not under simultaneous consideration by another journal. None of the authors have any conflict of interest or any financial ties to disclose.

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Authors Contributions

Data curation, Fuhua Li; Funding acquisition, Linyuan Feng and Aili Cui; Resources, Aili Cui; Software, Fuhua Li; Writing – original draft, Fuhua Li; Writing – review & editing, Linyuan Feng.

All authors will be updated at each stage of manuscript processing, including submission, revision, and revision reminder, via emails from our system or the assigned Assistant Editor.

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