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Overexpression of *CENPL* mRNA potentially regulated by miR-340-3p predicts the prognosis of pancreatic cancer patients

Zhongyuan Cui^{1†}, Ling Du^{2†}, Jielong Wang^{1,3†}, Zhongzhuan Li², Jiehong Xu², Shiyu Ou², Dongliang Li^{1,3}, Shasha Li^{1,3}, Hanfang Hu², Gang Chen^{2*} and Zhixian Wu^{1,2*}

Abstract

Background: In our previous study it was found that *CENPL* was overexpressed in hepatocellular carcinoma and significantly predicted patient's prognosis. However, the expression and prognostic value of *CENPL* in other gastrointestinal tumors remain unknown. Therefore, we investigated the expression and prognostic value of *CENPL* in esophageal carcinoma (ESCA), stomach adenocarcinoma (STAD), pancreatic adenocarcinoma (PAAD), colon adenocarcinoma (COAD) and rectum adenocarcinoma (READ).

Methods: In this study, OncoPrint, GEPIA, OncoPrint, TIMER, cBioPortal, miRWalk and ENCORI databases were used to analyze the level of *CENPL* mRNA, prognostic value and potential regulatory mechanism of *CENPL* mRNA in tumors. The *CENPL* expression and clinicopathological data regarding PAAD were from the UCSC Xena database and univariate and multivariate Cox regression analyses were performed using R (Version 3.6.3). Immunohistochemical staining was used to verify the expression of *CENPL* protein in clinical specimens. Cytoscape (Version: 3.7.2) was used to visualize microRNA (miRNA) that potentially regulates *CENPL*.

Results: Gene differential expression analysis showed that *CENPL* mRNA was significantly overexpressed in ESCA, STAD, PAAD, COAD and READ ($p < 0.01$). The overexpression of *CENPL* mRNA was significantly correlated with the poor prognosis of PAAD patients ($p < 0.05$). However, there was no significant correlation between the level of *CENPL* mRNA and the prognosis of ESCA, STAD, COAD and READ patients ($p > 0.05$). Univariate and multivariate Cox regression analyses suggested that *CENPL* was a prognostic risk factor for PAAD. The mutation rate of *CENPL* in PAAD was 2.2% (17/850). There was no significant correlation between the *CENPL* expression and the infiltration levels of immune cells in PAAD ($|Cor| < 0.5$). Immunohistochemical staining showed that *CENPL* was overexpressed in 42% (11/26) of PAAD specimens, which was significantly higher compared with that in the normal tissues. The expression of miR-340-3p and miR-484 in PAAD were significantly lower than in the normal tissues ($p < 0.05$) and PAAD patients with lower expression of miR-340-3p had poorer prognosis ($p < 0.05$).

[†]Zhongyuan Cui, Ling Du and Jielong Wang contributed equally to this work.

*Correspondence: 13667728003@163.com; zxwu@xmu.edu.cn

¹ Department of Hepatobiliary Disease, 900th Hospital of the Joint Logistics Support Force (Dongfang Hospital), Xiamen University, Fuzhou 350025, Fujian, China

² Department of Gastroenterology, the Fourth Affiliated Hospital (Liuzhou Workers' Hospital), Guangxi Medical University, Liuzhou 545000, Guangxi, China

Full list of author information is available at the end of the article



Conclusion: CENPL potentially regulated by miR-340-3p, is overexpressed in PAAD and predicts patient's prognosis, suggestive of a diagnostic and prognostic value in PAAD patients.

Keywords: PAAD, *CENPL*, Biomarkers, Prognosis, miR-340-3p

Introduction

Gastrointestinal (GI) tumors including esophageal carcinoma (ESCA), stomach adenocarcinoma (STAD), pancreatic adenocarcinoma (PAAD), colon adenocarcinoma (COAD), rectum adenocarcinoma (READ) and liver hepatocellular carcinoma (LIHC) are the major malignancies globally with significant mortality and morbidity [1–6]. Because the treatment for patients with, especially, advanced GI tumors are limited and the patient prognosis is poor [6–9], it is necessary to explore novel diagnostic and therapeutic markers for GI tumors.

Centromere protein L (CENPL) is a member of the centromere protein family. It is assembled with other centromere proteins to form the constitutive centromere associated network (CCAN), also known as inner kinetochore [10–12]. CENP-L-N complex plays an important role in centromere specificity and kinetochore stability [12]. The depletion phenotype of CENP-L is crucial to the stability of kinetochore microtubules, for a homogenous poleward microtubule flux rate and for the kinetochore pushing force [13]. These studies suggest that CENPL is indispensable during normal cell division. However, the understanding of CENPL in cancer is still limited. Yin et al. found that CENPL might be a diagnostic and prognostic marker for breast cancer [14]. In our previous study it was found that CENPL was overexpressed in hepatocellular carcinoma and predicted the prognosis of patients, and the overexpression of CENPL was positively correlated with the abundance of various tumor infiltrating lymphocytes [15]. Whether *CENPL* plays a role in the development and progression of other GI tumors remains unknown, and more studies are needed.

In this study, we investigated the expression and prognostic value of CENPL in GI tumors, including ESCA, STAD, PAAD, COAD and READ, by using bioinformatic methods and immunohistochemical staining.

Methods

Analysis of *CENPL* gene expression

The level of *CENPL* mRNA in esophageal, gastric, colon and pancreatic tumors and adjacent normal tissues was analyzed with OncoPrint (https://www.oncoPrint.org/) [16] and GEPIA: Gene Expression Profiling Interactive Analysis (http://gepia.cancer-pku.cn) [17] databases.

The default settings were used in all analyses, and Fold Change (FC) of ≥ 2 and a p value of < 0.05 were considered statistically significant.

Gene expression and clinical characteristics

OncoPrint (http://www.oncoPrint.org/) [18] and GEPIA database were used to analyze the prognosis of patients with ESCA, STAD, PAAD, COAD and READ. For each cancer, the patients were divided into high- and low-level groups according to the gene expression level, and the cutoff was 50%. UALCAN (http://ualcan.path.uab.edu/index.html) [19] database was used to analyze the relationship between the expression of *CENPL* mRNA and clinical characteristics including *TP53* mutation, age and sex. A p value of < 0.05 was considered statistically different.

CENPL gene expression and clinicopathological data regarding TCGA PAAD was from the UCSC Xena database (https://xenabrowser.net/) [20]. Univariate and multivariate Cox regression analyses were performed using survival package of R software (Version 3.6.3) to assess Hazard Ratio (HR) and p -values of prognostic risks for PAAD. The survminer package was used for visualization. The downloaded PAAD data included 181 patients' *CENPL* expression (FPKM) and clinicopathological data including sex, age, tumor size and survival. Of those, 82 were female and 99 were male, and 167 had tumor size data, with a median size of 3.5 cm, (Supplementary table 1).

Mutation and levels of immune cell infiltration

The cBioPortal (https://www.cbioportal.org/) [21] database was used to analyze the mutations of *CENPL* in tumors. The relationship between *CENPL* mRNA and levels of immune cell infiltration was analyzed with the TIMER: Tumor Immune Estimation Resource (https://cistrome.shinyapps.io/timer/) [22] database. A p value of < 0.05 and a correlation coefficient value of ≥ 0.5 were considered statistically significant.

Analysis of potential regulatory mechanisms

The miRWalk (http://mirwalk.umm.uni-heidelberg.de/) [23] database was used to predict potential microRNAs (miRNAs) that regulate *CENPL* mRNA. Cytoscape software (Version: 3.7.2) was used to screen and visualize top 9 potential miRNAs associated with *CENPL* expression. The Encyclopedia of RNA Interactomes (ENCORI,

<http://rna.sysu.edu.cn/encori/mirTarPathways.php>) database was used to analyze the expression of miRNA candidates in cancers [24]. Pan-cancer Analysis Platform model was selected. A p value of <0.05 were considered statistically different.

Immunohistochemical Staining

The study was conducted in accordance with the principles of the Declaration of Helsinki [25]. The specimen collection procedure was approved by the Hospital Ethics Committee. The need for informed consent was waived by the Ethics Committee of Dongfang Hospital. The investigation was approved by the Ethics Committee of Dongfang Hospital.

Five- μ m sections were obtained from paraffin-embedded PAAD tumor and non-tumor tissues (From Department of Pathology, Dongfang Hospital). All these sections were dewaxed in xylene and re-hydrated in alcohol followed by wet autoclave pretreatment in citrate buffer for antigen retrieval (10 min at 120°C, pH=6.0) and then rinsed with phosphate buffer saline. Immunohistochemical staining for antibody to CENPL (Rabbit: bs13836R, Beijing Biosynthesis Biotechnology, China) was performed using the avidin–biotin– peroxidase complex method. The primary antibody (1:200 dilution

for CENPL) was applied to the sections and allowed to react for 1 h at room temperature. The sections were then incubated with biotinylated anti-mouse/rabbit antibody for 30 min and avidin–biotin–peroxidase reagent for 20 min. After color development with diaminobenzidine, the sections were counterstained with hematoxylin.

Results

Levels of CENPL mRNA in ESCA, STAD, PAAD, COAD and READ

Levels of CENPL mRNA in colorectal and gastric cancers and PAAD were higher than those in para-tumor tissues ($p < 0.01$ for all, Fig. 1A–C and Table 1). The range of fold change (FC) in COAD were 2.168–3.007 (Fig. 1A and Table 1). In STAD it was 2.194–2.502 (Fig. 1B and Table 1). FC was 2.039 in PAAD (Fig. 1C and Table 1). Using the defined threshold, no results were retrieved for esophageal carcinoma. Analysis of GEPIA database showed that the level of CENPL mRNA in 182 cases of ESCA was significantly higher than that in 286 cases of normal tissue ($p < 0.01$, Fig. 1D). CENPL mRNA was significantly overexpressed in 408 STAD cases than in 211 cases of normal tissues ($p < 0.01$, Fig. 1E). In 275 cases of COAD and 349 cases of normal tissues, CENPL mRNA was significantly higher in

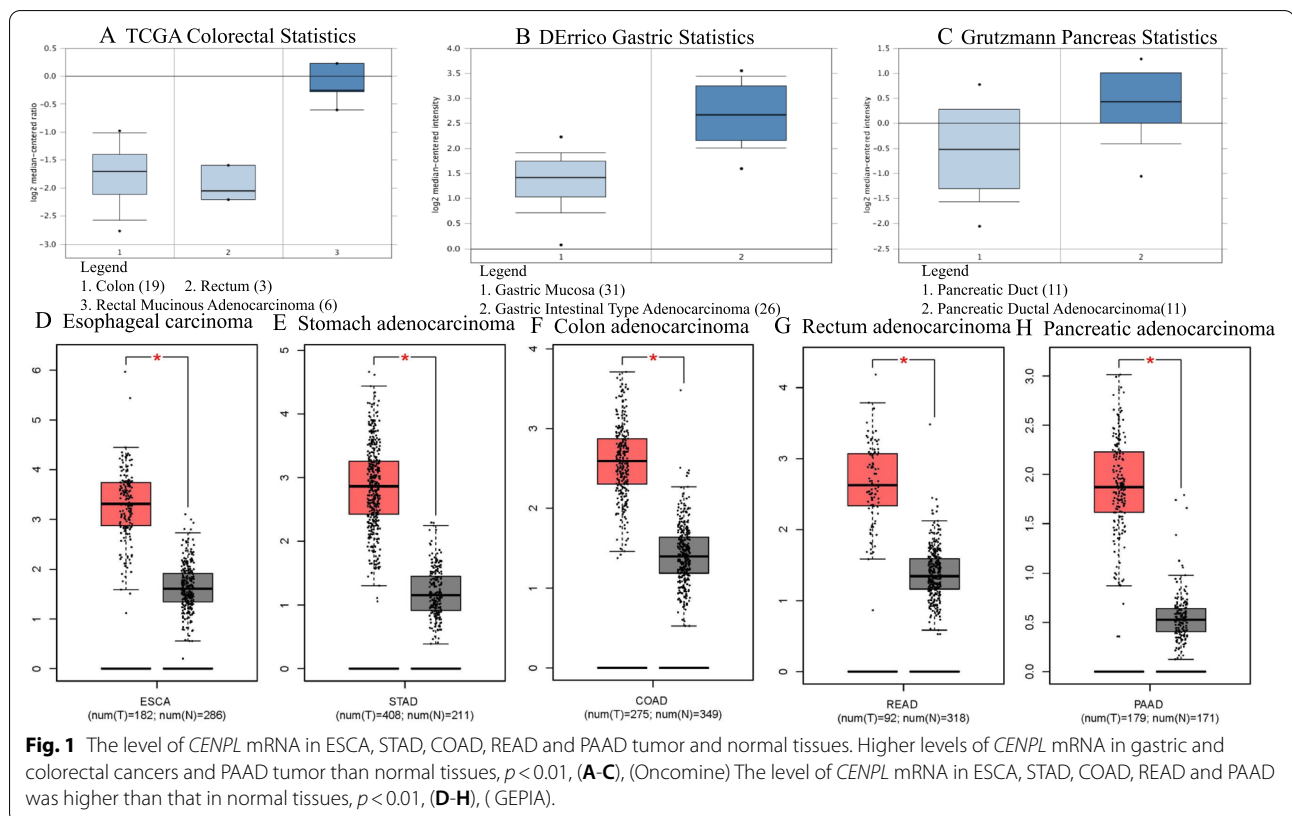


Table 1 The FC of *CENPL* mRNA in gastrointestinal tumors (Oncomine)

Cancer types	Datasets	Fold Change	p Value	t Test
Colorectal adenocarcinoma	TCGA Colorectal Statistics			
	Rectal mucinous adenocarcinoma	3.007	3.22E-8	10.614
	Colon mucinous adenocarcinoma	2.406	1.19E-10	8.338
	Cecum adenocarcinoma	2.541	2.93E-11	8.798
	Rectosigmoid adenocarcinoma	2.893	3.15E-5	10.243
	Rectal adenocarcinoma	2.441	7.43E-14	11.296
	Colon adenocarcinoma	2.596	2.64E-14	12.595
	Sabates Bellver Colon et al's Statistics			
	Rectal adenoma	2.561	6.41E-8	8.996
Gastric adenocarcinoma	Colon adenoma	2.168	2.15E-9	7.254
	D'Errico Gastric et al's Statistics			
	Gastric intestinal type adenocarcinoma	2.502	1.66E-12	9.078
PAAD	Gastric mixed adenocarcinoma	2.194	2.97E-4	6.656
	Grutzmann Pancreas et al's Statistics			
Esophageal carcinoma	Pancreatic ductal adenocarcinoma	2.039	0.002	3.255
	No	No	No	No

tumor ($p < 0.01$, Fig. 1F). Results of 92 cases of READ and 318 cases of normal tissues showed significantly increased levels of *CENPL* mRNA in tumors ($p < 0.01$, Fig. 1G). The expression of *CENPL* mRNA in 179 cases of PAAD was significantly higher than that in 171 cases of normal pancreatic tissues ($p < 0.01$, Fig. 1H).

Relationship between the level of *CENPL* mRNA and the prognosis of patients with ESCA, STAD, COAD, READ and PAAD

In 174 patients with PAAD, those with higher levels of *CENPL* mRNA had shorter survival ($p < 0.05$, Fig. 2A). In 144 patients with ESCA, there was no significant difference in the survival between the high- and low-expression groups ($p > 0.05$, Fig. 2B). No significant difference was found in the survival of STAD patients between the high- and low-expression groups ($p > 0.05$, Fig. 2C). In 440 patients with COAD, no significant difference in the survival was observed between high- and low-expression groups ($p > 0.05$, Fig. 2D). There was no significant difference in the survival of READ patients between high- and low-expression groups ($p > 0.05$, Fig. 2E).

In addition, GEPIA was analyzed regarding the prognostic value of *CENPL* mRNA in patients with PAAD. The results showed that patients with higher levels of *CENPL* mRNA had shorter overall survival (OS) ($p < 0.01$, Fig. 2F). Similarly, patients with higher expression of *CENPL* mRNA had shorter disease-free survival (DFS) ($p < 0.01$, Fig. 2G).

Univariate Cox regression analysis showed that *CENPL* mRNA was a risk factor for patient prognosis (HR = 1.9, CI = 1.1–3.1, $p < 0.05$) (Fig. 3A). Multivariate Cox

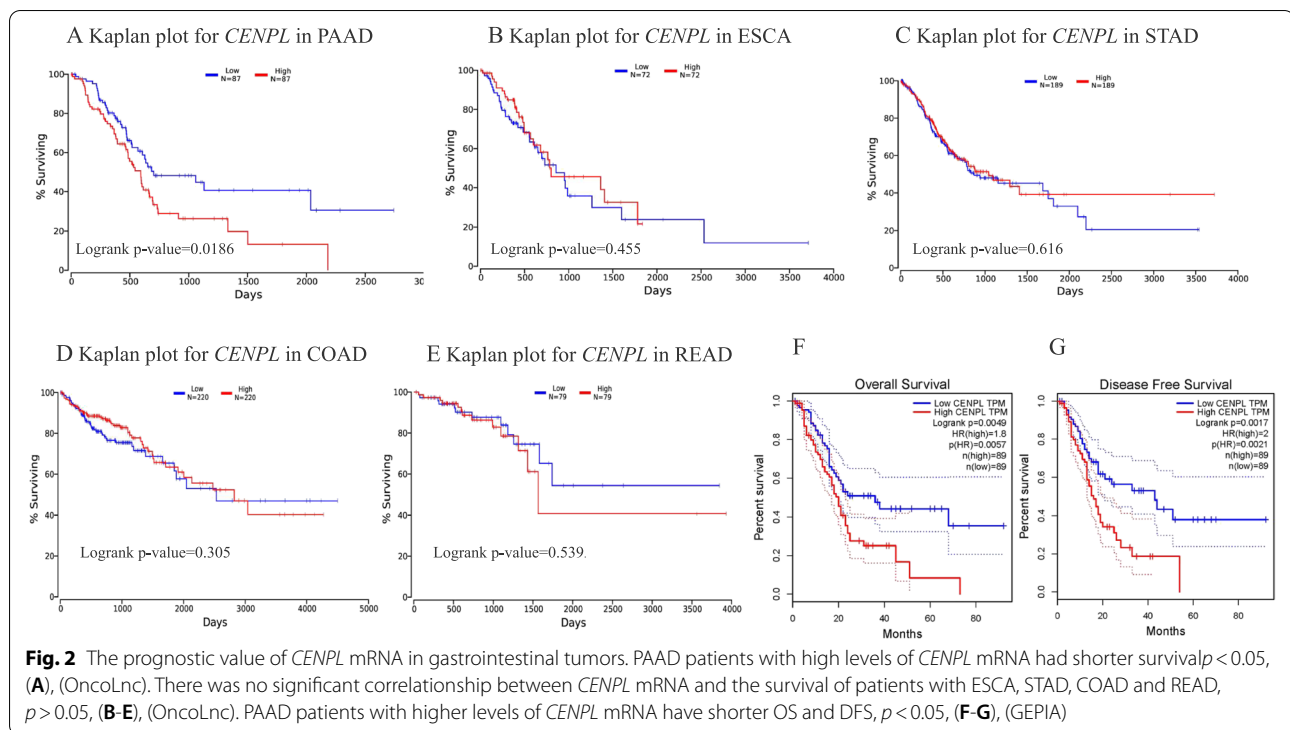
regression analysis included *CENPL* mRNA, age, sex and tumor size (dichotomized with a cut-off value of 3.5 cm) and *CENPL* mRNA (HR = 1.74, CI = 1.05–2.9, $p < 0.05$) and age (HR = 1.03, CI = 1.01–1.1, $p < 0.05$) were independent risk factors for the prognosis of PAAD patients (Fig. 3B). Sex and tumor size were not independent risk factors for the prognosis of PAAD patients (both $p > 0.05$) (Fig. 3B).

CENPL mutation and the correlation between its expression and tumor infiltrating lymphocytes

Gene mutation analysis showed that only 2% (17/850) of 850 patient from four independent datasets had mutations, and the main type of *CENPL* mutation was amplification (Fig. 4A). No significant correlations were observed between the expression of *CENPL* mRNA and PAAD tumor purity and levels of immune cell infiltration including B Cells, CD8+ T Cells, CD4+ T Cells, macrophages, neutrophils and dendritic cells ($|Cor| < 0.5$, Fig. 4B). However, it was found that the expression of *CENPL* mRNA was significantly associated with *TP53* mutations in PAAD. In 82 PAAD patients with *TP53* mutation, the level of *CENPL* mRNA was significantly higher than that in 93 patients without *TP53* mutation ($p < 0.01$, Fig. 4C).

miRNAs potentially regulating *CENPL* in PAAD

1086 miRNAs (supplement table 2) that potentially regulate *CENPL* mRNA were identified using the miR-Walk database. Cytoscape (Version: 3.7.2) screened the top 9 potential miRNAs with the strongest association with *CENPL* mRNA: hsa-miR-371a-3p, hsa-miR-382-5p,



hsa-miR-340-3p, hsa-miR-331-5p, hsa-miR-324-5p, hsa-miR-433-5p, hsa-miR-483-3p, hsa-miR-484 and hsa-miR-511-5p (Fig. 5A). Further analysis showed significant low expression of hsa-miR-340-3p in PAAD (FC = 0.44, $p < 0.01$ and FDR < 0.05, Fig. 5B). hsa-miR-484 was also significantly under-expressed (FC = 0.41, $p < 0.01$ and FDR < 0.05, Fig. 5C). Moreover, it was found that PAAD patients with lower expression of hsa-miR-340-3p had shorter survival ($p < 0.05$, Fig. 5D). The expression of hsa-miR-484 was not significantly correlated with the survival of PAAD patients ($p = 0.177$, Fig. 5E).

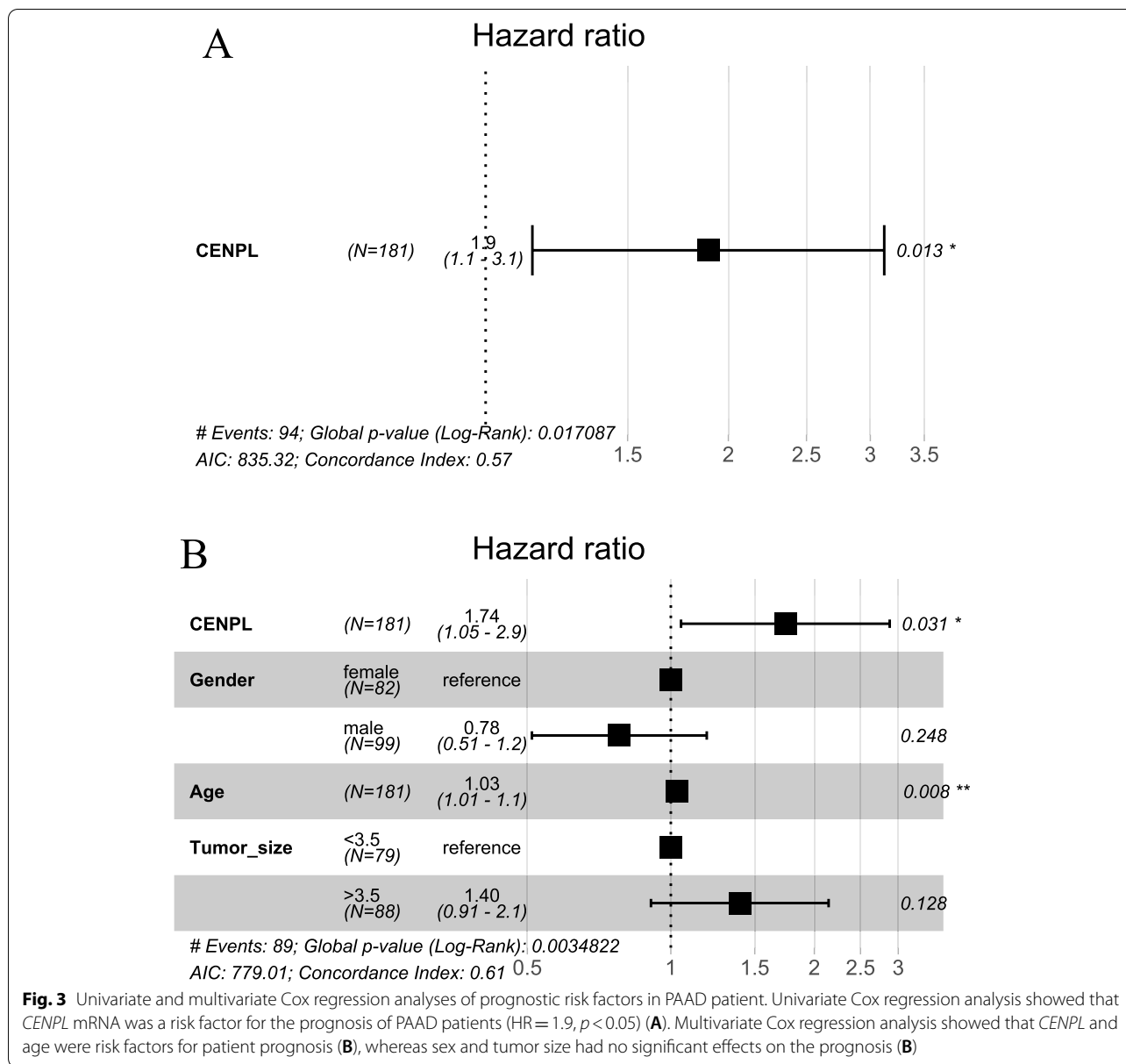
The expression of *CENPL* protein in PAAD and normal tissues

Immunohistochemical staining of clinical specimens showed that the expression of *CENPL* protein in PAAD was significantly higher than that in adjacent normal tissues. The expression of *CENPL* in tumor tissues (42%, 11/26) was higher than that in non-cancer tissues (Fig. 6). *CENPL* protein was mainly located in cytoplasm and membrane (Fig. 6).

Discussion

In this study, the expression of *CENPL* mRNA in gastrointestinal tumors was analyzed using multiple public databases. *CENPL* mRNA was overexpressed in ESCA, STAD, PAAD, COAD and READ tumors compared with adjacent normal tissues. Then, the prognostic

value of *CENPL* in patients with gastrointestinal tumors was assessed. The level of *CENPL* mRNA significantly predicted the prognosis of PAAD patients. Univariate and multivariate Cox regression analyses showed that *CENPL* mRNA was an independent risk factor for prognosis, suggesting that *CENPL* may play a critical role in PAAD and is worthy of further study. The mutation rate of *CENPL* was low and the relationship was not significant between *CENPL* expression and the abundance of immune cell infiltration in PAAD. However, it was found that the level of *CENPL* mRNA was significantly correlated with *TP53* mutation in PAAD. Immunotherapy plays an important role in the treatment of cancer [26]. Therefore, we analyzed the expression level of *CENPL* mRNA in skin cutaneous melanoma (SKCM), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), kidney renal clear cell carcinoma (KIRC), breast invasive carcinoma (BRCA), and bladder urothelial carcinoma (BLCA) by GEPIA [17], for which immunotherapy have been approved. The results showed that the expression of *CENPL* mRNA was significantly increased in SKCM, LUAD, LUSC and BRCA, and no significant overexpression in KIRC and BLCA (Supplement Fig. 1). This also suggests that *CENPL* may exert effects in a variety of tumors. miR-340-3p was not only significantly under-expressed in PAAD, but also associated with worse prognosis in these patients, suggestive of a potential role in regulation of *CENPL*

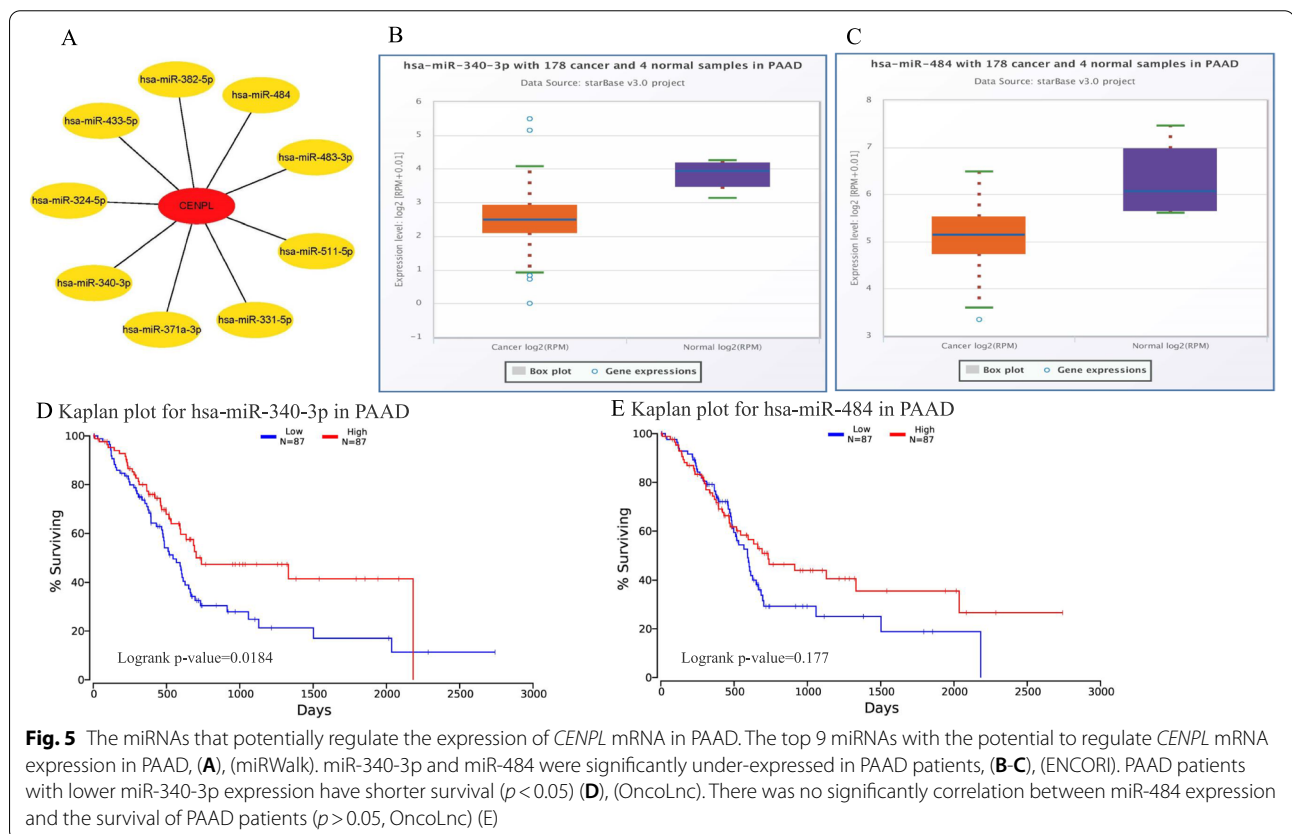
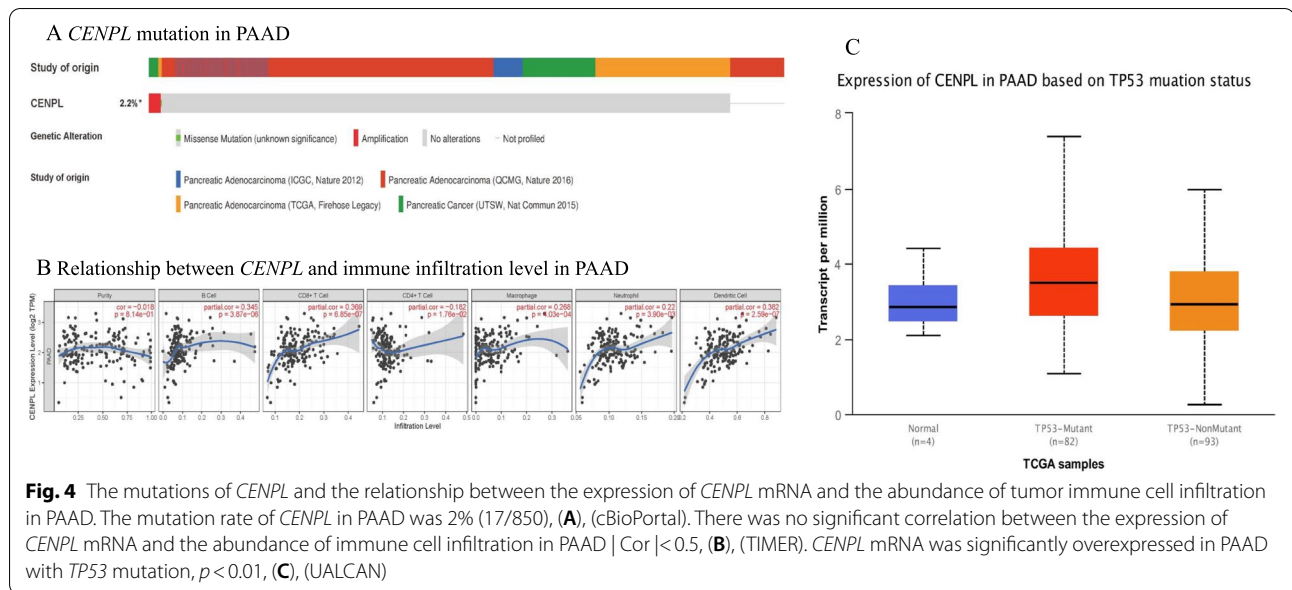


expression in PAAD. Finally, it was verified that *CENPL* protein was overexpressed in many clinical specimens from PAAD patients.

PAAD is the seventh leading cause of cancer-related deaths worldwide. Notably, the incidence of PAAD is growing, and the patient survival has barely improved [6, 27]. The pathogenesis, early diagnosis and precise treatment remain challenging. Studies have revealed that *TP53* mutation occurred in approximately 70% of patients with PAAD and was one of the major factors involved in development and progression of PAAD [28–31]. In this study, *CENPL* was rarely mutated in PAAD. However, the level of *CENPL* mRNA was higher in patients with

TP53 mutation. These results suggest that *CENPL* may have a robust association with *TP53* mutations in PAAD patients. *CENPL* is one of the proteins that constitute kinetosome, and overexpressed *CENPL* may affect the function of kinetochore. Previous studies have shown that kinetosome dysfunction might be a critical cause of chromosome instability and tumorigenesis [32–34]. Therefore, we hypothesize that overexpression of *CENPL* impairs the function of kinetosome and cause chromosomal instability, thereby causing or accelerating *TP53* mutation in pancreatic cancer, which is worthy of further exploration.

miRNA is a single-stranded non-coding RNA molecule with a length ranging from 19 to 25 nucleotides. It is



encoded by the endogenous gene. miRNA is involved in biological functions of cells by regulating its target genes [35]. miRNAs widely participate in signal activation, and cell proliferation, differentiation and death [35]. miR-484

is a key factor in cancer and non-cancerous diseases, and its targets in cancer include VEGFB, VEGFR2, MAP2, MMP14, HNF1A, TUSC5, and KLF12 [36]. miR-484 was found to precipitate tumorigenesis and metastasis in

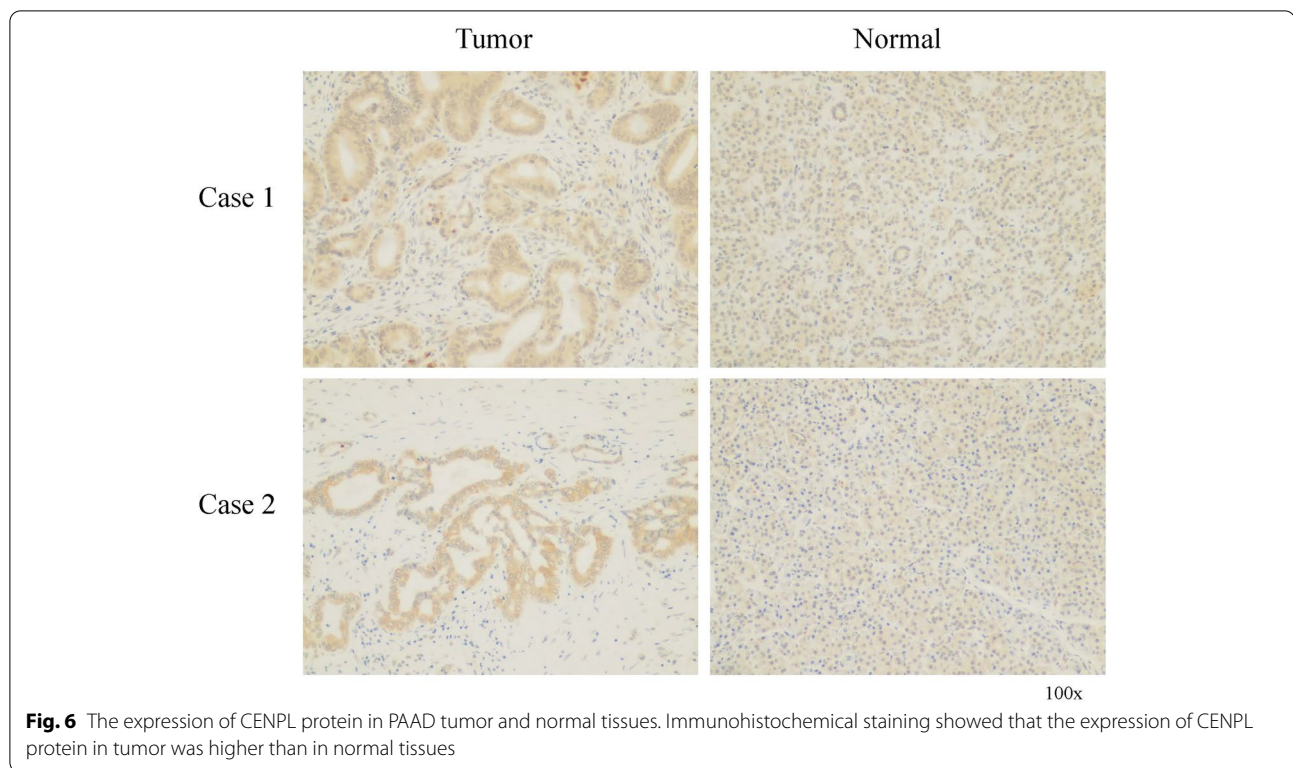


Fig. 6 The expression of CENPL protein in PAAD tumor and normal tissues. Immunohistochemical staining showed that the expression of CENPL protein in tumor was higher than in normal tissues

liver, prostate and lung cancers [36]. Nan et al. reported that in pancreatic ductal adenocarcinoma, the inhibitory effect of miR-484 on YAP was attenuated and predicted adverse patient outcomes [37]. In this study, we found that *CENPL* overexpression in PAAD might be the consequence of miR-484 suppression.

Previous studies have shown that miR-340 acted as an oncogenic or tumor suppressor by targeting genes related to proliferation, apoptosis, and metastasis. It showed significance in diagnosis, treatment, chemotherapy resistance, and prognosis [38]. Two studies have found that miR-340-3p might be closely related to the development of laryngeal squamous cell carcinoma and breast cancer [39, 40]. A recent study showed that miR-340-3p regulated by lncRNA HOXA10-AS could down-regulate HTR1D and inhibit the malignant biological behavior of pancreatic cancer through PI3K-Akt signaling pathway [41]. In this study, it was found to have a potential role in PAAD by targeting *CENPL*. In other words, the overexpression of *CENPL* mRNA in PAAD may be caused by insufficient miR-340-3p. Therefore, it may be a critical molecule in the pathway that regulates the expression of *CENPL*. Furthermore, by using the GEPIA [17] and DAVID [42, 43] databases, we found the top 200 genes that were significantly co-expressed with *CENPL* in PAAD, mainly enriched in endocytosis (Supplement table 3).

Endocytosis was revealed to be a pivotal pathway for regulation of metastasis [44]. Therefore, the overexpression of *CENPL* in PAAD may be involved in this process leading to disease deterioration.

There are some limitations in this study. Laboratory studies of the function of *CENPL* in PAAD cells is lacking, and the regulatory effects of miR-340-3p on *CENPL* mRNA expression should be verified through experiments. Furthermore, the number of PAAD patients involved in immunohistochemistry was small.

Conclusion

In summary, the current study suggests that *CENPL* may play an important pathologic role in PAAD, and *CENPL* mRNA is a prognostic predictor for PAAD patients.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12885-022-10450-5>.

Additional file 1.

Additional file 2.

Additional file 3.

Additional file 4.

Acknowledgements

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Authors' contributions

ZYC: Conceptualization, Analyzed the data, Visualization, Interpretation of data, Writing original draft. LD: Collected the data, Conceptualization, Writing original draft. JLW: Collected the data, Performed immunohistochemistry, Writing original draft. ZZL: Collected the data, Writing original draft. JHX: Collected the data, Writing original draft. SYO: Collected the data, Writing original draft. DLL: Conceptualization, Writing- reviewing and editing. SSL: Performed immunohistochemistry, Writing original draft. HFH: Collected the data, Writing original draft. GC: Project administration, Funding acquisition, Writing- reviewing and editing. ZXW: Project administration, Design of the work, Funding acquisition, Writing- reviewing and editing. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analysed during the current study are available in the GEPIA, OncoLnc, UALCAN, cBioPortal, UCSC Xena, TIMER, miRWalk and ENCORI repository. [GEPIA: (<http://gepia.cancer-pku.cn/detail.php?gene=&clicktag=boxplot>); OncoLnc: (http://www.oncolnc.org/kaplan/?lower=50&upper=50&cancer=PAAD&gene_id=91687&raw=CENPL&species=mRNA), (http://www.oncolnc.org/kaplan/?lower=50&upper=50&cancer=ESCA&gene_id=91687&raw=CENPL&species=mRNA), (http://www.oncolnc.org/kaplan/?lower=50&upper=50&cancer=STAD&gene_id=91687&raw=CENPL&species=mRNA), (http://www.oncolnc.org/kaplan/?lower=50&upper=50&cancer=COAD&gene_id=91687&raw=CENPL&species=mRNA), (http://www.oncolnc.org/kaplan/?lower=50&upper=50&cancer=READ&gene_id=91687&raw=CENPL&species=mRNA), (http://www.oncolnc.org/kaplan/?lower=50&upper=50&cancer=PAAD&gene_id=MIMAT0000750&raw=hsa-miR-340-3p&species=miRNA) (http://www.oncolnc.org/kaplan/?lower=50&upper=50&cancer=PAAD&gene_id=MIMAT0002174&raw=hsa-miR-484&species=miRNA); UALCAN: (<http://ualcan.path.uab.edu/cgi-bin/TCGAExResultNew2.pl?genenam=CENPL&ctype=PAAD>); cBioPortal: (https://www.cbioportal.org/results/oncprint?cancer_study_list=paad_icgc%2Cpaad_qcmg_uq_2016%2Cpaad_utsuw_2015%2Cpaad_tcga&Z_SCORE_THRESHOLD=2.0&RPPA_SCORE_THRESHOLD=2.0&profileFilter=mutations%2Cgistic&case_set_id=all&gene_list=CENPL&geneset_list=%20&tab_index=tab_visualize&Action=Submit); UCSC Xena: ([https://xenabrowser.net/datapages/?cohort=GDC%20TCGA%20Pancreatic%20Cancer%20\(PAAD\)&removeHub=https%3A%2F%2Fxcena.treehouse.gi.ucsc.edu%3A443](https://xenabrowser.net/datapages/?cohort=GDC%20TCGA%20Pancreatic%20Cancer%20(PAAD)&removeHub=https%3A%2F%2Fxcena.treehouse.gi.ucsc.edu%3A443)); TIMER: (<https://cistrome.shinyapps.io/timer/>); miRWalk: (<http://mirwalk.umm.uni-heidelberg.de/human/gene/91687/>) and ENCORI: (<https://rna.sysu.edu.cn/encori/panMirDiffExp.php>)].

Declarations

Ethics approval and consent to participate

The specimen collection procedure was approved by the Hospital Ethics Committee. The need for informed consent was waived by the Ethics Committee of Dongfang Hospital (IRB00006161—Dongfang Hospital, Xiamen University). The investigation was approved by the Ethics Committee of Dongfang Hospital.

Consent for publication

Not applicable.

Competing interests

All authors have declared that they have no competing interests and have confirmed its accuracy.

Author details

¹Department of Hepatobiliary Disease, 900th Hospital of the Joint Logistics Support Force (Dongfang Hospital), Xiamen University, Fuzhou 350025, Fujian, China. ²Department of Gastroenterology, the Fourth Affiliated Hospital (Liuzhou Workers' Hospital), Guangxi Medical University, Liuzhou 545000, Guangxi, China. ³Department of Hepatobiliary Disease, 900th Hospital of the Joint Logistics Support Force, Fujian Medical University, Fuzhou 350025, Fujian, China.

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