Clinicopathological features, prognostic significance, and associated tumor cell functions of family with sequence similarity 111 member B in pancreatic adenocarcinoma

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Abstract

Background: Among digestive tract tumors, pancreatic adenocarcinoma (PAAD) has a high degree of malignancy. Therefore, it is important to search for pancreatic adenocarcinoma-related differential genes and new oncogene therapeutic targets for early diagnosis, treatment, and prognosis of pancreatic adenocarcinoma.

Aims: This study aims to investigate the expression and clinical significance of Family with sequence similarity 111 member B (FAM111B) in PAAD.

Materials & Methods: Bioinformatics was used to analyze the relationship between FAM111B expression and pancreatic adenocarcinoma and to predict its role in related pathways. Tissue microarrays were used to assess the levels of FAM111B in pancreatic cancer tissues by immunohistochemical staining, and the effects of FAM111B expression levels on apoptosis, proliferation, invasion and migration of tumor cells were observed and verified by in vitro cellular assays.

Results: FAM111B expression was higher in PAAD tissue than in matched normal tissues (p<0.05). The expression level of FAM111B, the metastatic status of lymph nodes was an independent prognostic factor for PAAD survival (p<0.05). Meanwhile, overexpression of FAM111B promoted PAAD cell proliferation, migration, invasion and inhibited PAAD cell apoptosis (p<0.05). In contrast, knockdown of FAM111B triggered the opposite result (p<0.05). In the results of GSEA, it was shown that FAM111B may be involved in PAAD progression through p53 signaling pathway, cell cycle, and other signaling pathways (p<0.05 and FDR q-val<0.25). FAM111B is highly expressed in PAAD tissues and is closely associated with poor prognosis of PAAD.

Conclusion: FAM111B significantly promotes the proliferation, invasion, and migration of pancreatic adenocarcinoma cells while it inhibits their apoptosis. FAM111B may be a new biomarker for PAAD. It may provide a new direction for the treatment and diagnosis of PAAD.
1 | INTRODUCTION

One of the malignant tumors of the digestive system is pancreatic adenocarcinoma (PAAD). Tumor malignancy is greater than in other parts of the digestive system. According to the 2018 International Agency for Research on Cancer GLOBOCAN cancer incidence and mortality estimates, there were 458,918 new cases of pancreatic adenocarcinoma and 432,242 deaths worldwide, with pancreatic adenocarcinoma accounting for 2.5 percent of all new cancer diagnoses and 4.5 percent of all cancer deaths, respectively.1 In 2020, a total of 495,773 new cases of pancreatic adenocarcinoma were recorded globally, with 466,003 fatalities. The fatality rate was almost as high as the incidence rate in these patients.2 Pancreatic adenocarcinoma is currently growing in incidence and fatality rates throughout the world, indicating that it will become a major public health issue in the near future.3 Pancreatic adenocarcinoma does not have typical early signs, and most patients are already in late stages when they are discovered. Metastasis to distant organs such as the liver, lung, and bone is possible, and drastic surgery is no longer an option. Despite the availability of surgical treatment, radiotherapy, molecular-targeted therapy, and immunotherapy, the treatment effect and prognosis of pancreatic adenocarcinoma are still poor.4 Therefore, it is important to search for pancreatic adenocarcinoma-related differential genes and new oncogene therapeutic targets for early diagnosis, treatment, and prognosis of pancreatic adenocarcinoma.

Family with sequence similarity 111 member B (FAM111B), also named as CANP or POIKTMP, the gene is only 16 kb on human chromosome 11q12.1. The protein encoded by this gene has a trypsin-like cysteine/serine peptidase structural domain at the C-terminus. Mutations in this gene have been associated with autosomal dominant hereditary fibrotic dermatitis (HFP). (Courtesy of RefSeq, April 2014).

In a previous study, which FAM111B was shown by Sandra Mercier et al, is to be closely associated with a new syndrome: hereditary fibrous dermatosis combined with tendon contracture, myopathy, and pulmonary fibrosis (POIKTMP).5 Meanwhile, clinical cases and molecular biology evidence connected with POIKTMP reveal that FAM111B is linked to hereditary excocrine pancreatic dysfunction and pancreatic adenocarcinoma (PAAD).6,7 Other studies have shown that FAM111B has significant functions in various malignancies, such as cervical cancer, prostate cancer, and lung cancer.8-11

Based on previous findings, we hypothesized that FAM111B may be an independent predictor of poor prognosis in PAAD. In this study, we investigated the effect of FAM111B knockdown on PAAD cell migration and invasion. We investigated the expression level of FAM111B in tumor specimens from PAAD patients, determined the relationship between FAM111B expression and clinical prognosis of PAAD patients, and predicted its possible role in the relevant pathways.

2 | MATERIALS AND METHODS

2.1 | Bioinformatics Analysis

We analyzed differential gene expression of FAM111B in pancreatic adenocarcinoma and normal pancreatic tissues using the GEPIA database (http://gepia2.cancer-pku.cn/#index). The TCGA database (https://portal.gdc.cancer.gov/) was used to get mRNA expression data (4 normal samples and 178 tumor samples, Workflow Type: HTSeq-FPKM) and clinical data (185 samples, Data Format: bcr xml) for pancreatic adenocarcinoma. We examined associations between clinicopathological features and FAM111B expression using TCGA data. According to the median FAM111B expression levels, the gene expression data were separated into high and low groups based on the TCGA data. The signaling pathways linked with FAM111B were then predicted and evaluated using gene set enrichment analysis (GSEA).

2.2 | Tissue microarray visual immunoreactive score

Tissue microarray (TMA, n = 133, Cat No: T20-1179-12) was obtained from Shanghai Outdo Biotech Co., LTD, including 115 PAAD tissues which contain detailed clinical characteristics information (Table 2) and 18 adjacent normal tissues. EnVision System (Dako Diagnostics) was performed to stain the TMA specimens. The TMA slides were incubated overnight at 4°C with rabbit polyclonal antibody against FAM111B (Cat No: 14247-1-AP, 1:50, Proteintech, USA). After washing with phosphate-buffered saline (PBS), substrate-chromogen, and...
peroxidase labelled polymer were applied to visualize the protein staining. Then, the visual immunoreactivity score (IRS) was used to assess the expression of FAM111B protein. The CaseViewer 2.4 software (3DHISTECH Ltd) was used to read slices and analyzed the TMA. The score criteria of staining intensity (SI) as follows: none = 0, weak = 1, moderate = 2, and strong = 3. The percentage of positive cells: negative = 0, <10% positive cells = 1, 10%–50% positive cells = 2, 51%–80% positive cells = 3, >80% positive cells = 4. The final IRS was calculated by SI x percentage of positive cells. We divided the samples into low (IRS ≤4) or high expression (IRS >4).

2.3 | Cell culture

The Chinese Academy of Sciences’ Type Culture Collection provided the human PAAD cell line SW1990. The cells were grown in Dulbecco’s modified Eagle medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin–streptomycin solution (Gibco) (Beyotime). The cultivated cells were incubated at 37°C with 5% CO₂.

2.4 | Cells transfection

Six-well plates were used for cell transfection. The synthesized PAADDNA.31-FAM111B (FAM111B) and the empty plasmid PAADDNA.1 (Control) were purchased from the Miao Ling Plasmid Sharing Platform. The siRNA targeting FAM111B (siRNA-FAM111B) was designed, and the sequence was as follows: ACUUUUCAUAAUAGCUCCG. Meanwhile, the scrambled siRNA (siRNA-Control) was constructed as the control treatment. The transfection into cells of SW1990 was performed by using the Liofectamine 2000 (Thermo). The transfection efficiency was determined by Western blotting at 48 h post-transfection.

2.5 | Cell proliferation assay

The Cell Counting Kit-8 (CCK-8) (Beyotime) test was used to assess cell viability and proliferation. After transfection for 24 and 48 h, the cells were plated in 96-well plates at a concentration of 5 x 10³ cells per well in 100 μl complete growth medium. After that, 10 μl CCK-8 reagent was added to each well, and the cells were cultured for another 2 h. A microplate reader was used to measure the optical density (OD) of each well at 450 nm (Thermo).

2.6 | Wound-healing assay

A wound-healing experiment was used to track cell migration. Transfected cells (5 x 10⁵ cells/well) were planted onto 6-well plates with new media containing 10% FBS and incubated until they achieved >90% confluence. A linear scratch wound was created by scratching the cell monolayer with a 10 μl sterile plastic pipette tip. The floating cells were washed three times in PBS, and the media were replaced with serum-free medium containing 4 μg/ml mitomycin. An inverted light microscope (magnification, x200; Olympus Corporation) was used to collect scratch-wound pictures at 0 and 48 h, and wound healing rate was estimated using the formula wound healing rate (%) = [(width at 0 h – width at 48 h)/width at 0 h] * 100.

2.7 | Transwell invasion assay

The transwell assay was used to test the cell invasion ability. Cell suspensions (100 μl, 5 x 10⁴ cells in serum-free DMEM media) were placed in the upper chamber, which included an 8 μm polycarbonate filter (Millipore) that had been pre-coated with 100 μl diluted Matrigel (BD). The lower chamber was filled with 10 %FBS DMEM medium. The non-migrated cells on the top surface were removed after a 24-hour incubation at 37°C with 5% CO₂. The invading cells on the bottom surface were fixed for 15 min in 4 percent paraformaldehyde and stained for 20 min in 0.1% crystal violet. Under an inverted microscope, images were recorded, and cells were counted (magnification, x200; Olympus Corporation).

2.8 | Flow cytometry detection

The Annexin V-fluorescein isothiocyanate (FITC)/propidium iodide (PI) detection kit (BD) was used to detect cell apoptosis according to the manufacturer’s procedure. In 6-well plates, transfected cells (1 x 10⁶ cells/well) were planted. Following a 48-hour incubation period at 37°C with 5% CO₂. Harvested cells were washed twice in PBS before being resuspended in 100 μl binding buffer (Thermo). Then, Annexin V-FITC (5 μl) and PI (5 μl) were added and incubated at room temperature for 30 min in the dark. Finally, the proportion of apoptotic cells was determined using a FACS Calibur flow cytometer (BD).

2.9 | Statistical analysis

The statistics from TCGA were analyzed by R (v.4.1.1). Kruskal–Wallis test and Wilcoxon signed-rank test were used to evaluate relationships between clinicopathological characteristics and the expression of FAM111B. Using chi-squared tests to access the relationship between expression of FAM111B and clinicopathological characters was accessed by the SPSS 26.0 software (SPSS Inc, IL). Prognostic factors were evaluated using Cox regression and Kaplan–Meier method. Gene set enrichment analysis was performed using GSEA (v.4.1.0) software. The statistical analyses of cellular functions were performed using GraphPad Prism Software 8.0. Descriptive statistics were presented as the means±SD. p <0.05 was considered as statistically significant.
3 | RESULTS

In this study, we analyzed the expression of FAM111B in pancreatic adenocarcinoma, the relationship between its expression level and the clinicopathological features of pancreatic adenocarcinoma, and further experimentally validated the effect of FAM111B in pancreatic adenocarcinoma cells in terms of invasion, migration, and apoptosis in cytology, and observed and evaluated the expression level of FAM111B in TMA. Finally, the pathways involved in the development of pancreatic adenocarcinoma by FAM111B were predicted.

3.1 | Patients' characteristics

We downloaded data of PAAD from TCGA which were collected in October 2021. Total number of cases is 185. Then, eight cases with missing clinical information were removed, resulting in 177 cases with primary tumors whose clinical and gene expression data are summarized in Table 1. TMA with 115 PAAD tissues and 18 adjacent normal tissues contained relevant clinical records for all patients. The clinical data are presented in Table 2.

3.2 | Associations with FAM111B expression and clinical pathological variables

When compared to the TCGA and GTEx databases in GEPIA2, we discovered that the expression levels of FAM111B in tumor samples were considerably greater than normal tissue \((p < 0.05)\). (Figure 1A) The Kruskal–Wallis test revealed that FAM111B expression was significantly correlated with clinical grade \((p < 0.05)\). (Figure 1C). The findings showed that cancers with high FAM111B mRNA expression have a bad prognosis.

3.3 | FAM11B overexpressed is associated with poor prognosis in PAAD

We performed Kaplan–Meier survival analysis to assess the relationship between FAM111B expression levels in relation to prognosis. As a result, FAM111B expression was more strongly associated with poorer prognosis than low FAM111B expression \((p < 0.001)\) (Figure 1B). Univariate analysis showed that age \((HR: 1.02; 95\% CI: 1.00–1.04; p = 0.028)\), N stage \((HR: 2.00; 95\% CI: 1.19–3.35; p = 0.008)\), and FAM111B \((HR: 1.50; 95\% CI: 1.23–1.82; p = 0.001)\) were associated with a shorter overall survival. To further explore these factors in relation to survival, multivariate analysis using the Cox proportional hazards model showed that FAM111B \((HR: 1.01; 95\% CI: 0.99–1.03; p = 0.177)\), N stage \((HR: 1.90; 95\% CI: 1.10–3.28; p = 0.020)\), and age \((HR: 1.51; 95\% CI: 1.21–1.90; p < 0.001)\). (Table 3).

3.4 | GSEA recognizes FAM111B-related signaling pathway

Since there are many different signaling pathways involved in the progression of pancreatic adenocarcinoma, the poor prognosis of pancreatic adenocarcinoma due to high expression of FAM111B may be related to the activation of some signaling pathways by...
PAAD. We identified the key pathways associated with FAM111B by detecting the difference between the high- and low-FAM111B expression groups in GSEA (FDR p < 0.05, NOM p < 0.05). The top 6 key pathways based on NES scores were cell cycle pathway, p53 signaling pathway, mismatch repair pathway, DNA replication pathway, nucleotide excision repair pathway, and base excision repair pathway (Table 4).

### 3.5 Knockdown of FAM111B suppressed SW1990 cell proliferation, migration, invasion, and promoted SW1990 cell apoptosis

The biological function of cells is crucial in tumorigenesis and progression; therefore, it is necessary to investigate the effect of FAM111B expression level on apoptosis, proliferation, invasion, and migration of tumor cells. In the flow-through apoptosis assay, the SW1990 cell apoptosis rate was lower in the FAM111B high expression group compared with the control group (p = 0.008), indicating that high expression of FAM111B inhibited SW1990 cell apoptosis, while the siRNA-FAM111B group had a higher rate of SW1990 cell apoptosis compared with the control group (p = 0.005), indicating that silencing FAM111B expression could promote SW1990 cell apoptosis (Figure 2A). As shown in Figure 2B, in the assay of cell proliferation ability at 24 h and 48 h by CCK8 assay, the results of both groups showed that the FAM111B high expression group promoted SW1990 cell proliferation, while the siRNA-FAM111B group inhibited SW1990 cell proliferation (p < 0.01). This means that knocking down FAM111B decreased the growth of SW1990 cells considerably. The wound healing rate in the siRNA-FAM111B group was lower than in the siRNA control group, according to the results of the wound healing assay (Figure 2C; p < 0.01). In other words, the silencing of FAM111B expression significantly inhibited the migratory ability of SW1990 cells. The transwell assay was used to analyze the invasive ability of SW1990 cells. The results showed that the siRNA-FAM111B group had fewer cells in the lower lumen than the siRNA control group (Figure 2D; p < 0.05). Therefore, the expression of FAM111B could promote the invasive ability of SW1990 cells.

### 3.6 FAM111B was overexpressed in PAAD tissues samples

To validate the results of the above cellular experiments, we used TMA containing 115 PAAD tissues and 18 normal pancreatic tissues for IHC analysis to assess the expression of FAM111B (Figure 3A). FAM111B was significantly overexpressed in PAAD tissues (IRS: tumor = 7.15 ± 2.53 vs. normal = 4.33 ± 4.01, p < 0.01) than that of the normal tissues (Figure 3B). In addition, IHC staining showed that FAM111B expression was mainly localized in the nucleusplasm of PAAD cells (Figure 3C). the high expression rate of FAM111B in PAAD was significantly higher than that in normal pancreatic tissues (p < 0.001; Table 2). the expression of FAM111B was positively correlated with lymph node metastasis and TNM (p < 0.05). In summary, our findings suggest that FAM111B may play a key role in the development of PAAD.
The trypsin-like cysteine/serine peptidase structural domain is found at the C-terminus of FAM111B, which is found on human chromosome 11q12. Mercier et al. discovered in 2013 that missense mutations in FAM111B are linked to HFP pathogenesis and impact a variety of organ systems, including the pancreas exocrine, skin, liver, skeletal muscle, and lung. Subsequently Aaron Seo et al. identified the FAM111B mutation, which is linked to pancreatic exocrine dysfunction, early-life increased liver

4 | DISCUSSION

The trypsin-like cysteine/serine peptidase structural domain is found at the C-terminus of FAM111B, which is found on human chromosome 11q12. Mercier et al. discovered in 2013 that missense mutations in FAM111B are linked to HFP pathogenesis and impact a variety of organ systems, including the pancreas exocrine, skin, liver, skeletal muscle, and lung. Subsequently Aaron Seo et al. identified the FAM111B mutation, which is linked to pancreatic exocrine dysfunction, early-life increased liver
transaminases, and autosomal dominant rash. The phenotypic is comparable to Shwachman–Diamond syndrome, and patients with the FAM111B mutation have a higher risk of pancreatic adenocarcinoma than healthy people. FAM111B mutations, on the other hand, cause aberrant cell proliferation and DNA processing. When a PAAD cell line was treated with antiproliferative medicines, Yue et colleagues detected a downregulation of FAM111B in transcriptome analysis.13

In recent years, some studies have also reported the role and mechanism of FAM111B in other tumors. Akamatsu et al. identified FAM111B as a susceptibility gene for prostate cancer by genomewide association study.8 Sun et al. in lung cancer found that FAM111B expression was found to be prevalent among LUAD patients, and it was shown to be a risk factor for LUAD. FAM111B expression was found to have a positive correlation with more advanced clinicopathological features, and FAM111B expression was an independent risk factor for LUAD.10 Furthermore, FAM111B may be directly linked to BAG3, a member of the BAG family. BAG3 plays an important role in apoptosis with BCL2.14,15 BAG3 overexpression can synergize with BCL-2 to induce anti-apoptotic effects.14 In cervical cancer, gene

### Table 4 Gene sets enriched in phenotype high

| MSigDB collection | Gene set name                  | NES  | NOM p-Value | FDR q-val |
|-------------------|--------------------------------|------|-------------|-----------|
| c2.cp.kegg.v7.4.symptoms.gmt | KEGG_CELL_CYCLE                | 2.234| 0.000       | 0.000     |
|                   | KEGG_P53_SIGNALING_PATHWAY      | 2.176| 0.000       | 0.000     |
|                   | KEGG_MISMATCH_REPAIR           | 2.045| 0.000       | <0.001    |
|                   | KEGG DNA_REPLICATION           | 2.015| 0.000       | 0.001     |
|                   | KEGG NUCLEOTIDE_EXCISION_REPAIR| 2.013| 0.000       | 0.001     |
|                   | KEGG BASE_EXCISION_REPAIR      | 2.010| 0.000       | 0.001     |

Note: Gene sets with NOM p < 0.05 and FDR q-val <0.25 are considered as significant.
Abbreviations: FDR, false discovery rate; NES, normalized enrichment score; NOM, nominal.

### Figure 2

(A) Effect that overexpression of FAM111B and knockdown of FAM111B on apoptosis of SW1990 cells was analyzed by flow cytometry experiments. (B) The effect that overexpression of FAM111B and knockdown of FAM111B on the proliferation of SW1990 cells was detected by CCK8 assay at 24h and 48h. (C) Cell scratch assay to analyze the effect of overexpression of FAM111B and knockdown of FAM111B on the migration of SW1990 cells. (D) Overexpression of FAM111B promoted invasion of SW1990 cells, while knockdown of FAM111B inhibited invasion of SW1990 cells using Transwell invasion assay. Data are expressed as mean ± standard deviation. *: p < 0.05; **: p < 0.01; ***: p < 0.001.
cores and PCR were applied to examine 112 patients with advanced cervical cancer. The correlation analysis revealed that FAM111B was associated with distant metastasis of cervical cancer.11

FAM111B expression was observed to be greater in pancreatic adenocarcinoma tissues than in normal tissues in our investigation. Meanwhile, high-FAM111B expression was an independent predictor for poor PAAD prognosis, and multivariate analysis revealed that FAM111B was an independent factor for poor pancreatic adenocarcinoma prognosis. These findings imply that FAM111B might be a predictive factor for PAAD.

We employed siRNA to suppress FAM111B expression in the SW1990 cell line in vitro research. After FAM111B knockdown, cell invasion, proliferation, and migration were decreased, but apoptosis was enhanced. These findings are identical to FAM111B expression in the LUDA cell line.10

It has been shown that FAM111B is closely related to various tumors in biology and clinicopathology, but there are few studies on its possible signaling pathways in tumors and few reports in pancreatic adenocarcinoma. The results of GSEA analysis may provide some guidance for the discovery of new pathways.17 We compared the GSEA results of FAM111B low and high expression datasets. Among the GSEA-enriched results regarding cell cycle signaling pathways correlated with FAM111B in the first place. Normal DNA replication, PCNA chromatin loading, and cell proliferation are all aided by FAM111B. FAM111B mutations reduce cellular fitness by removing inhibitory restrictions on intrinsic protease activity, preventing DNA and RNA synthesis, and encouraging apoptotic cell death.18 FAM111B degraded p16 and favorably controlled cell cycle progression and proliferation by increasing cyclin D1-CDK4 activity, according to Kawasaki et al.9

Down-regulation of FAM111B raised the number of cervical cancer cells in G0/G1 phase cells and halted the cell cycle in G0/G1 phase, according to another study on the role of FAM111B in cervical cancer. To learn more about how FAM111B promotes apoptosis, researchers used Western blot to look for p53 protein production and discovered that inhibiting FAM111B expression enhanced p53 expression.19

Interestingly, the second most relevant pathway in the analysis about FAM111B enrichment is the p53 signaling pathway. p53 is the most frequently altered gene in human tumors, accounting for more
than half of all cancers.\textsuperscript{20} p53 is located on chromosome 17p and regulates DNA repair, cell apoptosis, cell cycle arrest, or senescence, thereby exerting its role in tumor suppression.\textsuperscript{21,22} p53 can directly target FAM111B’s transcripional start site and suppress its expression.\textsuperscript{23,24} Due to loss or mutation, p53 may have a lower inhibitory impact on FAM111B, resulting in its high expression in lung cancer.\textsuperscript{10} Because in vitro investigations revealed that silencing FAM111B might stop the cell cycle in the G2/M phase, resulting in increased apoptosis, which is also the function of the p53 signaling pathway in tumor cells. As a result, FAM111B is thought to be involved in the control of the p53 signaling pathway in malignancies.\textsuperscript{10} However, the specific regulation mechanism requires further experiments to verify.

MMR (DNA mismatch repair) is a highly conserved biological mechanism that is important for genomic integrity.\textsuperscript{25} MMR corrects DNA mismatches that occur during DNA replication, preventing mutations in dividing cells from becoming permanent. MMR mutations are linked to genome-wide instability and susceptibility to certain cancers.\textsuperscript{26} FAM111B may be involved in the MMR pathway process, leading to susceptibility to pancreatic adenocarcinoma.

Nucleotide excision repair (NER) is a multistep “cut and patch” process that removes diverse structurally unrelated DNA damages. Defects in the global genome NER (GG-NER) subpathway result in cancer susceptibility by searching the genome for helix-distorting lesions, which precludes mutagenesis.\textsuperscript{27} They have a 1000-fold greater risk of sun induced skin cancer as well as an elevated risk of other inside tumors.\textsuperscript{28} The enrichment results in GSEA showed that FAM111B may have a relevant role in the GG-NER pathway. So, mutations in FAM111B thus lead to increased susceptibility to cancer.

Base excision repair (BER) is a critical DNA repair system that corrects a basic sites and minor base lesions caused by deamination, oxidation, and alkylation. BER proteins are important for maintaining genomic integrity because they engage in the single-strand break repair (SSBR) process.\textsuperscript{29} Increased proliferation, greater quantities of endogenous mutagens (i.e., reactive oxygen species), and deficiencies in DNA repair pathways all contribute to cancer cells’ intrinsic genomic instability.\textsuperscript{30} In BER, APE1 is required for the excision of a basic sites. Wild-type p53 is responsible for APE1 downregulation.\textsuperscript{31} Activated p53 interacts to the APEX1 promoter at the Sp1 binding site after DNA damage, inhibiting APE1 expression.\textsuperscript{31} APEX1 is additionally inhibited by APE1 binding to several negative Ca\textsuperscript{2} response elements (nCaRE) in the APEX1 promoter, which acts as a self-inhibitory mechanism.\textsuperscript{32} Mutations in FAM111B may activate the p53 signaling pathway, further blocking the APEX1 promoter, which leads to expression of the BER pathway and increased genomic instability of the cells.

Our study has several limitations. First, predicting the overall expression of FAM111B using only mRNA levels is not complete. In addition, due to the limitations of our study design, a single SW1990 cell line is not representative of other cell lines in human PAAD, and the experimental results of adding multiple cell lines would be more convincing. Meanwhile, the study of the pathway mechanism of FAM111B is only at the prediction stage, and further investigation of the mechanism of FAM111B in PAAD is the direction of our future research.

5 | CONCLUSION

In conclusion, the results of this study indicate that FAM111B is highly expressed in PAAD tissues and is closely associated with poor prognosis of PAAD. FAM111B significantly promotes the proliferation, invasion, and migration of pancreatic adenocarcinoma cells and inhibits their apoptosis. FAM111B may be a new biomarker for PAAD and provides a new direction for the treatment and diagnosis of PAAD.

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CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

DATA AVAILABILITY STATEMENT

We analyzed differential gene expression of FAM111B in pancreatic adenocarcinoma and normal pancreatic tissues using the GEPIA database (http://geopia2.cancer #x2010;pkk.cn/#index). The TCGA database (https://portal.gdc.cancer.gov/) was used to get mRNA expression data (4 normal samples and 178 tumor samples, Workflow Type: HTSeq #x2010;FPKM) and clinical data (185 samples, Data Format: bcr xml) for pancreatic adenocarcinoma. The data of TMA and experiments In vitro that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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