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ORIGINAL RESEARCH ARTICLE

Prognostic and predictive significance of altered microRNA expression in pancreatic cancer

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Abstract

Introduction: Pancreatic cancer (PC) remains one of the most lethal malignancies with a dismal 5-year survival rate of 13%. MicroRNAs (miRNAs) have emerged as critical regulators in tumor progression, yet their clinical relevance in PC requires validation through large-scale datasets.

Objective: This study aims to detect irregularities in miRNA expression within PC patients by analyzing data sourced from the Cancer Genome Atlas (TCGA) database.

Methods: Expression profiles of 14 miRNAs in 183 PC patients were analyzed using data from the TCGA database, correlating them with survival, tumor-node-metastasis stage, tumor grade, recurrence, and lymph node metastasis. Molecular mechanisms were explored via target prediction and correlation analysis.

Results: Reduced miR-107 expression and elevated miR-21 expression were each independently linked to worse overall survival ($p<0.05$). Lower miR-107 levels were correlated with advanced stage (Stage I vs. Stage II: $p<0.05$) and lymph node metastasis ($p<0.05$), whereas higher miR-21 levels were associated with higher T stage (T3+4 vs. T1+2: $p<0.0001$), advanced overall stage (Stage I vs. Stage II: $p<0.0001$), higher tumor grade (G3+4 vs. G1: $p<0.001$) and increased recurrence rates (*$p<0.05$). Mechanistically, the degradation of oncogenic miR-21—mediated by poly(A) polymerase-associated protein D5—was disrupted ($p<0.001$), leading to the overexpression of miR-21, thereby reducing the expression of tumor suppressor gene programmed cell death 4 ($p<0.0001$). MiR-107 was a candidate for targeting Notch2 and cyclin-dependent kinase 6 ($p<0.05$).

Conclusion: MiR-21 and miR-107 are pivotal prognostic biomarkers in PC, warranting further exploration as therapeutic targets.

Keywords: MiR-107; MiR-21; Pancreatic cancer; The cancer genome atlas database

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1. Introduction

Pancreatic cancer (PC) poses a severe global health challenge. Global cancer registry data indicate a notable rise in the incidence of various cancer types between 2014 and 2020, with an overall increase of 1% within this period. While some cancers (thyroid, prostate, testis, and melanoma cancers) now achieve survival rates of 90% or higher, PC remains among the deadliest, alongside lung (27%) and esophageal (22%) cancers, with a 5-year survival rate of only 13%.[1] In European and Western societies, the incidence of PC is projected to rise significantly, placing a heavy burden on social life and healthcare systems.[2,3]

The high lethality of PC stems from multiple factors. Its insidious early symptoms often result in delayed diagnosis, and treatment options remain limited. An aging population further expands the pool of at-risk individuals, exacerbating the impact of PC on medical resource allocation, family finances, mental well-being, and overall social productivity. This underscores the urgency of addressing PC as a critical public health issue.[3,4]

The pathogenesis of PC involves a complex interplay of multiple factors across various levels, including the progression of pre-cancerous lesions, key molecular genetic changes, remodeling of the tumor microenvironment, and genetic susceptibility.[5] Among them, molecular genetic changes are the core link driving carcinogenesis, specifically manifested as abnormal regulation of multiple genes, including activation of oncogenes (e.g., Kirsten rat sarcoma viral oncogene homolog [*KRAS*] mutation rate approximately 88%), inactivation of tumor suppressor genes (e.g., tumor protein 53 [*TP*53] mutation rate 61–74%, cyclin-dependent kinase inhibitor 2A [*CDKN2A*] mutation rate 16–44%, and mothers against decapentaplegic homolog 4 [*SMAD*4] mutation rate 20–22%), along with abnormalities of DNA damage repair genes and homologous recombination deficiency genes.[6] Within the tumor microenvironment, neurons and nerve fibers stand as key structural elements, exerting a notable influence on the initiation and progression of tumors.[7]

The molecular changes in PC are superimposed on each other and synergistically interact with processes such as the gradual progression of pre-cancerous lesions and abnormal remodeling of the tumor microenvironment, collectively promoting the occurrence and malignant development of PC.[5] Early diagnosis and prompt therapeutic intervention are therefore paramount for improving patient outcomes.[8] Unraveling the molecular mechanisms underpinning PC pathogenesis holds significant promise for developing innovative diagnostic and treatment strategies.[9] Urgent efforts to identify novel early diagnostic biomarkers and actionable therapeutic targets are imperative to overcoming the current challenges and enhancing survival prospects for PC patients.

MicroRNAs (miRNAs) have drawn growing attention as important post-transcriptional regulators in recent years. These small non-coding RNAs (20–24 nucleotides) modulate gene expression through mechanisms such as messenger RNA (mRNA) degradation and translational repression.[10] Accumulating evidence underscores their critical roles in modulating hallmark tumor behaviors, including cell proliferation, differentiation, invasion, metastasis, and apoptosis.[11] Notably, functional studies have linked dysregulated miRNA expression profiles to cancer pathogenesis, establishing their utility as diagnostic or prognostic biomarkers across multiple tumor types.[12,13]

miRNAs possess a dual role as both tumor suppressors and oncogenes, contributing to the complex involvement in the mechanisms of carcinogenesis. Therapeutic strategies leveraging miRNA biology include:

(i) MiRNA mimics (tumor suppressor restoration): Synthetic miRNA mimics are employed to replenish functionally deficient tumor suppressor miRNAs. For example, a miR-34 mimic advanced to Phase I clinical trials for treating melanoma, demonstrating acceptable safety and feasibility—though challenges in delivery efficiency and off-target effects persist.

(ii) Antisense oligonucleotides (antimiRs; oncogenic miRNA inhibition): Using antimiRs to block overexpressed oncogenic miRNAs. A notable example is miravirsen, an antimiR targeting miR-122 (highly expressed in hepatocytes and linked to hepatitis C virus [HCV] replication and liver carcinogenesis). It reached Phase II trials for chronic HCV infection, significantly reducing viral load in treated patients.[14] Deciphering miRNA expression patterns and identifying miRNAs with prognostic or predictive value are therefore critical steps toward translating miRNA-based therapies into clinical applications for PC and other malignancies.

Tumor stage remains a cornerstone prognostic factor for disease-specific outcomes in cancer. The tumor-node-metastasis (TNM) staging system, standardized by the American Joint Committee on Cancer (AJCC), serves as a critical framework for categorizing pancreatic and hepatobiliary malignancies. This system not only enables accurate prognosis prediction but also informs therapeutic strategies.[15] By providing objective and reproducible tumor classification, the TNM staging system is indispensable for guiding individualized treatment planning and clinical decision-making. This study refers to the TNM staging system formulated in the AJCC Staging System for PC (8th Edition) (Table 1).[16] Tumor grade, a key indicator of tumor cell differentiation, complements staging in prognostic evaluation.[17] For each AJCC stage, patients with higher-grade tumors had a significantly lower survival than those with lower-grade tumors. Multivariate analyses have validated tumor grade as an independent predictor of survival across diverse patient populations.[18] Tumor grading was performed in accordance with the four-tier classification system established by the College of American Pathologists. Under this system, tumors were categorized into four grades: Well-differentiated (designated as G1), moderately differentiated (designated as G2), poorly differentiated (designated as G3), and undifferentiated (designated as G4).[19]

Table 1. American Joint Committee on Cancer (AJCC) 8th ed.ition staging system for pancreatic cancer

Primary tumor (T-category)	Regional lymph node (N-category)	Distant metastasis (M-category)	Stage
T1: Maximum tumor diameter ≤2 cm	N0: No regional lymph node metastasis	M0: No distant metastases	Stage IA: T1, N0, M0 Stage IB: T2, N0, M0
T2: Maximum tumor diameter >2 cm and ≤4 cm	N1: Metastasis in 1–3 regional lymph nodes	M1: Distant metastases	Stage IIA: T3, N0, M0 Stage IIB: T1–3, N1, M0
T3: Maximum tumor diameter >4 cm	N2: Metastasis in≥4 regional lymph nodes	-	Stage III: AnyT, N2, M0 or T4, AnyN, M0
T4: Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)	-	-	Stage IV: AnyT, AnyN, M1

Within the scope of this research, our objective was to detect irregularities in miRNA expression within PC patients by analyzing data sourced from the Cancer Genome Atlas (TCGA) database. This endeavor was undertaken with the intention of furnishing evidence to support the development of miRNA-based therapeutic strategies for PC. The study focused on 14 miRNAs that have been indicated to play clear roles in regulating the occurrence and development of PC,[20-33] as specifically shown in Figure 1. However, most of them lack large-scale clinical data to reveal their relationship with PC patients. This study analyzed the survival time, TNM stage, tumor grade, and potential molecular mechanisms of PC using the TCGA database, identifying potentially relevant miRNAs, thus providing more possibilities for the clinical treatment of PC.

2. Materials and methods

2.1. Data source and miRNA selection

Clinical data related to miRNAs (survival, TNM stage, tumor grade, recurrence, and lymph node metastasis) from 183 PC patients were retrieved from the TCGA database via the Firehose website (https://gdac.broadinstitute.org/). Patients with a survival of <1 month post-surgery were excluded to avoid confounding through perioperative mortality.

Fourteen miRNAs (miR-10a, miR-10b, miR-107, miR-132, miR-146a, miR-148, miR-150, miR-155, miR-20a, miR-21, miR-210, miR-212, miR-222, and miR-27a) were selected based on prior evidence of roles in PC pathogenesis.

2.2. Expression stratification

MiRNA expression profiles were analyzed using the Illumina HiSeq sequencing platform (HiSeq 2500, Illumina, Inc., United States [US]). Patients were classified into high-expression and low-expression subgroups by applying the median miRNA expression value as the cutoff threshold for stratification. Survival differences between subgroups were assessed using log-rank tests. Student's *t*-test was used to compare miRNA expression across T stages (T1–T4), Stage I–IV, tumor grades (G1–G4), recurrence, and lymph node metastasis between high and low miRNA groups.

2.3. Molecular mechanism exploration

Putative mRNA/protein targets of miR-107 and miR-21 were predicted using TargetScan (https://www.targetscan.org/). Pearson correlation analysis was performed between the miRNA and mRNA/protein expression to explore potential molecular mechanisms.

2.4. Statistical analysis

Analyses of statistical data were conducted using the SPSS Statistics Version 16.0 (IBM, US). A $p<0.05$ was set as the threshold for statistical significance, and a hierarchical labeling system was employed to enhance precision: $^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; and $^{****}p<0.0001$.

3. Results

3.1. Association with survival outcomes

Among the 14 miRNAs analyzed using the survival curve, miR-107 and miR-21 showed significant correlations with patient survival. Notably, patients with high miR-107 expression and low miR-21 expression had longer post-surgical survival times ($p<0.05$; Figure 1).

3.2. Correlation with clinical pathological features

Subsequently, we explored how miR-107 and miR-21 relate to TNM stage, tumor grade, recurrence, and lymph node metastasis in patients with PC. The findings revealed that reduced miR-107 expression was linked to more advanced disease stages (Stage I vs. Stage II: $p<0.05$) and lymph node metastasis ($p<0.05$), but showed no significant correlations with tumor recurrence or grade ($p>0.05$; Figure 2). High miR-21 expression was significantly correlated with higher T stage (T3+4 vs. T1+2: $p<0.0001$), tumor stage (Stage I vs.

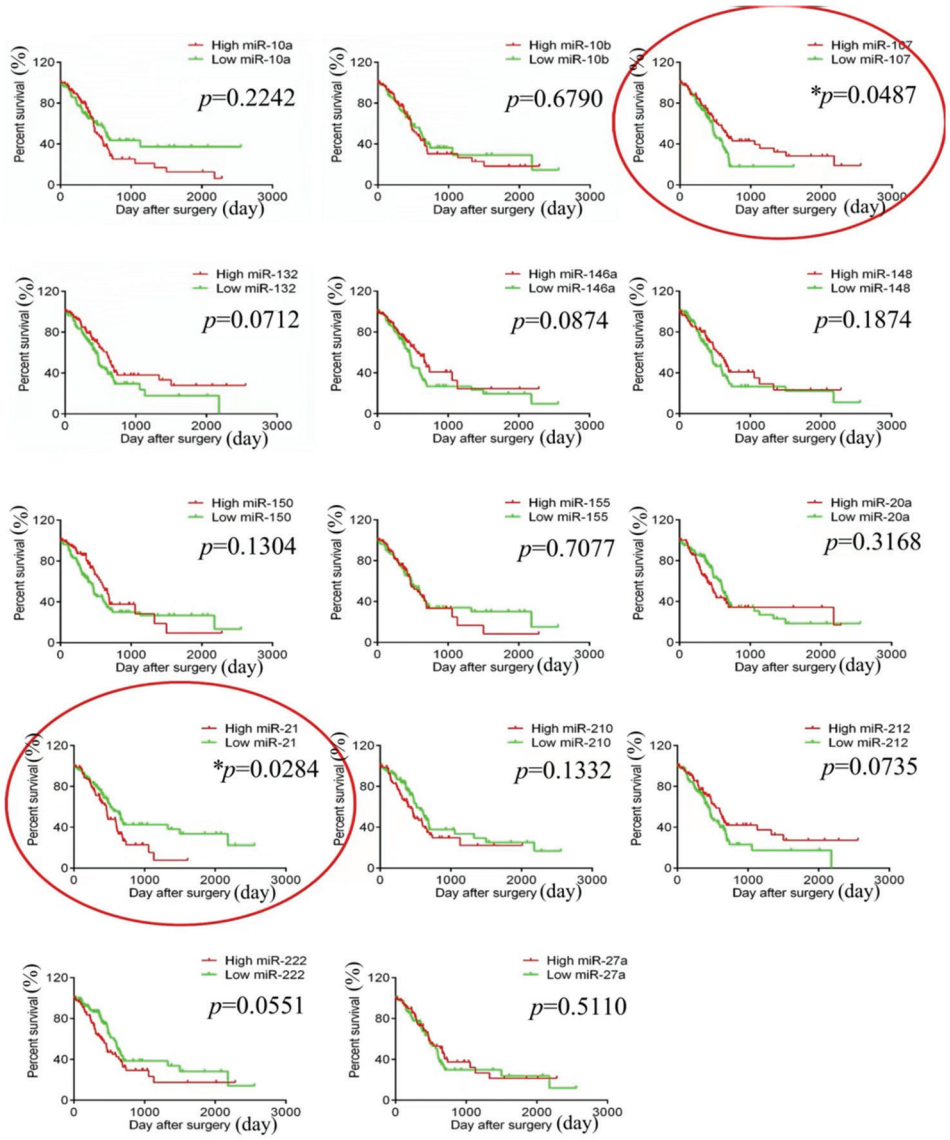


Figure 1. Kaplan–Meier survival curves for the 14 microRNAs revealed an association with the prognosis of pancreatic cancer patients from the Cancer Genome Atlas (TCGA) database
Note: *$p<0.05$.

Stage II: $p<0.0001$), grade (G3+4 vs. G1: $p<0.001$), and recurrence rates ($p<0.05$). However, when comparing with the low miR-21 expression group, no significant association was found in terms of lymphatic metastasis ($p>0.05$), as illustrated in Figure 2.

3.3. Potential molecular mechanisms

Furthermore, we explored the potential molecular mechanisms through the TCGA database. Firstly, relevant mRNA expression data that may be related to miR-21were extracted (Figure 3). The results indicated that changes in miR-21 expression might be related to the programmed cell death protein 4 (*PDCD4*) gene and the polymerase-associated protein D5 (*PAPD5*) gene ($p<0.05$) (Figure 3). Next, the expression patterns of downstream proteins that were potentially regulated by miR-21 were analyzed (Figure 4). MiR-21 overexpression was associated with downregulated PDCD4 protein expression ($p<0.001$; Figure 4), a known tumor suppressor. However, no significant difference was observed between the expression of phosphatase and tensin homolog deleted on chromosome ten (PTEN) protein and miR-21 ($p>0.05$; Figure 4). In addition, novel target mRNAs that may be regulated by miR-107 were extracted (Figure 5). Results

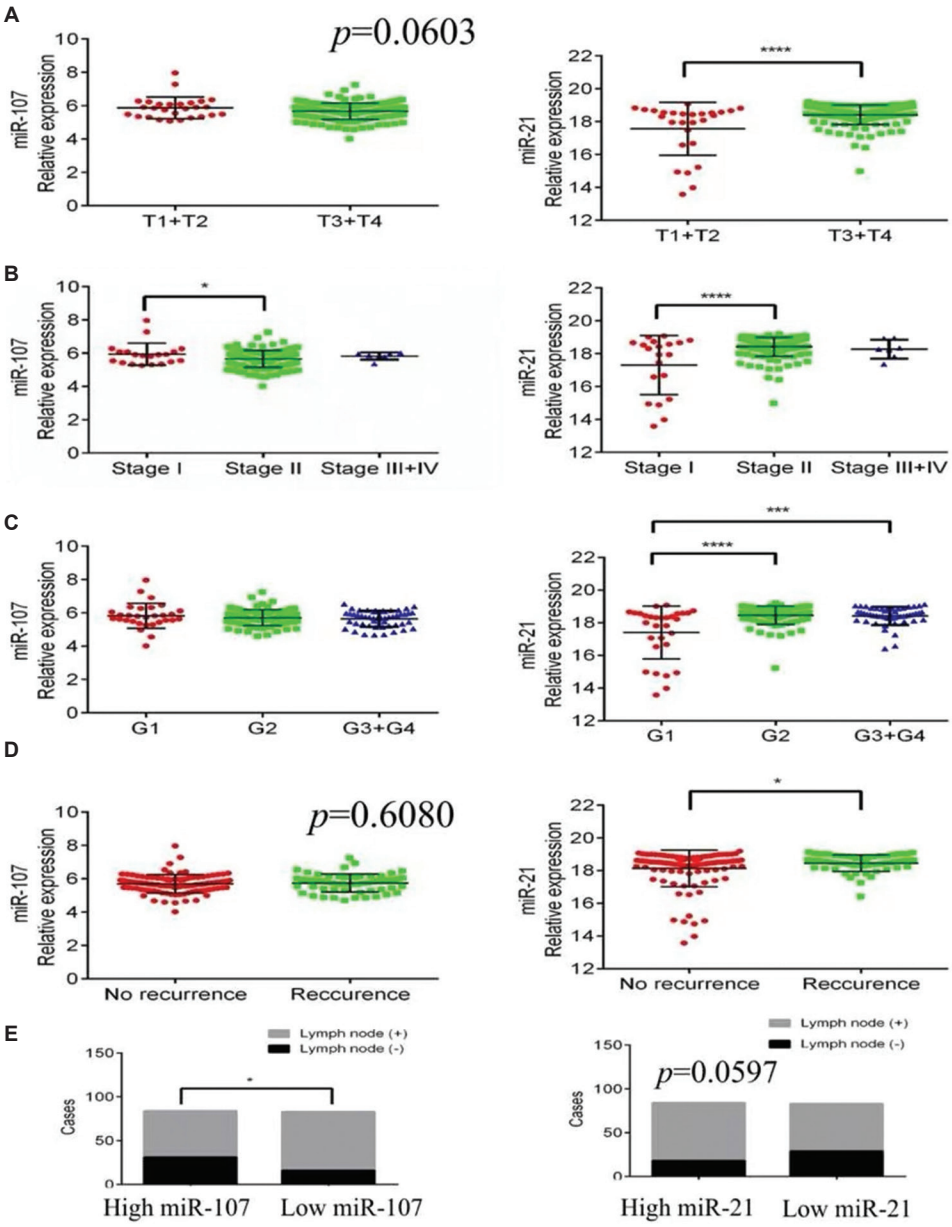


Figure 2. The relationship between miR-107 and miR-21 with regard to (A) tumor-node-metastasis stage, (B) tumor stage, (C) tumor grade, (D) recurrence, and (E) lymphatic metastasis in pancreatic cancer patients
Notes: *p<0.05, ***p<0.001, ****p<0.0001.

from the TCGA database analysis suggest that Notch2 and CDK6 may be direct candidates targeted by miR-107 (p<0.05; Figure 5). No corresponding protein data were retrieved from the TCGA database.

4. Discussion

PC continues to rank among fatal malignancies globally, with survival rates remaining critically low. This grim prognosis highlights the urgent need to identify new prognostic biomarkers and actionable therapeutic targets. Abnormal expression patterns of miRNAs have been linked to the onset and development of specific cancers. Moreover, the diagnostic or prognostic features of certain cancers can be differentiated according to the unique miRNA expression patterns.[12,13] To gain insights into the biological implications of the alteration of miRNA expression in PC, a systematic analysis of the clinical relevance and molecular mechanisms of 14 miRNAs in PC was conducted using data from the TCGA database, with a focus on miR-21 and miR-107 due to their notable associations with patient

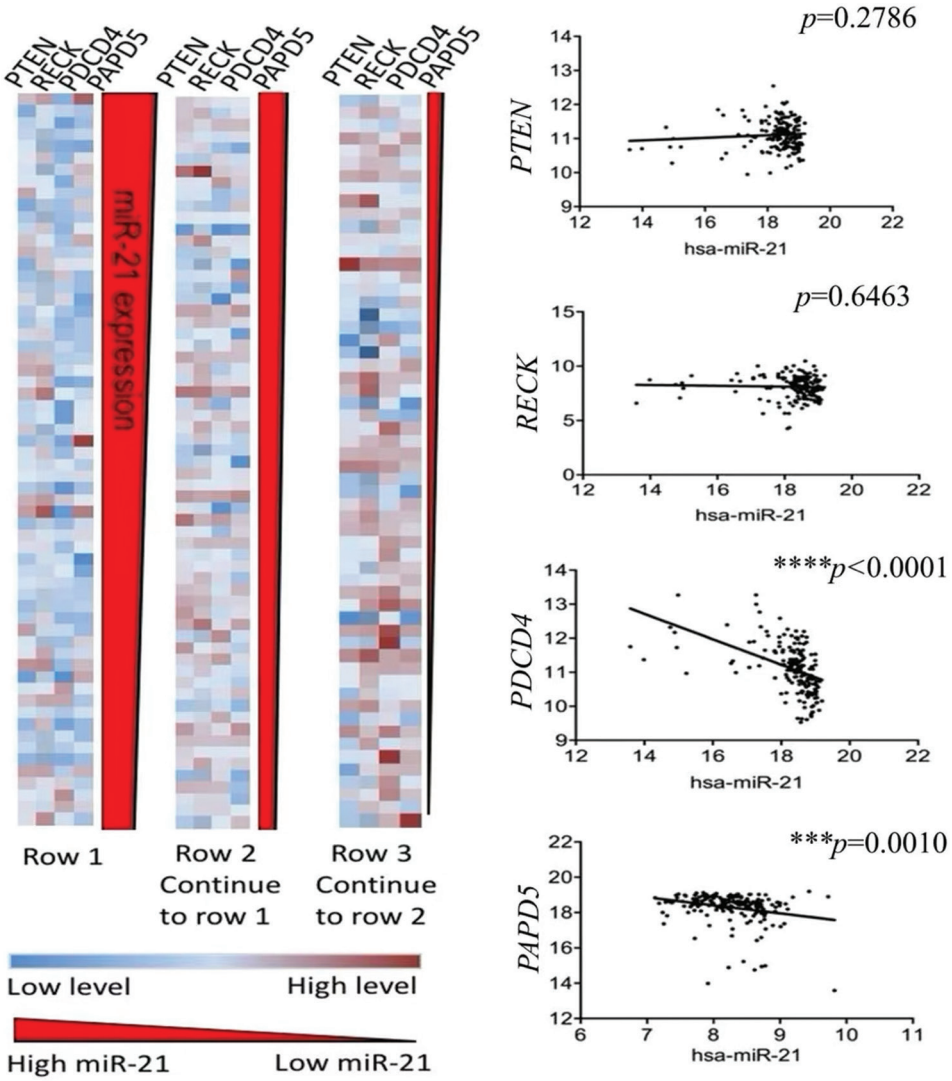


Figure 3. Relevant mRNA expression data that may be related to miR-21
Notes: ***p<0.001, ****p<0.0001.

outcomes. Previous basic studies demonstrated that the 14 genes targeted in this study play important roles in the proliferation, invasion, metastasis, and apoptosis of PC cells.[20-33] However, most of them lack large-scale clinical data to reveal their relationship with PC patients. In the present study, the analysis of miRNA expression patterns revealed that altered expressions of miR-107 and miR-21 were linked to the post-operative survival duration of PC patients. Notably, reduced miR-107 expression often indicated higher lymphatic metastasis and advanced overall stage, whereas elevated miR-21 expression often indicated higher T stage, advanced overall stage, poorer tumor differentiation, and increased recurrence rates.

Previous research has shown that miR-21 is overexpressed in a variety of tumor types, such as glioblastoma, colorectal cancer, breast cancer, lung cancer, and PC.[34,35] Other investigations have indicated that in PC, miR-21 not only exhibits high expression but is also related to increased tumor aggressiveness and unfavorable patient outcomes.[13,35,36] In addition, miR-21 has been identified as an independent factor for predicting prognosis in PC.[37-39]

As an atypical poly(A) polymerase, PAPD5 specifically identifies mature miR-21 and catalyzes the addition of adenosine tails to its 3' end, thereby achieving adenylation. Previous experiments have shown that this adenylation, mediated by PAPD5, directly marks miR-21 as a degradation target. The results indicated that silencing PAPD5 expression markedly elevates miR-21 expression levels, while reducing the degree of its adenylation. This suggests that adenylation serves as an initiating signal

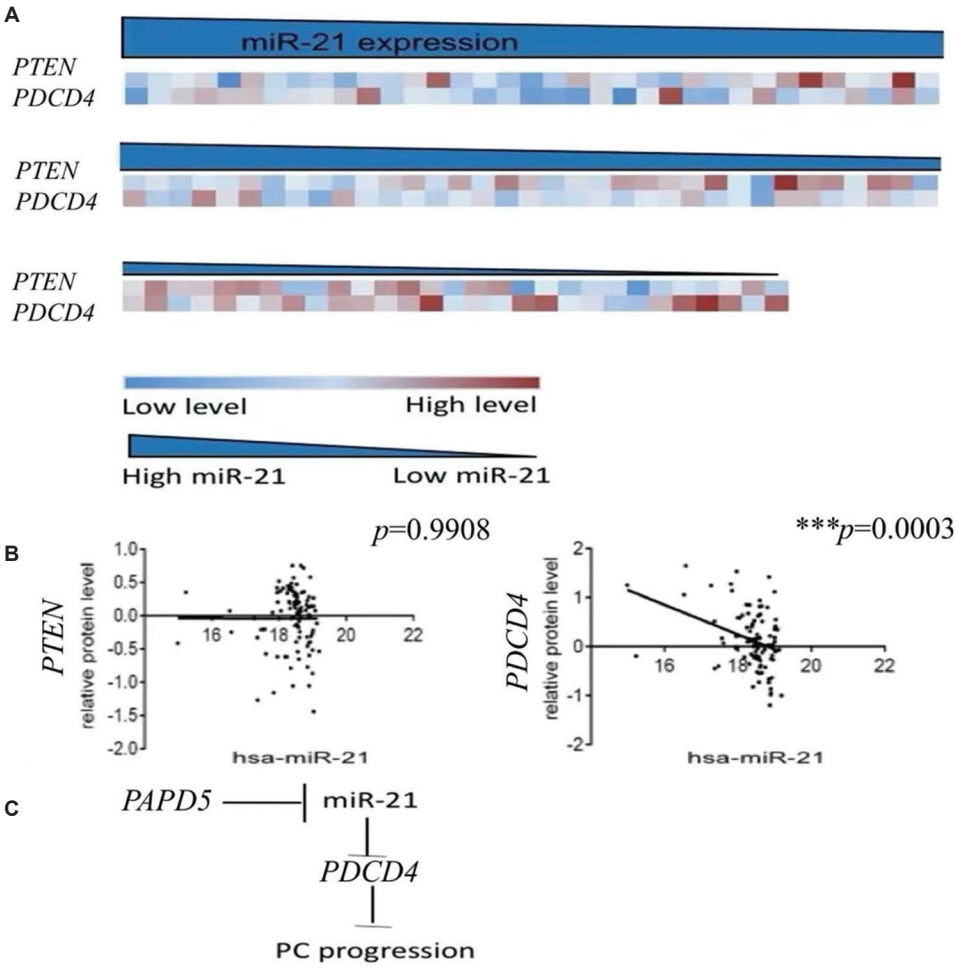


Figure 4. (A-C) Relevant protein expression data that may be related to miR-21
Note: ***p<0.001.

for miR-21 degradation, which may facilitate subsequent steps by altering RNA structure or recruiting degradation factors. The adenylated miR-21 is then recognized and progressively degraded by 3'-5' exonuclease poly (A)-specific ribonuclease (PARN). PARN knockdown experiments demonstrated a notable rise in the adenylation level of miR-21, further supporting the core role of the PAPD5–PARN axis in miR-21 degradation. In addition, PAPD5 may indirectly affect the functional network of miR-21 by regulating the stability of other RNAs (such as *TP53* mRNA). Data from the TCGA database showed that the adenylation level of miR-21 is reduced in various tumors, resulting in its abnormal accumulation and promotion of tumor progression. This suggests that PAPD5 could be a potential therapeutic target.[40,41]

The 3' untranslated region (3'UTR) of the *PDCD4* gene harbors a conserved binding site for miR-21. By binding to this specific site, miR-21 suppresses the translation of PDCD4, rather than affecting the stability of its mRNA. The downregulation of PDCD4 expression is widespread in tumors and is negatively correlated with high miR-21 levels. Multiple studies have indicated that suppressed miR-21 degradation leads to the downregulation of multiple tumor suppressor genes, including *PDCD4,*[42] *PTEN,*[43] B-cell lymphoma-2 (*BCL2*),[44] tropomyosin 1 (*TPM1*),[45] reversion-inducing cysteine-rich protein with kazal motifs (*RECK*),[46] and *SPRY2.*[29] In our research findings, *PDCD4* stands out as having an important role. Notably, *PDCD4* expression is suppressed in advanced carcinomas of the colon, breast, lung, prostate, and neuroendocrine tumors, with its tumor suppressive roles documented in cellular invasion and metastasis.[34] Of particular interest, miR-21-mediated targeting of the *PDCD4* gene significantly reduces its expression in metastatic and highly proliferative pancreatic endocrine tumors, exhibiting an inverse correlation with miR-21 abundance.[43] As a tumor suppressor, PDCD4 can inhibit tumor growth and invasion,

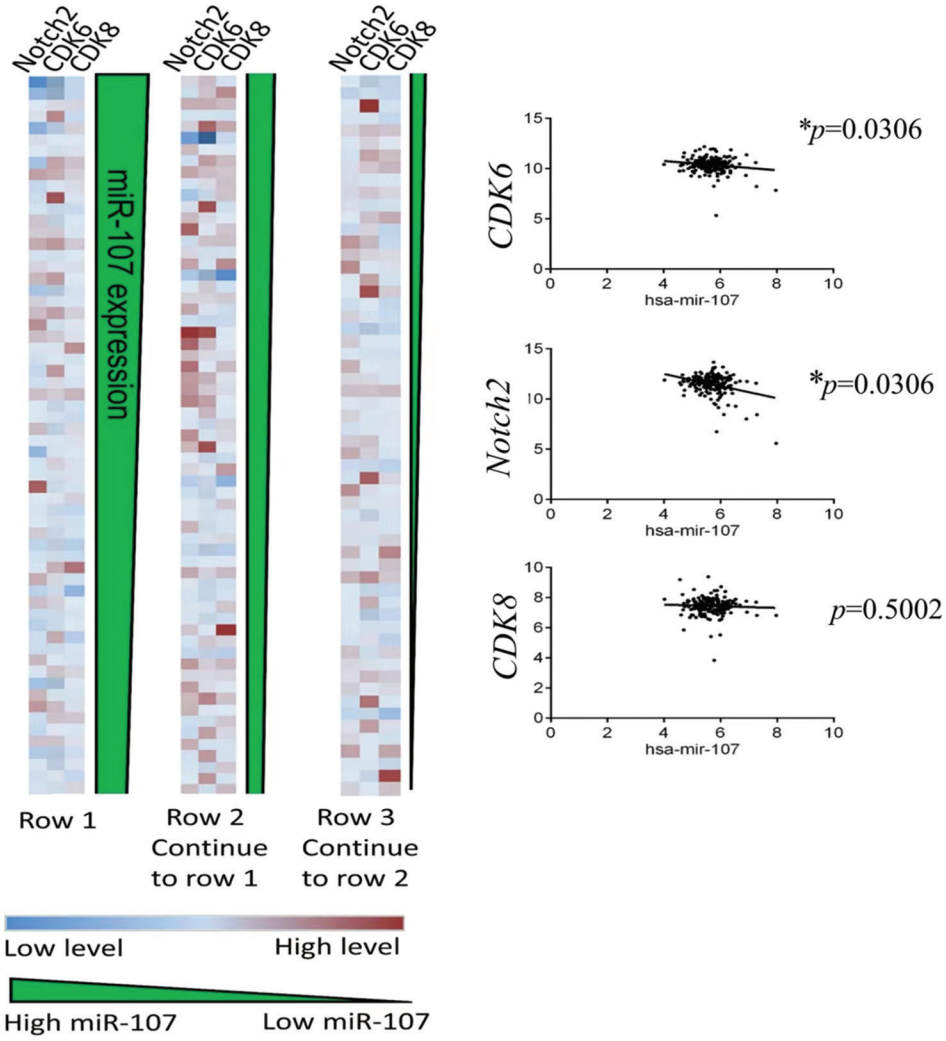


Figure 5. Relevant mRNA expression data that may be related to miR-107
Note: *$p<0.05$.

as well as reduce miR-21-induced 5-fluorouracil resistance in PC. Earlier research has linked miR-21's pro-resistance effects to reduced expression of tumor suppressor genes, such as *PTEN*, *PDCD4*, and *RECK*. However, findings from the current study indicate that miR-21 exerts no significant regulatory impact on *PTEN* and *RECK*.

Both PAPD5 and PDCD4 are involved in the degradation process of miR-21 through direct modification and indirect regulation, respectively. The adenylation of PAPD5 serves as a molecular switch for miR-21 degradation, and PDCD4, as a downstream target of miR-21, affects the homeostasis of miR-21 through a feedback mechanism via its expression level. This dual regulation forms a negative feedback loop: miR-21 promotes cell proliferation by inhibiting PDCD4, and PAPD5 limits the excessive accumulation of miR-21 by degrading it. In PC, the imbalance of this loop (such as reduced PAPD5 activity and excessive miR-21 expression) results in the continuous inhibition of PDCD4, thereby exacerbating the malignant phenotype. Targeting the PAPD5–PARN axis or the miR-21–PDCD4 axis may emerge as a novel therapeutic approach for PC management. For example, activating PAPD5 or inhibiting PARN with small molecules can enhance the degradation of miR-21, whereas inhibiting miR-21 with antisense oligonucleotides can restore the tumor-suppressive function of PDCD4.

Prior research has repeatedly shown that miR-107 functions as a tumor-suppressive factor in various types of cancer, with its downregulated expression widely documented across diverse malignancies.[47-60] Emerging evidence highlights the multifaceted molecular mechanisms that underpin miR-107's antitumor effects. In PC and

gastric cancer, miR-107 exerts an inhibitory effect on cell proliferation through targeting CDK6.[47,48] In breast cancer, its tumor-suppressive activity involves the regulation of CDK8.[49] In non-small cell lung cancer, miR-107 modulates both CDK6 and CDK8 to impede tumor progression.[50,51] In glioma, miR-107 exerts dual effects on cell cycle control and angiogenesis by targeting CDK6, vascular endothelial growth factor (VEGF), and Notch-2.[52-55] In colon cancer, its mechanisms of action include the inhibition of cyclin D1, dicer ribonuclease III, ribonuclease III drosha, nuclear factor kappa B subunit 1, hypoxia-inducible factor-1β, and VEGF, thereby regulating cell cycle progression and angiogenic signaling.[56,57] Additional pathways regulated by miR-107 include the ataxia telangiectasia and Rad3-related protein/checkpoint kinase 1 signaling cascade in cervical cancer,[58] granulin expression in prostate cancer,[59] and eukaryotic translation initiation factor 5 in renal clear cell carcinoma.[60] Collectively, these findings highlight that miR-107 acts as a multifunctional tumor suppressor, with its context-specific mechanisms encompassing cell cycle regulation, angiogenesis, and oncogenic signaling. Its dysregulation across multiple cancer types highlights potential therapeutic opportunities for miR-107-based interventions.

Epigenetic aberrations, including promoter methylation and histone modification, are prevalent across diverse cancer types.[61] Notably, the transcriptional silencing of tumor suppressor genes via promoter hypermethylation has been documented in virtually all malignant neoplasms.[62,63] In most cases, the reactivation of these genes through chromatin-modifying interventions leads to growth arrest in cancer cells, emphasizing the indispensable role of epigenetic silencing in oncogenesis.[64] Previous investigations have additionally revealed miR-107 promoter hypermethylation in pancreatic carcinoma cells, an epigenetic mark that is reversible by histone deacetylase inhibitors or DNA methyltransferase inhibitors. Furthermore, functional assays revealed that forced miR-107 expression in PC cell lines not only suppresses clonogenic growth *in vitro* but also reduces CDK6 protein abundance, thereby delineating a mechanistic axis linking miRNA epigenetic inactivation to cell cycle dysregulation.[48] A separate study has also shown that miR-107 overexpression induces G1/S phase arrest through p21 upregulation and suppresses proliferative signaling via transcriptional repression of Notch2 in PC cells.[22] In orthotopic mouse tumor models, the systemic delivery and sustained presence of miR-107-mimic molecules retarded tumor growth and metastasis. Conversely, low circulating levels of miR-107 showed a strong association with aggressive tumor phenotypes and unfavorable patient prognoses.

The present research suggests that miR-107 may exert tumor-suppressive effects by targeting Notch2 and CDK6. Notch2, CDK6, and miR-107 form a multi-level regulatory network in PC: Notch2 drives proliferation and metastasis by activating pro-cancer signaling pathways; CDK6 accelerates growth through cell cycle dysregulation; and miR-107 dynamically regulates tumor phenotypes by targeting key nodes such as Notch2 and CDK6. Future studies should further investigate the spatiotemporal expression patterns of the three proteins and their dependence on the tumor microenvironment, as well as explore the clinical transformation pathway of multitarget combination therapy.

Previous research has indicated that elevated miR-21 expression is closely linked to malignant characteristics of PC, such as clinical stage, lymph node metastasis, and vascular invasion.[38] Reduced miR-107 expression in PC patients is strongly associated with tumor size, lymph node metastasis, advanced disease stage, and shortened survival time, making it a potential indicator of poor prognosis.[22] In the initiation and progression of PC, miR-21 functions as a "driver" by means of high expression: It targets tumor suppressor genes (such as *PDCD4* and *PTEN*), activates oncogenic pathways (such as phosphatidylinositol 3-kinase/protein kinase B), and promotes the proliferation, invasion, and drug resistance of PC cells while inhibiting their apoptosis. MiR-107 relieves the inhibition of oncogenes (such as *CCNE1* and *CDK6*) through low expression, resulting in cell cycle disorders and enhanced invasiveness. Its deficiency acts as a "promoting factor" in the progression of PC. However, many of these results lack support from large-scale sample studies.

Through the mining and analysis of the TCGA database, it was found that low expression of miR-107 and high expression of miR-21 were each linked to unfavorable clinical outcomes in PC patients. The reduced expression of miR-107 was linked to advanced disease stages and lymph node metastasis. Notably, *NOTCH2*, and *CDK6* were recognized as potential target genes of miR-107. Meanwhile, miR-21 overexpression was linked to higher T stage, tumor stage, tumor grade, and recurrence rates. Mechanistically, PAPD5 may initiate the degradation of miR-21, whereas PDCD4, as a downstream target of miR-21, has its expression inhibited by miR-21 (Table 2). These findings indicate that restoring the expression of the tumor suppressor miR-107 or inhibiting miR-21 activity may be a novel therapeutic approach for PC. Previous studies have shown that the promoter of miR-107 undergoes methylation in PC cells, a process that can be reversed by chromatin-modifying agents.[48] In addition, PAPD5-mediated 3'-terminal adenylation of miR-21 promotes

Table 2. Comparison of the roles of miR-107 and miR-21 in pancreatic cancer

Characteristics	miR-21	miR-107
Expression in pancreatic cancer	High expression (vs. normal tissues/cells)	Low expression (vs. normal tissues/cells)
Clinical correlation	High expression is associated with high T stage, tumor stage, tumor grade, and recurrence	Low expression is associated with high stage and high lymphatic metastasis
Core role	Oncogenic microRNA	Tumor-suppressive microRNA
Key target genes	*PDCD4*	*CDK6* and *NOTCH2*
Clinical potential	Potential therapeutic target (inhibiting miR-21 can block tumor progression)	Potential therapeutic target (restoring miR-107 can inhibit tumors)

miR: microRNA

its degradation.[40] These mechanisms provide promising directions for the clinical application of miRNA-based therapies through nucleic acid medicine. The current research provides large-scale clinical data support for the clinical utility of miR-21 and miR-107 as therapeutic targets in PC patients.

The prognosis of PC is jointly regulated by gene mutations (such as *KRAS* and *SMAD4*), epigenetic modifications (such as miR-21 and DNA methylation), protein markers (such as CA19-9), clinicopathological features (such as TNM stage), and the immune microenvironment. A single factor is difficult to accurately predict the prognosis. Clinically, it is necessary to conduct a comprehensive assessment by combining multidimensional indicators (such as genetic testing + serum markers + pathological features). In recent years, in response to the rising incidence of cancer, personalized medicine has emerged. This notion is built on an in-depth grasp of the molecular mechanisms underlying disease pathogenesis, facilitating the use of targeted therapies intended to interrupt the key mechanisms of disease.[65] Further in-depth research on the molecular mechanisms of PC is a crucial link to its personalized diagnosis and treatment. This research is of great significance for elucidating the molecular mechanism of PC and advancing personalized medicine.

This research is constrained by its retrospective study design and reliance on TCGA data, which lack functional validation. Further studies in PC cell lines (e.g., MiaPaCa-2 and PANC-1) and patient-derived xenografts are needed to confirm the mechanistic insights. In addition, the complex crosstalk between miRNAs and other non-coding RNAs (e.g., long non-coding RNAs) was not explored, representing a critical future direction.

5. Conclusion

In the present study, a systematic analysis of the expression patterns of 14 miRNAs in 183 PC patients was performed using the TCGA database, focusing on their clinical relevance and molecular mechanisms. The research confirms that dysregulated expressions of miR-21 and miR-107 hold significant prognostic value in PC, shedding light on their potential roles as biomarkers and therapeutic targets. Mechanistically, the results unravel specific molecular pathways underlying their functions: miR-21's oncogenic activity is partially mediated by PAPD5-induced degradation, suppressing the expression of the tumor suppressor gene *PDCD4*. Conversely, miR-107 exerts its tumor-suppressive effects by targeting Notch2 and CDK6, key regulators of cell cycle progression and invasion. These insights deepen our understanding of the post-transcriptional regulatory networks driving PC malignancy.

In summary, this study provides large-scale theoretical support for the clinical treatment of PC using miR-21 and miR-107. Their well-defined molecular targets (e.g., PDCD4 for miR-21 and Notch2/CDK6 for miR-107) and regulatory pathways (e.g., PAPD5-mediated miR-21 degradation) offer promising avenues for therapeutic intervention, such as miR-21 inhibitors or miR-107 mimics, both of which could restore tumor-suppressive pathways or block oncogenic signaling. These miRNAs not only enhance our comprehension of PC pathogenesis but also hold significant potential for clinical translation—from improving risk stratification to enabling targeted miRNA-based therapies. With further validation, they may contribute to addressing the unmet clinical needs of PC patients, ultimately improving outcomes in this lethal disease.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Conceptualization: Junran Xie
Methodology: Yaping Zhang
Formal analysis: Dongju Xiao
Writing–original draft: Yaping Zhang
Writing–review & editing: Yaping Zhang, Dongju Xiao, Junran Xie

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

The data used in this study are publicly available from TCGA. Readers can access the data via the official database website (https://gdac.broadinstitute.org/).

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