doi: 10.53446/actamednicomedia.1843004

Acta Medica Nicomedia

Cilt: 9 (2026), 1-7 / Vol: 9 (2026), 1-7
https://dergipark.org.tr/tr/pub/actamednicomedia

Research Article | Araştırma Makalesi

EVALUATION OF THE EFFECTS OF miR-21-5p, miR-125b-5p, AND miR-196a-3p ON PANCREATIC CANCER CELL MIGRATION AND INVASION

miR-21-5p, miR-125b-5p, AND miR-196a'NIN PANKREAS KANSERİ HÜCRE MİGRASYONU VE İNVAZYONU ÜZERİNE ETKİLERİNİN ARAŞTIRILMASI

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ABSTRACT

Objective: Pancreatic cancer is one of the most aggressive malignancies and is characterized by early dissemination and poor prognosis. MicroRNAs (miRNAs) are important post-transcriptional regulators of gene expression and have been implicated in pancreatic cancer progression. In this study, we evaluated the functional effects of miR-21-5p, miR-125b-5p, and miR-196a-3p in human PANC-1 pancreatic cancer cells. These miRNAs were selected based on preliminary observations from previous analyses identifying them among the most upregulated candidates in pancreatic cancer–associated miRNA profiles.

Methods: Gain- and loss-of-function approaches were performed using miRNA mimics and inhibitors. Cell migration and invasion were assessed using wound healing and Matrigel transwell assays, respectively. Epithelial mesenchymal transition (EMT)-associated protein expression was analyzed by Western blotting at 24 and 48 hours following transfection.

Results: Kaplan–Meier survival analysis demonstrated that high expression of miR-21-5p and miR-196a was associated with reduced overall survival, whereas miR-125b-5p showed no significant prognostic association. Functional assays revealed that miR-125b-5p significantly modulated PANC-1 cell migration, while miR-21-5p exerted time-dependent effects on migratory capacity. In contrast, modulation of these miRNAs did not result in significant changes in invasive behavior. Analysis of EMT-associated markers showed limited alterations, with reduced N-cadherin expression observed following inhibition of miR-125b-5p and miR-196a-3p at early time points.

Conclusion: Overall, this study provides a general functional insight into miRNA-mediated regulation of pancreatic cancer cell motility. Further studies employing more complex in vitro systems and in vivo models are needed to fully elucidate the roles of these miRNAs in pancreatic cancer progression.

Keywords: Pancreatic cancer, microRNA, miRNA, migration, invasion

ÖZ

Amaç: Pankreas kanseri, erken metastaz ve kötü prognoz ile karakterize, son derece agresif bir kanser türüdür. MikroRNA'lar (miRNA'lar), gen ekspresyonunu post-transkripsiyonel düzeyde düzenleyen önemli moleküller olup pankreas kanseri progresyonunda rol oynadıkları gösterilmiştir. Bu çalışmada, miR-21-5p, miR-125b-5p ve miR-196a-3p'nin insan PANC-1 pankreas kanseri hücrelerindeki fonksiyonel etkileri değerlendirilmiştir. Bu miRNA'lar, pankreas kanseri ile ilişkili eksozomal miRNA profillemesi yaptığımız bir projede en fazla artış gösteren adaylar arasında yer aldığından, bu çalışmada incelenmek üzere doğrultusunda seçilmiştir.

Yöntem: Hedef miRNA'ların ekspresyonu miRNA mimik ve inhibitörleri kullanılarak artırılmış veya baskılanmıştır. Migrasyon ve invazyon analizleri için sırasıyla yara iyileşme ve Matrijel invazyon testleri gerçekleştirilmiştir. Epitelyal–mezenkimal dönüşüm (EMT) ile ilişkili protein ekspresyonları, miRNA'lar ile transfeksiyondan 24 ve 48 saat sonra Western blot yöntemiyle analiz edilmiştir.

Bulgular: Kaplan–Meier sağkalım analizleri, miR-21-5p ve miR-196a'nın yüksek ekspresyonunun azalmış genel sağkalım ile ilişkili olduğunu, miR-125b-5p'nin ise prognostik açıdan anlamlı bir ilişki göstermediğini ortaya koymuştur. Fonksiyonel analizler, miR-125b-5p'nin PANC-1 hücre migrasyonunu anlamlı düzeyde modüle ettiğini, miR-21-5p'nin ise hücre migrasyonu üzerinde zamana bağlı etkiler gösterdiğini ortaya koymuştur. Buna karşılık, incelenen miRNA'ların modülasyonu hücre invazyonunda anlamlı değişikliklere yol açmamıştır. EMT belirteçlerinin analizi, erken zaman noktalarında miR-125b-5p ve miR-196a-3p inhibisyonu sonrası N-kaderin ekspresyonunda azalma olduğunu göstermiştir.

Sonuç: Sonuç olarak, bu çalışma miRNA'ların pankreas kanseri hücre migrasyonunun düzenlenmesindeki rollerine ilişkin genel bir fonksiyonel bakış açısı sunmaktadır. Bu miRNA'ların pankreas kanseri progresyonundaki rollerinin tam olarak aydınlatılabilmesi için, daha kompleks in vitro sistemler ve in vivo modeller kullanılarak yapılacak ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Pankreas kanseri, mikroRNA, miRNA, migrasyon, invazyon

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Submitted/Başvuru: 16.12.2025 • **Accepted/Kabul:** 25.02.2026 • **Published Online/Online Yayın:** 10.03.2026

Introduction

Pancreatic cancer (PC) remains one of the most aggressive and lethal malignancies, with a five-year survival rate of around 10% and a median survival of approximately six months after diagnosis.[1] Due to the absence of specific clinical symptoms and reliable diagnostic biomarkers, most patients are diagnosed at advanced stages of the disease.[2]

The poor prognosis of PC is largely attributed to the highly invasive and migratory behavior of pancreatic cancer cells.[3] Recent studies have highlighted the critical role of microRNAs (miRNAs), small single-stranded non-coding RNAs that regulate gene expression at the post-transcriptional level, as key regulators of various cellular processes including, proliferation, differentiation, apoptosis, migration, and invasion.[4] In pancreatic cancer, miRNA expression profiles are frequently dysregulated, thereby contributing to tumor progression and aggressiveness.

Several miRNAs, including miR-21-5p and miR-196a, have been reported to be associated with pancreatic cancer progression. Specifically, miR-21-5p has been shown to promote tumor invasion and is linked to poor patient prognosis.[5,6] Similarly, miR-196a is upregulated in pancreatic cancer and has been associated with enhanced proliferative and migratory properties.[7,8] Although the functional role of miR-125b-5p in pancreatic cancer remains less clearly defined, accumulating evidence suggests that its expression is altered in pancreatic cancer and correlates with disease progression, indicating a potential role in tumor malignancy.[9,10]

The focus on these three miRNAs was further informed by preliminary data from our previous analyses[11] of pancreatic cancer–derived exosomal miRNA profiles, in which miR-21-5p, miR-125b-5p, and miR-196a-3p were among the most upregulated candidates. Based on these observations, these miRNAs were selected for functional investigation in the present study.

Therefore, in this study, we compared the functional effects of three miRNAs (miR-21-5p, miR-125b-5p, and miR-196a-3p) on the migratory, invasive, and epithelial mesenchymal transition (EMT)-associated behavior of human PANC-1 cells. Using gain- and loss-of-function approaches combined with wound-healing assays, transwell invasion assays, and EMT marker analysis, we aimed to investigate how modulation of these miRNAs influences tumor cell motility and molecular features associated with pancreatic cancer progression.

Methods

Cell Culture

Human pancreatic cancer PANC-1 cells were obtained from American Type Culture Collection (ATCC) and maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin–streptomycin. Cells were cultured at 37 °C in a humidified incubator with 5% CO_2 and routinely passaged at 70–80% confluence. Cells used in experiments were within passages 20-25 and were routinely tested for mycoplasma contamination.

Overexpression and Inhibition of Target microRNAs

To investigate the functional roles of the selected microRNAs (miR-21-5p, miR-125b-5p, and miR-196a-3p) in PANC-1 cells, their expression levels were either increased or suppressed. For this purpose, cells were seeded into 6- or 24-well plates, and on the following day, commercially available miRNA mimics or inhibitors* were complexed with HiPerfect transfection reagent in serum-free medium according to the manufacturer's instructions. The transfection complexes were added to the cells and incubated under serum-free conditions for 6 hours. Afterward, the medium was replaced with complete growth medium containing 10% fetal bovine serum (FBS), and cells were maintained under standard culture conditions for an additional 24 or 48 hours prior to downstream analyses.

Transfection efficiency was monitored using a fluorescently labeled control oligonucleotide (BLOCK-iT™ Fluorescent Oligo, Thermo Fisher Scientific), consistently yielding high transfection efficiency (>70%) in PANC-1 cells. All miRNA mimics and inhibitors were purchased from Thermo Fisher Scientific and are commercially validated reagents, with target specificity and functional efficacy documented by the manufacturer.

**miRNA inhibitor negative control (abm, MIH00000), miRNA mimic negative control (abm, MCH00000), miR-21-5p inhibitor (abm, MIH01562), miR-21-5p mimic (abm, MCH01562), miR-125-5p inhibitor (abm, MIH01158), miR-125-5p mimic (abm, MCH01158), miR-196-5p inhibitor (abm, MIH01468), miR-196-5p mimic (abm, MCH01468).*

Wound Healing Assay

The effects of miRNA overexpression or inhibition on PANC-1 cell migration were assessed using a wound-healing assay. PANC-1 cells were seeded into 24-well plates and transfected with the indicated miRNA mimics or inhibitors as described above. A scratch was then generated in each well using a sterile pipette tip, and images of the wound area were captured at 0, 24, and 48 hours. Wound closure was quantified by measuring the remaining wound area at each time point using ImageJ software, and cell migration was expressed as the percentage of wound closure relative to initial wound area.

Transwell Invasion Assay

Cell invasion was evaluated using Matrigel-coated transwell inserts. Following 48 hours of treatment with miRNA mimics or inhibitors, transfected PANC-1 cells, along with untreated control cells, were harvested, counted, and seeded into the upper chambers in serum-free medium (50,000 cells per insert). Complete growth medium containing 10% FBS was added in the lower chambers to serve as a chemoattractant. Cells were

allowed to invade for 24 hours, after which non-invading cells were removed from the upper surface of the membrane. Invaded cells on the lower surface were then fixed and stained with crystal violet. For each insert, three random fields were imaged, and the number of invaded cells was quantified using ImageJ software.

Western Blot Assay

To evaluate the effects of the selected miRNAs on protein expression, Western blot analysis was performed. PANC-1 cells were treated with miRNA mimics or inhibitors for 24 or 48 hours as described above, after which total protein lysates were prepared using RIPA lysis buffer. Equal amounts of protein were separated on 10% SDS–polyacrylamide gels and transferred onto PVDF membranes. The membranes were incubated with the appropriate primary antibodies followed by species-specific HRP-conjugated secondary antibodies. Protein bands were visualized using standard chemiluminescence-based detection methods.

Statistical Analyses

All statistical analyses were performed using GraphPad Prism version 6.0. Differences among groups were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test for multiple comparisons. A p-value of <0.05 was considered statistically significant. Data from all experiments, each performed in triplicate, are presented as mean ± standard deviation

Results

Survival analysis based on miR-21-5p, miR-125b-5p, and miR-196a expression levels in pancreatic cancer patients

To explore the clinical relevance of the selected miRNAs, survival analyses were performed using publicly available pancreatic cancer patient datasets (https://kmplot.com). Kaplan–Meier analyses revealed that high expression of miR-21-5p was significantly associated with reduced overall survival compared to low expression levels (HR=1.72, log-rank p=0.015; Figure 1A). Similarly, elevated miR-196a expression correlated with poorer overall survival (HR=1.7, log-rank p=0.011; Figure 1A). No significant association was observed between miR-125b-5p expression and overall survival (HR=0.84, log-rank p=0.48; Figure 1A). Despite the lack of a significant prognostic association, miR-125b-5p was included in experimental flow (Figure 1B) based on previous reports indicating its dysregulated expression in pancreatic cancer and suggesting a potential context-dependent role in tumor progression.

Modulation of miR-125b-5p Regulates PANC-1 Cell Migration

Wound-healing assays were performed to evaluate the impact of miRNA modulation on PANC-1 cell migration. Representative images acquired at 0, 24, and 48 hours following transfection with miRNA mimics or inhibitors are shown in Figure 2A and B. Overexpression of miR-125b-5p resulted in a significant increase in wound closure at both 24 and 48 hours, indicating a pronounced pro-migratory effect. In contrast, transfection with miR-21-5p or miR-196a-3p mimics did not lead to significant changes in migration compared to control cells.

Consistent with these findings, inhibition of miR-125b-5p led to a significant reduction in wound closure at both 24 and 48 hours. Inhibition of miR-21-5p resulted in a significant decrease in migratory capacity specifically at 48 hours, while no significant effect was observed at 24 hours. Inhibition of miR-196a-3p did not significantly affect cell migration at either time point (Figure 2B). Together, these results indicate that both miR-125b-5p and miR-21-5p contribute to the regulation of PANC-1 cell migration, with miR-125b-5p exerting an earlier and more consistent effect.

Modulation of Target miRNAs Does Not Significantly Alter PANC-1 Cell Invasion

The impact of miRNA overexpression or inhibition on the invasive capacity of PANC-1 cells was assessed using Matrigel transwell assay (Figure 3A). Overexpression of the examined miRNAs resulted only modest changes in invasion. miR-21-5p and miR-196a-3p mimics caused a slight decrease in the number of invaded cells. Conversely, miR-125b-5p overexpression resulted in a mild increase in invasion, but all these changes was statistically non-significant (Figure 3A).

Similarly, inhibition of the target miRNAs led to minor changes in invasive behavior. Suppression of miR-125b-5p was associated with a modest reduction in invasion, whereas inhibition of miR-21-5p or miR-196a-3p produced no appreciable effects (Figure 3A). Overall, these findings indicate that, unlike their effects on migration, modulation of the examined miRNAs does not substantially affect the invasive capacity of PANC-1 cells under the experimental conditions used.

miRNA Inhibition is Associated with Reduced N-cadherin Levels in PANC-1 Cells

To examine whether modulation of the selected miRNAs influences EMT-associated protein expression, western blot analyses were performed at 24 and 48 hours following transfection with miRNA mimics or inhibitors (Figure 3B). At 24 hours, N-cadherin levels were comparable between the miR-125b-5p mimic group and the mimic control, indicating no clear increase upon miR-125b-5p overexpression under these conditions. In contrast, inhibition of miR-125b-5p was associated with reduced N-cadherin expression compared to the inhibitor control. A similar reduction in N-cadherin was also observed following inhibition of miR-196a-3p. At 48 hours, N-cadherin expression appeared broadly similar across groups, with no consistent differences relative to the corresponding controls. Across the same conditions, E-cadherin, vimentin, and Snail did not show a consistent pattern of change in response to miRNA modulation.

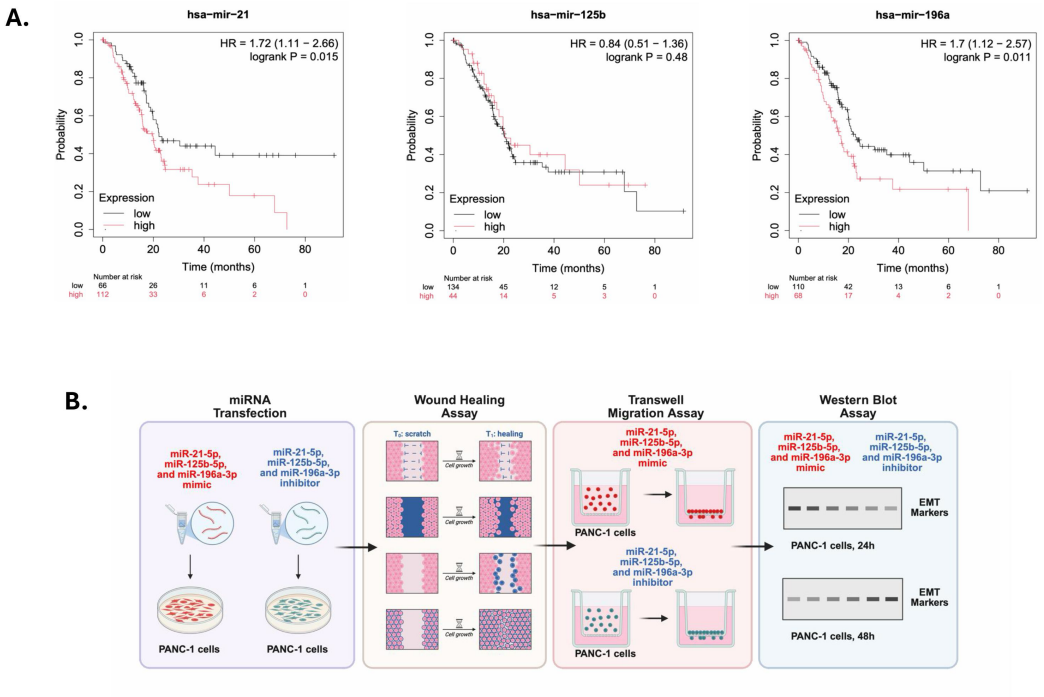

Figure 1. Clinical relevance of selected miRNAs and experimental workflow. (A) Kaplan–Meier survival analysis of pancreatic cancer patients stratified according to high and low expression levels of miR-21-5p, miR-125b-5p, and miR-196a. High expression of miR-21-5p and miR-196a was associated with reduced overall survival, whereas miR-125b-5p expression did not show a significant association with patient survival. Hazard ratios (HR) and log-rank p values are indicated. (B) Schematic overview of the experimental design. PANC-1 cells were transfected with miRNA mimics or inhibitors targeting miR-21-5p, miR-125b-5p, or miR-196a-3p, followed by functional analyses including wound healing assays, transwell migration/invasion assays, and western blot analysis of EMT-associated markers at 24 and 48 hours. Created with BioRender.com.

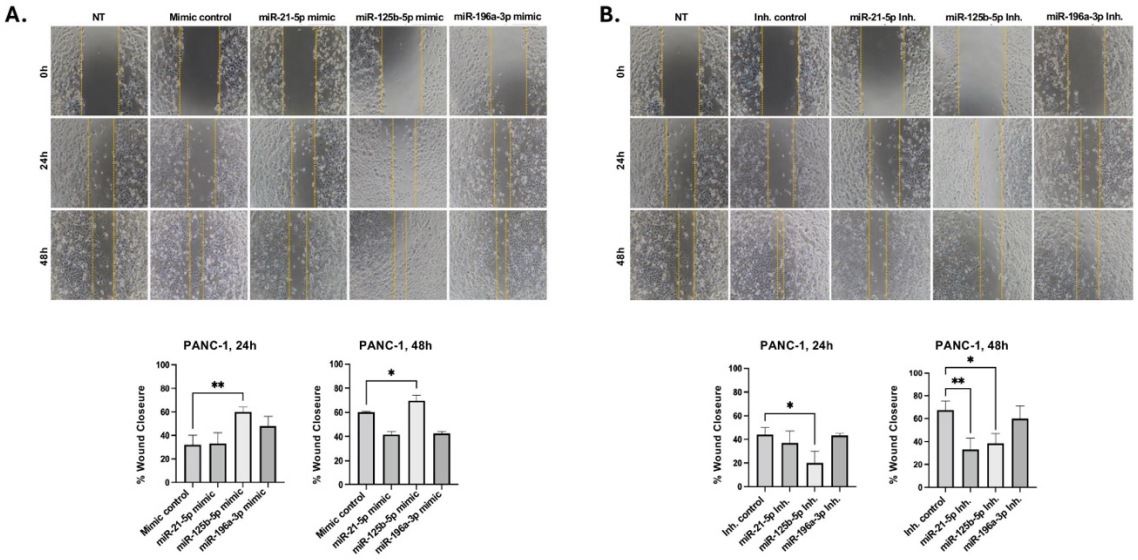

Figure 2. Effects of miRNA modulation on PANC-1 cell migration. (A) Representative phase-contrast images of wound healing assays showing migration of PANC-1 cells transfected with miRNA mimics (miR-21-5p, miR-125b-5p, or miR-196a-3p) or mimic control at 0, 24, and 48 hours. (B) Representative images of wound healing assays following transfection with miRNA inhibitors or inhibitor control at the indicated time points. Quantification of wound closure is shown below each panel and expressed as percentage wound closure relative to the initial wound area. Overexpression of miR-125b-5p significantly enhanced migration at both 24 and 48 hours, while miR-21-5p overexpression increased migration at 48 hours only. Inhibition of miR-125b-5p and miR-21-5p significantly reduced migratory capacity, with time-dependent effects. Data are presented as mean ± standard deviation. *p<0.05, **p<0.01.

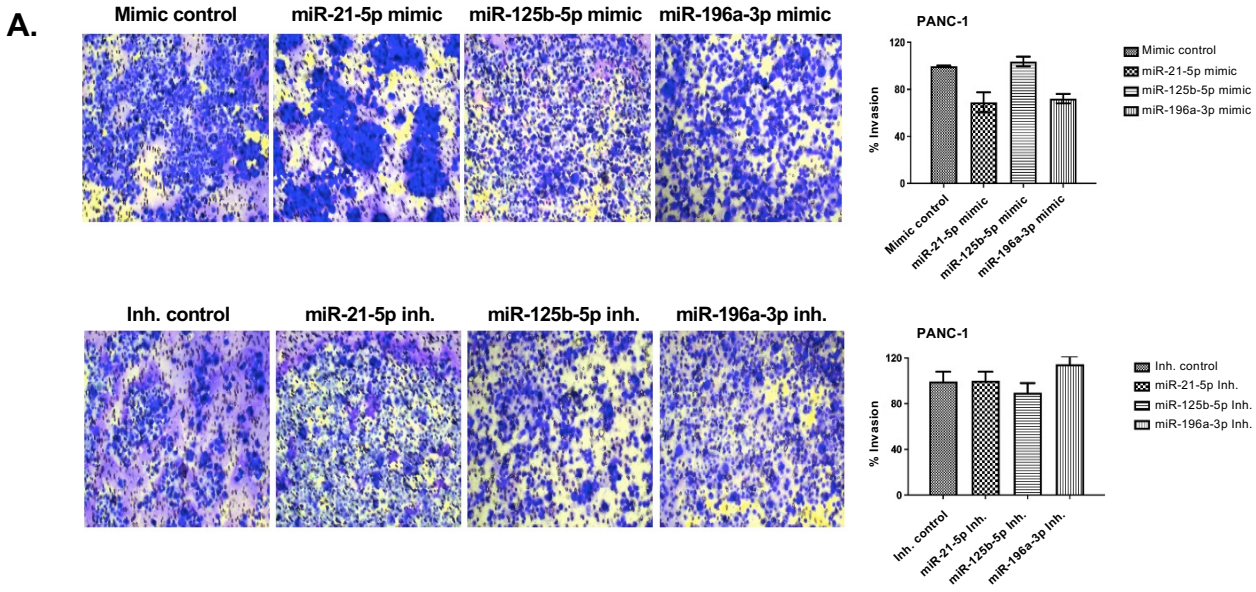

Figure 3. miRNA modulation does not significantly affect invasion but alters N-cadherin expression. (A) Representative images and quantification of Matrigel-coated transwell invasion assays performed on PANC-1 cells following transfection with miRNA mimics or inhibitors. Modulation of miR-21-5p, miR-125b-5p, or miR-196a-3p resulted in only modest, non-significant changes in invasive capacity compared to the corresponding mimic or inhibitor controls. (B) Western blot analysis of EMT-associated proteins (N-cadherin, E-cadherin, vimentin, and Snail) in PANC-1 cells at 24 and 48 hours following transfection with miRNA mimics or inhibitors. At 24 hours, inhibition of miR-125b-5p and miR-196a-3p was associated with reduced N-cadherin expression relative to inhibitor control, whereas miRNA overexpression did not induce clear changes compared to mimic control. No consistent alterations in EMT marker expression were observed at 48 hours. β-actin was used as a loading control.

Discussion

Pancreatic cancer remains one of the most lethal malignancies, with a five-year survival rate around 10% and a median post-diagnosis survival of only 4–6 months.[1] Its aggressive nature is closely linked to the characteristic tumor microenvironment, where cancer cells interact with activated fibroblasts, immune cells, adipocytes, endothelial structures, and a dense extracellular matrix. Dynamic interactions among these components drive multiple hallmarks of cancer progression.[11] Increasing evidence also indicates that miRNAs participate to these intercellular communicatio networks and modulate tumor aggressiveness.

Although numerous miRNAs have been implicated in pancreatic cancer biology, the specific roles of individual miRNAs in regulating tumor cell migration, invasion, and EMT-associated processes remain incompletely understood. In this study, we focused on three miRNAs—miR-21-5p, miR-125b-5p, and miR-196a-3p—that have previously reported to exhibit tumor-promoting properties in different cancer types.

For instance, miR-21 has been shown to enhance proliferation[13] correlate with poor overall survival[13] associate with metastasis and poorly differentiated tumors[15] and even serve as a potential early diagnostic marker when detected in exosomes.[16] Similarly, miR-125b is linked to increased migration and disease progression.[17] chemoresistance,[18] postoperative recurrence,[19] and enhanced metastatic potential through exosomal transfer.[20] miR-196a has also been implicated in PDAC aggressiveness and proposed as a prognostic biomarker associated with reduced survival.[21-24]

In this study, we modulated the expression of three miRNAs in PANC-1 cells to assess their functional impact on migration, invasion, and EMT-related protein expression. Among the examined miRNAs, miR-125b-5p exerted the most consistent impact on cell migration, with both overexpression and inhibition significantly altering migratory capacity in wound-healing assays. Importantly, the effects of miR-125b-5p on PANC-1 cell migration appear to be dependent on experimental timing and cellular context, suggesting a transient and condition-specific regulatory role rather than a stable or universal pro-migratory phenotype. Interestingly, this bidirectional effect was not mirrored in invasion assays, where neither mimic nor inhibitor treatments resulted in significant changes.

Likewise, EMT-associated protein expression showed only limited modulation. When evaluated relative to the appropriate mimic and inhibitor controls, miRNA overexpression did not result in a clear induction of classical EMT markers. Notably, inhibition of miR-125b-5p and miR-196a-3p was associated with reduced N-cadherin expression at 24 hours, whereas corresponding mimic treatments did not produce significant changes. At 48 hours, no consistent alterations in N-cadherin or other EMT-related proteins were observed across conditions. Notably, modulation of the examined miRNAs did not result in statistically significant or consistent effects on

invasive capacity or EMT-associated marker expression. These findings indicate that, under the experimental conditions used, the observed miRNA-mediated effects are limited and do not support the induction of a robust invasive or mesenchymal phenotype. These findings suggest that miRNA-dependent regulation of EMT-associated markers in PANC-1 cells is limited and highly dependent on experimental context and timing.

Together, these results indicate that the examined miRNAs—particularly miR-125b-5p—primarily modulate early migratory behavior rather than inducing stable EMT programs or invasive phenotypes in PANC-1 cells. This context-dependent activity is consistent with the broader concept that miRNA function in pancreatic cancer is strongly shaped by microenvironmental cues. Factors such as TGF-β signaling can reprogram miRNA expression by inducing pro-tumorigenic miRNAs, including miR-100 and miR-125b, while suppressing tumor-suppressive miRNAs such as let-7a.[25] In addition, long non-coding RNAs and extracellular vesicle components may further modulate miRNA availability, stability, and target interactions.[26]

Overall, our findings provide experimental evidence that selected miRNAs, particularly miR-125b-5p, modulate specific aspects of PANC-1 cell behavior, primarily by influencing migratory capacity. The observed effects were primarily restricted to migratory behavior, while effects on invasion and EMT-associated features remained limited and context-dependent under the conditions tested. However, the effects on invasion and EMT-associated marker expression were limited under the experimental conditions used. Importantly, this study represents a preliminary functional assessment conducted in a single pancreatic cancer cell line and under simplified *in vitro* conditions. The lack of a complex tumor microenvironment, as well as the absence of additional pancreatic cancer models, may restrict the generalizability of the observed effects. Therefore, further studies incorporating multiple cell lines, three-dimensional culture systems, and *in vivo* models will be necessary to better define the context-dependent roles of these miRNAs in pancreatic cancer progression.

Compliance with Ethical Standards

This study does not require approval from an ethics committee.

Conflict of Interest

The authors declare that they have no financial or non-financial conflict of interest related to this study or with any other author.

Author Contributions

All authors contributed equally to this work.

Financial Disclosure

The authors declare that they did not receive any financial support for this study.

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