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Review Article

Advances in MicroRNA-Based Approaches for Early Detection, Targeted Treatment, and Prognostic Prediction in Pancreatic Cancer

Running title: MicroRNA Advances in Pancreatic Cancer

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Abstract

Pancreatic cancer (PC) remains one of the most lethal malignancies worldwide, characterized by late diagnosis, rapid progression, and poor therapeutic response. Despite incremental advances, survival rates remain dismal, underscoring the urgent need for innovative diagnostic and therapeutic strategies. MicroRNAs (miRNAs) are small noncoding RNAs that regulate gene expression post-transcriptionally, and they have emerged as critical modulators of PC pathogenesis. They influence key oncogenic and tumor-suppressive pathways including KRAS, NF- κ B, and AKT/STAT3. Dysregulated miRNAs such as miR-21 and miR-155 drive tumor proliferation, epithelial–mesenchymal transition, and chemoresistance. Conversely, tumor-suppressive miRNAs like miR-34a inhibit these processes, highlighting their dual biological roles. Mounting evidence supports the value of circulating and extracellular vesicle-associated miRNAs in distinguishing PC from benign lesions. Integrated biomarker panels combining miRNAs with CA19-9 have achieved sensitivities and specificities exceeding 90%, outperforming conventional assays. Furthermore, machine learning models have enhanced the predictive power of miRNA signatures for personalized diagnosis. Therapeutically, miRNA modulation offers novel opportunities. Strategies include restoring tumor-suppressive miRNAs or inhibiting oncogenic ones using antagomirs and delivery systems like nanoparticles and viral vectors. Emerging approaches such as CRISPR-Cas9 gene editing further expand this potential. Preclinical studies demonstrate the efficacy of miRNA-based interventions in reducing tumor growth, though clinical translation is limited by delivery challenges. In conclusion, miRNAs represent a multifaceted frontier in PC research, serving as noninvasive biomarkers and promising therapeutic targets. Continued integration of molecular biology with computational innovations is poised to accelerate the implementation of miRNA-based precision oncology.

Keywords: MicroRNA, pancreatic cancer, early detection, prognosis, precision therapy, extracellular vesicles, CRISPR-Cas9, nanomedicine

List of abbreviations

PC: Pancreatic Cancer; PDAC: Pancreatic Ductal Adenocarcinoma; miRNA: MicroRNA; lncRNA: Long Non-Coding RNA; circRNA: Circular RNA; ceRNA: Competitive Endogenous RNA; EV: Extracellular Vesicle; EMT: Epithelial-Mesenchymal Transition; TAS: Tumor-Associated Stroma; IPMN: Intraductal Papillary Mucinous Neoplasm; pNET: Pancreatic Neuroendocrine Tumor; CA19-9: Carbohydrate Antigen 19-9; CRISPR-Cas9: Clustered Regularly Interspaced Short Palindromic Repeats–CRISPR-Associated Protein 9; AKT: Protein Kinase B; STAT3: Signal Transducer and Activator of Transcription 3; ERK/MAPK: Extracellular Signal-Regulated Kinase/Mitogen-Activated Protein Kinase; NF- κ B: Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; IKK1/IKK α : I κ B Kinase 1 (α subunit); PTEN: Phosphatase and Tensin Homolog; VEGF: Vascular Endothelial Growth Factor; SOCS1: Suppressor of Cytokine Signaling 1; Foxp3: Forkhead Box P3; MDM4: Mouse Double Minute 4; BA: Betulinic Acid; EGFR: Epidermal Growth Factor Receptor; TGF- β : Transforming Growth Factor Beta; HIF-1 α : Hypoxia-Inducible Factor 1 Alpha; MIIP: Migration and Invasion Inhibitory Protein; BTG2: B-Cell Translocation Gene 2; ADAM17: A Disintegrin and Metalloproteinase 17; GEM: Gemcitabine; cfDNA: Circulating Free DNA; ctDNA: Circulating Tumor DNA; OS: Overall Survival; AUC: Area Under the Curve; RBP: RNA-Binding Protein; LIN28 Homolog A/B; FOXA2: Forkhead Box A2; RUNX2: Runt-Related Transcription Factor 2; HIPK2: Homeodomain-Interacting Protein Kinase 2; PD-L1: Programmed Death Ligand 1; SERPINA4: Serpin Family A Member 4 (Kallistatin); USP22: Ubiquitin-Specific Protease 22; RRM2: Ribonucleotide Reductase Regulatory Subunit M2; ASO: Antisense Oligonucleotide; SP: Side Population; LV: Lentiviral Vector; PLGA: Poly(lactic-co-glycolic acid); CC9: Cell-Cycle Control Peptide 9; AI: Artificial Intelligence; GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; FDA: U.S. Food and Drug Administration; EMA: European Medicines Agency; MRX34: Liposomal Formulation of miR-34a Mimic; CAFs: Cancer-Associated Fibroblasts; MEK/ERK: Mitogen-Activated Protein Kinase Kinase/Extracellular Signal-Regulated Kinase; TUT4/7: Terminal Uridyl Transferase 4 and 7; DIS3L2: DIS3 Like 3'-5' Exoribonuclease 2; HMGAI1/2: High-Mobility Group AT-Hook 1/2; IGF1R: Insulin-Like Growth Factor 1 Receptor; IGF2BP2: Insulin-Like Growth Factor 2 mRNA-Binding Protein 2; VEGFA: Vascular Endothelial Growth Factor A; TCGA: The Cancer Genome Atlas; GEO: Gene Expression Omnibus; AI/ML: Artificial Intelligence/Machine Learning; RISC: RNA-Induced Silencing Complex; pri-miRNA: Primary microRNA; pre-miRNA: Precursor microRNA.

Introduction

Pancreatic cancer (PC) is recognized as one of the most lethal types of cancer worldwide.¹ According to the most recent American Cancer Society report (Cancer Statistics, 2025), PC remains one of the most lethal malignancies, with an estimated 67,440 new cases and 51,980 deaths projected in the United States in 2025, ranking as the third leading cause of cancer-related mortality after lung and colorectal cancer.² PC is associated with various risk factors, encompassing both environmental and genetic triggers. However, the relative contribution of some factors, such as obesity, remains debated, with cohort studies showing inconsistent associations depending on population and methodological design.³ MicroRNAs (miRNAs) are a class of small, non-coding RNA molecules that play a crucial role in the regulation of gene expression in a wide range of biological processes.^{4,5} miRNAs are pivotal in cancer, exerting either tumour-suppressive or oncogenic influences by modulating gene expression at the post-transcriptional level. Literature highlights the dysregulation of specific miRNAs, such as the upregulation of miR-155⁶ and miR-21,⁷ and the downregulation of miR-128⁸ and miR-29c,⁹ which influence critical signaling pathways, including ERK/MAPK, AKT/STAT3, and NF- κ B. In particular, miR-21's role appears multifaceted—it is implicated in proliferation, EMT, anti-apoptosis, and angiogenesis via targets like PTEN and VEGF, yet its expression and prognostic power vary across studies and patient cohorts, raising concerns about reproducibility and standardization in biomarker development.^{10,11} These miRNAs act as oncogenic or tumor-suppressive agents, affecting processes like apoptosis, proliferation, invasion, and metastasis.¹² Nevertheless, clinical translation remains hindered by limited validation in large, ethnically diverse cohorts and the inherent variability among study platforms and normalization protocols. Extracellular vesicles (EVs) are small, membrane-enclosed structures released by virtually all cell types.¹³ Extracellular vesicles are classified into several subtypes, including exosomes, microvesicles, and apoptotic bodies, each with unique biogenesis and cargo.¹⁴ Of these, exosomes, which are small vesicles (30-150 nm in diameter), are particularly noteworthy for their role in miRNA transmission.¹⁵ However, the practical implementation of EV-miRNA biomarkers is complicated by challenges in EV isolation and characterization, which can significantly affect detected miRNA profiles. Moreover, patient-to-patient heterogeneity in EV cargo raises concerns about the robustness of candidate biomarkers across clinical settings.^{16,17} Noninvasive prediction of outcomes is a critical objective in medicine, as it can facilitate early diagnosis, prognosis, and therapeutic decision-making. The use of miRNAs transported via EVs for this purpose is gaining increasing attention due to their potential as diagnostic and prognostic biomarkers. The analysis of miRNAs carried by EVs in body fluids such as blood, urine, and saliva can provide valuable insights into cancer development and progression. Altered miRNA profiles within EVs have been linked to specific cancer types, making them potential noninvasive biomarkers for early detection and prognosis.¹⁸ Tumour-associated stroma (TAS) is the supportive, non-cancerous tissue that surrounds and interacts with a tumor, playing a significant role in tumor development and progression.¹⁹ TAS has a significant effect on PDAC progression.²⁰ Crucially, emerging evidence shows that the desmoplastic stroma can play a dual role—while often promoting chemoresistance and immune suppression, certain stromal subtypes or contexts have been found to restrain tumor growth, indicating a context-dependent complexity that must be accounted for in therapeutic targeting.²¹ Despite modest increments in detection and treatment, PC survival remains critically low, with only about 12% of patients surviving five years after diagnosis and improvements have been minimal over recent decades.²² Furthermore, CA199, the most widely used serum biomarker, has well-recognized limitations; its sensitivity and specificity are insufficient for early-stage detection, and it fails entirely in Lewis antigen-negative individuals.²³ Recent meta-analytic data show that miRNA-only biomarker panels achieve high diagnostic accuracy with pooled sensitivity of 88%, specificity of 91% and an AUC of 0.95.²⁴ Accuracy improves further when miRNAs are combined with CA19-9. Exosome-derived biomarkers, especially surface proteoglycans, demonstrated remarkable performance with sensitivity of 96% and specificity of 90%.²⁵ By contrast, combining CA19-9 with circulating miRNAs has shown significantly improved diagnostic accuracy. In recent years, particularly after 2022, the field has moved toward translational applications. Artificial intelligence and machine-learning-based approaches have enabled the construction of multi-miRNA biomarker panels, which show superior diagnostic performance compared to single miRNAs, especially when combined with established markers like CA19-9.²⁶ In parallel, translational momentum is building through ongoing prospective clinical studies, such as the PANXEON trial, which aims to validate an exosome-based miRNA signature for noninvasive early detection of PDAC.²⁷ In light of this challenging outlook, there

has been a growing focus on elucidating the genetic and epigenetic characteristics of PC and gaining insights into the molecular mechanisms that drive its onset, rapid advancement, and resistance to treatment. MiRNAs have risen to prominence as pivotal molecules governing the pathobiology of PC. This review aims to consolidate the current understanding of microRNAs in PC, highlighting their multifaceted roles as potential biomarkers for early detection, facilitators of precision targeting, and providers of valuable prognostic insights. By comprehensively examining the existing literature, we intend to shed light on the promise and challenges of harnessing microRNAs in the fight against PC.

microRNA biogenesis and activity

miRNAs are non-coding small RNA molecules crucial for gene regulation. Their formation involves a complex, tightly regulated process from nuclear transcription to functional miRNA maturation, highlighting their importance in biological processes and diseases.^{28,29} miRNA biogenesis begins in the nucleus, where RNA polymerase II transcribes miRNA genes into primary miRNA transcripts (pri-miRNAs) containing hairpin structures. The Microprocessor complex, composed of Drosha (an RNase III enzyme) and DGCR8, processes pri-miRNAs into precursor miRNAs (pre-miRNAs) about 70 nucleotides long. Exportin-5, along with Ran-GTP, then transports the pre-miRNAs to the cytoplasm.³⁰ In the cytoplasm, Dicer, an RNase III enzyme, processes pre-miRNAs by cleaving the loop, resulting in a double-stranded RNA of 20-25 base pairs. This duplex contains the guide strand (mature miRNA) and the passenger strand. The guide strand is incorporated into the RNA-induced silencing complex (RISC), which includes Argonaute proteins, essential for miRNA function. The passenger strand is usually degraded. The mature miRNA in RISC directs the complex to its target mRNA, leading to gene silencing.³¹ miRNAs bind to target mRNAs, typically in the 3' UTR, through partial sequence complementarity. This binding can lead to translational repression or degradation of the mRNA, resulting in reduced expression of the target gene.³² (Fig 1).

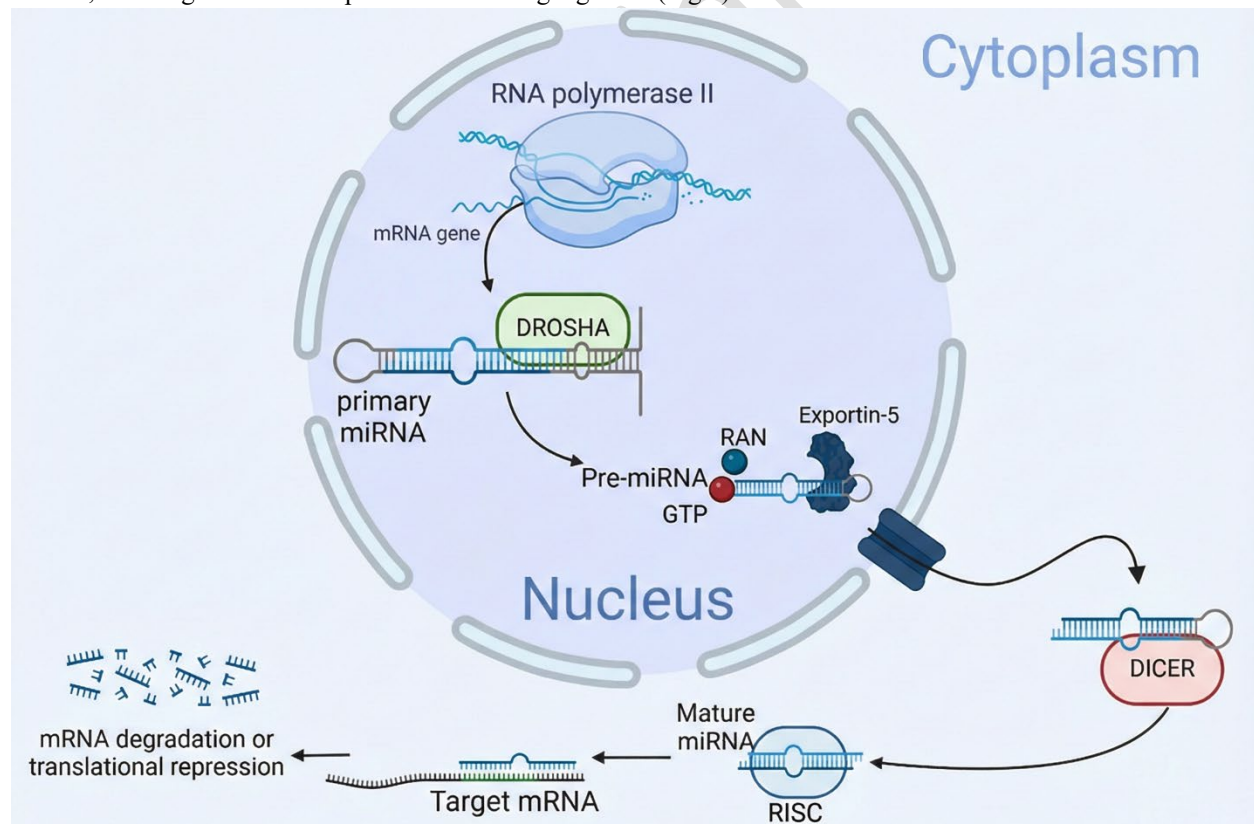


Fig. 1 Schematic representation of the microRNA (miRNA) biogenesis and gene silencing pathway. Primary miRNAs (pri-miRNAs) are transcribed in the nucleus by RNA polymerase II from miRNA genes and form hairpin structures. The pri-miRNAs are cleaved by the microprocessor complex containing the RNase III enzyme DROSHA, generating precursor miRNAs (pre-miRNAs). Pre-miRNAs are then exported from the nucleus to the cytoplasm by Exportin-5

in a Ran-GTP-dependent manner. In the cytoplasm, the RNase III enzyme DICER further processes pre-miRNAs into ~22 nucleotide-long double-stranded mature miRNAs. One strand of the mature miRNA is incorporated into the RNA-induced silencing complex (RISC), which guides the complex to complementary sequences within target mRNAs. Binding of the miRNA-RISC complex to target mRNAs leads to post-transcriptional gene regulation through mRNA degradation or translational repression.

The role of miRNAs in pancreatic cancer

The role of miRNAs in the pathogenesis of pancreatic cancer

The downregulation of miR-128, which promotes apoptosis, is closely associated with the protein MDM4 (MDMX), a key regulator of the tumor suppressor p53. MDM4 binds to p53, inhibiting its activity and preventing it from carrying out tumor-suppressive functions, such as regulating the cell cycle and inducing apoptosis.⁸ The balance of p53 activity is crucial for proper cellular responses to stress and damage. Dysregulation or overexpression of MDM4 can lead to p53 inactivation, contributing to the development and progression of PC.^{33,34} The upregulation of miR-155, leading to structural and metabolic changes in pancreatic cells, is mediated through the SOCS1 and Foxp3 pathway, with reduced SOCS1 and Foxp3 levels associated with the severity of cachexia in PC patients.⁶ The protein family known as Suppressors of Cytokine Signaling (SOCS1) is characterized as direct controllers of the JAK/STAT signaling pathway in cancer,³⁵ while Foxp3 is crucial for the development and function of regulatory T cells, preserving immune tolerance. In recent findings, elevated expression levels of Foxp3, have shown a notable association with tumor invasion in PDAC.^{36,37} This intricate pathway highlights the regulatory connection between miR-155, SOCS1, and Foxp3, unveiling the molecular mechanisms underlying structural and metabolic alterations in pancreatic cells.⁶ Within the realm of PC, the downregulation of miR-29c assumes a pivotal role, as it directly influences essential signaling pathways. Specifically, miR-29c plays a central role in modulating the ERK/MAPK pathway, a signaling cascade that holds profound relevance for PC progression.⁹ The ERK/MAPK pathway plays a key role in transducing extracellular signals and regulating essential cellular processes such as proliferation, differentiation, and survival. In PC, dysregulated activation of this pathway is often linked to uncontrolled cell growth and the aggressive behavior of cancer cells.³⁸ In PC, the critical role of I κ B kinase complex 1 (IKK1), also known as IKK α , emerges in regulating the NF- κ B signaling pathway, which is intricately linked to the initiation and advancement of this malignancy.³⁹ The majority of PDAC patients manifest constitutive activation of NF- κ B, and this activation is associated with a mutation in the KRAS gene, a connection facilitated through the action of IKK1.⁴⁰ Furthermore, the upregulation of miR-31-5p and miR-1290 contributes to the promotion of cell proliferation, invasion, and migration, with these effects being significantly influenced by the presence and activity of IKK1.⁴¹ The AKT/STAT3 axis is crucial in pancreatic cancer (PC), driving disease progression and treatment resistance. Activation of AKT and STAT3 promotes cell survival, proliferation, invasion, metastasis, and chemoresistance, while also fostering an inflammatory microenvironment and immune evasion, contributing to the cancer's aggressiveness.⁴² Targeting the AKT/STAT3 pathway offers potential for more effective PC therapies. In a study, Betulinic acid (BA) was used to suppress miR-365, resulting in reduced cell proliferation and invasion, along with increased apoptosis. These effects are closely linked to the AKT/STAT3 axis.⁴³ ADAM17 plays a crucial role in PC by promoting tumor growth and progression, mainly through the activation of EGFR/MEK signaling and the modulation of immune cell populations within the tumor microenvironment.⁴⁴ Downregulation of miR-4299d inhibits cell proliferation, invasion, and promotes apoptosis in PC, while reducing tumor growth, mainly through ADAM17's role in regulating immune escape.⁴⁵ EMT is crucial in PC pathogenesis, driving the transition of epithelial cells to a mesenchymal phenotype, which is linked to increased tumor aggressiveness, invasiveness, and metastasis.⁴⁶ miR-492 plays a key role in EMT by upregulating processes like cell proliferation, migration, and invasion. It targets genes such as NR2C1, NDUFA12, and TMCC3, and activates the TGF- β /Smad3 pathway, promoting EMT in PC.⁴⁷ Also it was shown that miR-561-5p, when upregulated, is associated with the promotion of cell proliferation, migration, invasion, EMT, and cell growth.⁴⁸ Migration and Invasion Inhibitory Protein (MIIP) is a protein that plays a role in regulating cell migration and invasion.⁴⁹ HIF-1 α is a transcription factor that responds to hypoxia by regulating genes involved in cellular adaptation. miR-646 upregulation promotes proliferation and invasion, involving MIIP/HIF-1 α in these processes.⁵⁰ A study by Mortoglou and colleagues explored the role of miRNAs in EMT. They found that knocking out miR-21 in PDAC cells reversed EMT, resulting in decreased cell proliferation and invasion⁷ (Table 1).

Role of miRNAs in Differentiating Pancreatic Neoplasms

Pancreatic neoplasms, including PDAC, Intraductal papillary mucinous neoplasms (IPMNs), and pancreatic neuroendocrine tumors (pNETs), present diagnostic challenges due to overlapping clinical and imaging features. miRNAs have emerged as potential biomarkers capable of distinguishing these entities, thereby aiding in accurate diagnosis and personalized treatment strategies. Studies have identified distinct miRNA expression profiles between PDAC and IPMNs. In a study by Fernandez-Castañer and colleagues, they investigated the role of miRNAs in the development and progression of IPMN into PDAC by identifying miRNA-mRNA pairs associated with cell structure, actin cytoskeleton, and metabolism, with miR-181a emerging as a key regulator. The findings suggest that miRNA alterations play a role in the structural and metabolic changes seen in both IPMN and PDAC.⁶⁶ miR-21 and miR-155 are significantly upregulated in PDAC compared to IPMNs, correlating with tumor aggressiveness and invasion potential. Additionally, miR-181a has been implicated in structural and metabolic changes during IPMN progression, serving as a marker to differentiate low-risk IPMNs from those transitioning to PDAC.⁹⁶ MiR-483-3p and miR-21 have been found to be significantly higher in PDAC patients compared to healthy controls and IPMN patients, suggesting their potential as biomarkers for distinguishing PDAC from other pancreatic lesions.⁹⁷ The integration of miRNA profiling into clinical practice holds promise for non-invasive diagnostic strategies. Serum MAPK-associated miRNAs, for example, have been identified as novel noninvasive biomarkers for differentiating between PDAC, IPMN, and autoimmune pancreatitis (AIP). Such biomarkers can improve specificity and reduce misdiagnosis in clinical practice.⁹⁸

Targeting miRNAs by other non-coding RNAs play an important role in the pathogenesis of pancreatic cancer

Competitive endogenous RNAs (ceRNAs) are pivotal players in gene regulation, acting as molecular sponges that bind miRNAs to modulate their availability for targeting mRNAs. This mechanism involves a complex network of non-coding RNAs, including lncRNAs, circRNAs, and even protein-coding mRNAs, which compete for shared miRNAs to influence gene expression. CircRNAs can sponge miRNAs and alter their target gene expression through a mechanism known as ceRNA regulation.⁹⁹ A bioinformatics study on gemcitabine resistance in PC cells identified suppressed hsa_circ_0007401, increased hsa-miR-6509-3p, and downregulated FLI1 mRNA through negative regulation in the ceRNA network. FLI1 expression was significantly reduced in gemcitabine-resistant pancreatic cancer patients.⁵¹

A similar study on gemcitabine resistance in PC cells found that circACTR2 reversed resistance by inhibiting the PI3K/AKT pathway. It acted as a sponge for miR-221-3p, increasing PTEN expression.⁷⁶ SLC38A2, a glutamine transporter, has been recognized for their significant implications in cancer. Moreover, separate investigations have underscored the pivotal role of SLC38A2 in the context of PC.¹⁰⁰ miR-21-5p contributes to the proliferation, invasion, and migration of PC cells. Suppressing circRNA, circ_001859, targets miR-21-5p, effectively inhibiting EMT, proliferation, and invasion while increasing SLC38A2 levels.⁷⁵ The circRNA hsa_circ_0006215, which is found to be upregulated in PC, has been shown to elevate the levels of miR-378a-3p. Consequently, this increase in miR-378a-3p leads to an upregulation of SERPINA4.⁸⁵ Notably, SERPINA4 is recognized as a prognostic factor in cancer, suggesting that its expression level may have clinical significance in predicting the disease's outcome or progression.^{101,102} Hsa_circ_0046523, overexpressed in PC, promotes an immunosuppressive microenvironment by upregulating PD-L1 via miR-148a-3p, indicating potential therapeutic targets for modifying the immune microenvironment in PC.⁶³

Emerging research highlights the role of lncRNAs and their sponging activity in PC pathogenesis. Once regarded as “genomic dark matter,” lncRNAs are now recognized as key players in post-transcriptional gene regulation.¹⁰³ By acting as molecular sponges for microRNAs, lncRNAs can influence the expression of key genes and signal transduction pathways, thereby impacting the development and progression of PC.¹⁰⁴ Studies show that lncRNA XIST promotes PC cell proliferation by interacting with miR-137 and reducing its expression. XIST also acts as a ceRNA to upregulate Notch1 expression. A negative correlation exists between miR-137 and XIST/Notch1, while a positive correlation is observed between Notch1 and XIST in PC tissues.⁵⁷ Another study on XIST in PC shows its high expression in PC tissues and the downregulation of miR-141-3p. Silencing XIST inhibits PC cell proliferation, migration, and invasion, with miR-141-3p acting as a mitigating factor. The study demonstrates a direct interaction between miR-141-3p and XIST, and miR-141-3p negatively regulates TGF- β 2 expression.⁶⁰ XIST promotes PC cell proliferation, migration, invasion, and inhibits apoptosis. miR-34a-5p, downregulated in PC tissues, targets XIST and

counteracts its malignant effects, highlighting the therapeutic potential of targeting both XIST and miR-34a-5p in PC.⁸⁴ miR-141-3p, targeted by lncRNAs CTBP1 AS2 and TP73-AS1, significantly impacts PC progression and migration. These lncRNAs enhance the expression of USP22 and BDH2, driving PC carcinogenesis.^{59,61} Yuan and colleagues found that LINC00152 is upregulated and miR-150 is downregulated in PC cells. Elevated LINC00152 promotes cell proliferation, migration, and invasion by directly targeting miR-150. Inhibiting miR-150 counteracts the effects of LINC00152 knockdown on these processes.⁶⁴ lncRNA ABHD11-AS1 is another non-coding RNA which can sponge miR-1231 and its downstream target, cyclin E1.⁵⁴ HNF1A plays a pivotal role in inhibiting the development of chemotherapy resistance and acts as a tumor suppressor in PC.^{105,106} It has been shown that LINC00673 can suppress invasion and migration in pancreatic cancer by modulating the miR-504/HNF1A pathway. Additionally, miR-504 has been identified as a target of LINC00673 in pancreatic cancer.⁸⁷ Overexpression of LINC02532 and underexpression of miR-145 are associated with increased cancer stem cell aggressiveness while downregulating LINC02532 and upregulating miR-145 inhibits proliferation, migration, and invasion and induces apoptosis.⁵⁵ The increased expression of the lncRNA AFAP1-AS1 in PC contributes to tumor advancement by functioning as a ceRNA that sequesters miR-133a, thereby activating IGF1R and the MEK/ERK pathway. This suggests that AFAP1-AS1 has promise as both a diagnostic marker and a therapeutic focus for PC.⁵⁶ In PC, the upregulated long non-coding RNA SNHG14 accelerates tumor progression by acting as a ceRNA for miR-613, modulating Annexin A2 expression.⁹² Silencing LINC00491 inhibited PC cell migration, invasion, proliferation, and tumor growth. LINC00491 interacts with miR-188-5p, which targets ZFP91. Inhibiting miR-188-5p restored LINC00491 effects, suggesting that LINC00491 promotes PC progression via the miR-188-5p/ZFP91 axis.⁷⁰ lncRNA GAS5 expression is decreased, while miR-181c-5p is increased in PC cells. GAS5 overexpression reduces cell viability and negatively regulates miR-181c-5p. MiR-181c-5p promotes chemoresistance by inactivating the Hippo pathway, and GAS5 overexpression inhibits tumor growth in a PC mouse model.⁶⁸ lncRNA CASC2 was identified as a direct regulator of miR-21, and overexpression of miR-21 reversed the antimetastatic effects of CASC2. Furthermore, downregulation of PTEN also reversed the antimetastatic effects of CASC2.⁷³ SLCO4A1-AS1 is upregulated in PC, and its knockdown inhibits cell proliferation, migration, invasion, and induces apoptosis. It modulates KIF21B expression by binding to miR-4673, functioning as an oncogene that exacerbates malignancy by upregulating KIF21B through miR-4673 sponging.⁷⁴ lncRNA DGCR5 is downregulated in PC tissues and cells, acting as a decoy for miR-27a-3p, which negatively regulates BNIP3. DGCR5 influences the BNIP3 and p38 MAPK pathways through miR-27a-3p, promoting apoptosis and attenuating PC development. This suggests DGCR5 plays a tumor-suppressive role by regulating the miR-27a-3p/BNIP3 pathway and p38 MAPK signaling.⁷⁸ Angiogenesis, characterized by the formation of new blood vessels, is a fundamental process in cancer, including pancreatic cancer. This hallmark is often associated with the development of poor vascular networks and dense stromal tissue in tumors.¹⁰⁷ lnc00511 is upregulated in PDAC tissues and cell lines, correlating with poor prognosis. Depletion of lnc00511 in PDAC cells inhibits proliferation, migration, invasion, and endothelial tube formation. Mechanistically, lnc00511 upregulates VEGFA by acting as a ceRNA for hsa-miR-29b-3p.⁷⁹ LINC00994 negatively correlates with miR-765-3p expression.⁸⁰ Runt-related transcription factor 2 (RUNX2), associated with aggressive cancer behavior,¹⁰⁸ is identified as a novel miR-765-3p target and is upregulated in PC. LINC00994 and RUNX2 reciprocally regulate each other's expression. They both compete to bind miR-765-3p. When miR-765-3p is antagonized, LINC00994-silenced cells regain aggressive behavior with RUNX2 re-expression.⁸⁰ lncRNA BC037916 correlates with clinical stage, primary tumor size, and regional lymph node invasion, making it an independent prognostic marker for PC. Inhibition of BC037916 suppresses the JAK2/STAT3 and TGF- β pathways. It also positively regulates Twist expression via miR-3145-3p, enhancing proliferation, invasion, and reducing apoptosis.⁸¹ In a study by Zhao and colleagues it was noted that PVT1 acts as an intrinsic "sponge," competing with miR-448 to regulate the miRNA target SERBP1, ultimately enhancing the proliferation and migration of PC cells.⁸⁶ lncRNA SLCO4A1-AS1 is upregulated in PC, and its inhibition reduces cell proliferation, migration, invasion, and promotes apoptosis. SLCO4A1-AS1 regulates KIF21B expression by binding to miR-4673. It acts as an oncogene in PC, enhancing aggressiveness by increasing KIF21B levels through miR-4673 sequestration.⁷⁴ Elevated LINC01128 expression in pancreatic cancer correlates with poor patient prognosis. Silencing LINC01128 inhibits tumor progression, including proliferation, migration, and invasion, both in vitro and in vivo. LINC01128 acts as a sponge for miR-561-5p, with its downstream target being lactate dehydrogenase A (LDHA). MiR-561-5p is reduced in pancreatic cancer, showing a

negative correlation with LINC01128.⁹⁰ A summary of miRNAs involved in PC pathogenesis and their targets are shown in Table 1.

Table 1 The role of miRNAs in the pathogenesis of pancreatic cancer

miRNA(biomarker)	Alteration	Cellular function	Target	References
hsa-miR-6509-3p	Upregulation	Inhibition of gemcitabine resistance	FLI1	51
miR-491-3p	Downregulation	Promotion of cell proliferation, invasion, and migration ability	LncRNA LINP1	52
miR-107	Downregulation	Promotion of cell migration and invasion in vitro	FEZF1-AS1/miR-107/ZNF312B axis	53
miR-1231	Downregulation	Promotion of proliferation, migration and invasion and inhibits apoptosis	cyclin E1	54
miR-128	Downregulation	Promotion of apoptosis	MDM4	8
miR-145	Upregulation	Promotion of migration, invasion and apoptosis of pancreatic cancer stem cells.	LINC02532	55
miR-133a	Downregulation	Promotion of growth, migration and invasion	MIAT, IGF1R repression	56
miR-137	Downregulation	Promotion of cell proliferation	Long non-coding RNA XIST and Notch1 pathway	57
miR-138-5p	Upregulation	Promotion of growth and migration	FOXK1	58
miR-141-3p	Upregulation	Promotion of cell proliferation, migration and invasion and inhibition of cell apoptosis	CTBP1-AS2/ USP22	59
miR-141-3p	Downregulation	Inhibition of cell proliferation, migration, and invasion	TGF- β 2	60
miR-141-3p	Downregulation	Promotion of cell migration and invasion	BDH2	61
miR-143-5p	Downregulation	Promotion of cell apoptosis and autophagy	AGR2	61
miR-143	Downregulation	Suppressed autophagy and the metastasis of pancreatic cancer	HIF-1 α	62

miRNA(biomarker)	Alteration	Cellular function	Target	References
miR-148a-3p	Downregulation	Suppressed tumor growth	PD-L1	63
miR-150	Downregulation	Promotion of cell proliferation, migration and invasion	LINC00152	64
miR-155	Upregulation	Structural and metabolic changes in pancreatic cells	SOCS1 and Foxp3	6
miR-155	Upregulation	Promotion of lymph node metastasis in PDAC	NiCl ₂	65
miR-181a	Downregulation	Promotion of cachexis	Actin Cytoskeleton Related Pathways-EPB41L4B and SEL1L	66
miR-181b	Upregulation	Promotion of cell viability, migration and invasion	ZEB2	67
miR-181c-5p	Upregulation	Promotion of GAS5 regulated chemoresistance and Hippo pathway	Hippo pathway/GAS5	68
miR-185-5p	Upregulation	Decreased proliferation, migration, and invasion Promotion of growth	Capan-2, AsPC-1, PANC1, BxPC-3, HPDE	69
miR-188-5p	Upregulation	Promotion of migration, invasion and proliferation and tumor growth	ZFP91/LINC00491	70
miR-199b-5p	Upregulation	Promotion of tumor growth and metastasis of PC cells	LINC01133	71
miR-200c-3p	Downregulation	Promotion of cell proliferation and metastasis	MALAT-1	72
miR-21	Downregulation	Inhibition of cell migration and invasion	PTEN	73
miR-21	-	Promotion of metastasis	EMT/ Wnt-11	74

miRNA(biomarker)	Alteration	Cellular function	Target	References
miR-21-5p	Upregulation	Promotion of cell proliferation, migration, invasion, and EMT	SLC38A2	75
miR-221	Upregulation	Promotion of migration, metastasis, and uncontrolled proliferation of PDAC cells	NiCl ₂	65
miR-221-3p	Upregulation	Regulation of PI3K/AKT signaling pathway	PTEN	76
miR-223-5p	-	Promotion of tumor growth and metastasis of PC cells	LINC01705	77
miR-27a-3p	Downregulation	Promotion of cell apoptosis	BNIP3	78
miR-29b-3p	Upregulation	Promotion of proliferation, migration, invasion and endothelial tube formation	linc00511 could up-regulate VEGFA via its competing endogenous RNA (ceRNA) activity on hsa-miR-29b-3p	79
miR-29c	Downregulation	Inhibition of the ERK/MAPK pathway	MAPK1	9
miR-302a-3p	Downregulation	Inhibition of cell proliferation and migration	RELA and NEAT1	80
miR-3064	Upregulation	Promotion of cell proliferation, invasion, clone formation, and sphere formation	PIP4K2B	
miR-31	Downregulation	Promotion of apoptosis	BxPC-3	7
miR-3145-3p	Upregulation	Promotion of proliferation, invasion, decreases apoptosis	N/R	81
miR-31-5p and miR-1290	Upregulation	Promotion of cell proliferation, invasion, and migration	IKK1	41
miR-3173-5p	-	Promotion of gemcitabine resistance, Inhibition of ferroptosis	ACSL4	82
miR-345	Upregulation	Tumor development, metastasis, and chemoresistance,	BCL2 and CCL8	83

miRNA(biomarker)	Alteration	Cellular function	Target	References
miR-34a-5p	Downregulation	Promotion of migration, invasion, proliferation	XIST	84
miR-365	Downregulation	Inhibition of proliferation and invasion, promotion of apoptosis	AKT/STAT3	43
miR-378a-3p	Downregulation	Promotion of Cell migration//hsa_circ_0006215, miR-378a-3p and SERPINA4 signaling pathways	SERPINA4	85
miR-4299d	Downregulation	Inhibition of PC cell proliferation, invasion, promotion of apoptosis, reduction of PC tumor growth, regulation of immune escape	ADAM17	45
miR-448	Downregulation	Promotion of proliferation and migration	SERBP1	86
miR-4673/miR-876-3p	Downregulation	Promotion of cell growth, migration, invasion, and induced cell apoptosis	SLCO4A1-AS1	74
miR-492	Upregulation	Promotion of cell proliferation, migration, and invasion, activation of NR2C1/NDUFA12/TMCC3 genes, activation of the TGF- β /Smad3 pathway, promotion of epithelial-mesenchymal transition (EMT)	NR2C1, NDUFA12, TMCC3, TGF- β /Smad3	47
miR-497-5p	Downregulation	Promotion of cell proliferation, invasion, and migration	IGF1R	73
miR-504	Upregulation	Promotion of cell apoptosis, viability, migration	HNF1A	87
miR-532	Downregulation	Inhibition of proliferation, metastasis, promotion of autophagy	TWIST1	88
miR-552-5p	Upregulation	Promotion of migration and invasion	FOXO3	89
miR-561-5p	Upregulation	Promotion of cell proliferation, migration and invasion and epithelial-mesenchymal transition and cell growth	LINC01128	90

miRNA(biomarker)	Alteration	Cellular function	Target	References
miR-577	Downregulation	Promotion of cell proliferation, migration and invasion	FGD5-AS1	91
miR-613	Downregulation	Promotion of cell proliferation, growth, and invasion	ANXA2	92
miR-646	Upregulation	Promotion of proliferation and invasion	MiP/(HIF-1 α)	50
miR-663a	Downregulation	Promotion of proliferation, invasion, migration	Sox12	93
miR-665	Downregulation	Promotion of proliferation, cell migration, invasion, and tumor metastasis	hsa_circ_0006215, miR-378a-3p and SERPINA4 signaling pathways	94
miR-765-3p	Downregulation	Inhibition of growth, migration, invasion, promotion of G1 cell cycle arrest, and apoptosis	RUNX2	80
miRNA-320b	Downregulation	Promotion of proliferation, invasion and epithelial-mesenchymal transition	SNHG12	95

The significance of miRNAs in the diagnosis of pancreatic cancer

MiRNAs show significant promise in the diagnosis of PC, a disease often diagnosed at advanced stages with limited treatment options and poor prognosis.^{109,110} Altered miRNA expression patterns in PC tissues, along with their presence in easily accessible biological fluids like blood, urine, and saliva, make them attractive biomarkers.¹¹¹ Their high sensitivity, specificity, and ability to distinguish cancer from benign conditions highlight their potential for routine screening and risk assessment in at-risk populations, ultimately improving patient outcomes through early intervention and personalized treatment strategies.¹¹² It was shown that serum hsa-miR-4516, hsa-miR-4669, hsa-miR-3135b, hsa-miR-6126, and hsa-miR-486-5p may have diagnostic relevance. Furthermore, hsa-miR-4669 has been linked to lymph node metastasis, while hsa-miR-4516 has been identified as an independent factor in survival determination and has been associated with cancer progression via targeting Wnt and p53 pathways.¹¹³ A combination of multiple miRNAs in a panel offers higher accuracy for cancer detection because it captures complementary information and reduces the risk of false positives, improving sensitivity and specificity compared to individual miRNAs. This combination provides a more robust and reliable diagnostic tool.^{111,112} A panel of three serum miRNAs (miR-125a-3p, miR-4530, and miR-92a-2-5p) in plasma has shown substantial promise for the noninvasive detection of pancreatic cancer, surpassing the diagnostic accuracy of individual miRNAs.¹¹⁴ Álvarez-Hilario and their research team identified a novel diagnostic panel comprising serum miR-222-3p and miR-221-3p for the detection of PDAC and observed that elevated expression of miR-221-3p and miR-222-3p was associated with reduced survival rates.¹¹⁵ Elevated levels of tissue miR-552-5p are associated with enhanced cell migration and invasion, while concurrently leading to reduced expression of FOXO3 and components of the Wnt signaling pathway.⁸⁹ Another tissue miRNA with potential for pancreatic cancer detection is miR-340-3p. Research by Cui and their team revealed that miR-340-3p is upregulated in pancreatic adenocarcinoma and targets CENPL, which is associated with decreased overall survival (OS).¹¹⁶ Table 2 provides a summary of the miRNAs associated with diagnosis of PC.

Table 2 Diagnostic and prognostic role of miRNAs in pancreatic cancer

miRNA(biomarker)	Prognosis	Diagnosis	Endpoint	Sample	References
miR-25	N/A	Yes	N/A	Serum	12
hsa-miR-4516, hsa-miR-4669, hsa-miR-3135b, hsa-miR-6126, hsa-miR-486-5p	Poor	Yes	Poor OS	Serum	113
miR-125a-3p/ miR-4530/ miR-92a	N/A	Yes	N/A	Serum	114
miR-155	Poor	N/A	N/A	Blood	6
miR-190b	Good	N/A	Low expression correlated with shorter OS	Pancreatic duct epithelial cell line	117
miR-200c-3p	Good	N/A	Low expression correlated with shorter OS	Tissue	72
miR-222-3p / miR-221-3p	N/A	Yes	Poor OS	Serum	115
miR-340-3p	Poor	Yes	Poor OS	Tissue	116
miR-4653-3p	Poor	N/A	Poor OS	Tissue	118
miR-491-3p	Poor	N/A	Poor OS	Tissue	52
miR-552-5p	Poor	Yes	N/A	Tissue	89
miR-561-5p	Poor	N/A	N/A	Tissue	90

The important role of miRNAs in the detection of early-stage pancreatic cancer

Early detection of pancreatic cancer is pivotal for improving patient outcomes, as the disease often remains asymptomatic until advanced stages. An 80-patient clinical trial revealed that the expression of miR-25 in PC patients was notably elevated compared to non-PC patients. When utilized in conjunction with CA19-9, miR-25 exhibited significantly improved diagnostic performance for early-stage PC (stages I+II) compared to the individual use of CA19-9 or miR-25 alone.¹² A large-scale study conducted on 212 pancreatic cancer patients and 213 healthy controls revealed the diagnostic potential of a panel of 100 highly expressed miRNAs. When combined with CA19-9, these miRNAs achieved an area under the curve (AUC) of 0.99, with a sensitivity of 90% and specificity of 98%. Notably, the model maintained high diagnostic accuracy for early-stage pancreatic cancer (stage 0-I) in an independent cohort, achieving an AUC of 0.97, sensitivity of 67%, and specificity of 98%. This demonstrates that integrating miRNAs with CA19-9 significantly enhances early detection accuracy.²⁶ Another study focused on identifying specific miRNAs from both tumor and serum samples, analyzing datasets from multiple centers. It pinpointed hsa-miR-1246,

hsa-miR-205-5p, and hsa-miR-191-5p as potential serum biomarkers for pancreatic cancer. The diagnostic model incorporating these miRNAs achieved accuracy values exceeding 94% in test datasets. Furthermore, elevated levels of hsa-miR-205-5p were strongly associated with advanced disease stages and poor clinical outcomes. These findings emphasize the role of circulating miRNAs in not only diagnosing pancreatic cancer early but also in distinguishing it from pancreatitis and assessing disease progression.¹¹⁹ An innovative approach involved using urinary extracellular vesicle-derived miRNAs for pancreatic cancer detection. A study evaluated samples from 153 pancreatic cancer patients and 309 healthy controls, identifying miRNA patterns that mirrored tumor and microenvironmental signals. The diagnostic model demonstrated robust performance, with AUC values of 0.972 and 0.963 for training and test datasets, respectively. Early-stage detection (stage I/IIA) showed sensitivity rates of 97.0% in the training set and 77.8% in the test set. Compared to CA19-9, which had limited sensitivity (37.5%) for early-stage detection, urinary miRNAs provided a more reliable alternative for non-invasive diagnosis.¹²⁰ A plasma-based three-miRNA signature (let-7i-5p, miR-130a-3p, and miR-221-3p) was identified as a promising tool for PDAC detection. This signature achieved exceptional diagnostic accuracy (AUC > 0.97 for all stages) and enhanced the performance of CA19-9, particularly for early-stage disease. Additionally, it effectively differentiated pancreatic cancer from chronic pancreatitis, with AUC values exceeding 0.93. Validation in a separate cohort showed a progressive increase in diagnostic accuracy months before clinical diagnosis, highlighting its potential in early intervention and patient stratification.¹²¹

Prognostic value of miRNAs in pancreatic cancer

The expression patterns of specific miRNAs can provide insights into the aggressiveness of the disease, the likelihood of metastasis, and the overall survival of patients.¹²² High or low expression levels of certain miRNAs have been linked to different prognostic outcomes, and they can help stratify patients into risk categories. Additionally, miRNAs can be indicative of treatment response and disease recurrence, offering a means to monitor a patient's progress over time.¹¹¹ Aita and their colleagues demonstrated that novel circulating miRNAs, including hsa-miR-3135b, hsa-miR-6126, hsa-miR-486-5p, hsa-miR-6821-5p, hsa-miR-4669, and hsa-miR-4516, show promise as valuable biomarkers for PDAC prognostic assessment. These miRNAs are upregulated in PDAC and, once independently validated, could be quantified in the serum of PDAC patients. This development holds the potential to improve PDAC management and extend patient survival.¹¹³ Research has shown that miRNAs can be linked to the severity of cachexia in cancer.¹²³ In their study, Yehia and his fellow researchers observed elevated expression levels of MiR-155 in individuals with cachexia, and this expression was positively correlated with the severity of cachexia within the cachectic group when compared to the non-cachectic group in PC patients.⁶ Certain miRNAs are associated with good prognostic outcomes in PC. For instance, the expression of MicroRNA-190b is indicative of a favourable prognosis and plays a role in mitigating the malignant advancement of PC by targeting MEF2C and TCF4. On the other hand, miR-200c-3p inhibits cell migration and invasion in PDAC but is predictive of an unfavourable prognosis.^{72,117} Overexpression of CENPL mRNA, potentially regulated by miR-340-3p, serves as a prognostic marker, while miR-4653-3p upregulation is indicative of an adverse outcome due to its negative regulation of HIPK2 in pancreatic ductal adenocarcinoma.¹¹⁸ Additionally, the long non-coding RNA LINP1 has been implicated in the promotion of PC cell proliferation and metastasis by modulating microRNA-491-3p, thereby influencing the incidence of lymph node or distant metastasis and overall patient prognosis.⁵² Elevated miR-552-5p levels in PC cells correlate with a poor prognosis and concurrent downregulation of FOXO3 and Wnt signaling pathway members.⁸⁹ Lastly, LINC01128 functions as a microRNA sponge, particularly miR-561-5p, and is associated with an unfavourable prognosis in PC patients. These findings underscore the intricate molecular landscape that impacts the prognostic outlook for individuals with PC.⁹⁰

Noninvasive prediction of outcomes through the transmission of miRNAs via extracellular vesicles

Research reveals that miR-145 is expressed differently in PDAC and TAS cells, influencing their interactions within the tumor microenvironment. By using EVs, these miRNAs are exchanged between the cells, primarily through exosomes secreted by TAS cells. Notably, these exosomes exhibit tumor-suppressive properties, inducing apoptosis in PDAC cells. This suggests the potential for TAS cells to release exosomes carrying tumor-suppressive genetic material, which could have therapeutic implications for inoperable PDAC.¹²⁴ Verel-Yilmaz and colleagues¹²⁵ designed a study to address the urgent need for reliable early detection of PDAC. Researchers focused on ADAM8-positive EVs) and specific miRNAs, including miR-451 and miR-720, as potential biomarkers to distinguish PDAC and

precursor lesions from healthy controls. ADAM8-enriched EVs were successfully isolated from patient serum, and the study found that miR-451 and miR-720 showed diagnostic potential with high sensitivity and specificity in discriminating PDAC from healthy individuals. Research has shown that miR-27a is highly expressed in PC tissue and cell lines. What's intriguing is that EVs derived from PC, which carry miR-27a, can stimulate the proliferation, invasion, and angiogenesis of human microvascular endothelial cells (HMVECs). This effect occurs by inhibiting the expression of B-cell translocation gene 2 (BTG2), which, in turn, facilitates the survival and growth of PC cells.^{126,127} Conversely, miR-339-5p, which lowers the levels of the zinc finger protein ZNF689, hinders cell invasion and migration in animal models of PC. Consistent with this, the levels of EV-associated miR-339-5p are diminished in metastatic PC cells, and the external introduction of miR-339-5p results in decreased migration and invasion of PC cells.¹²⁶ Interestingly it was found that extremely invasive PC cells exhibit elevated levels of miR-222, which is then encapsulated within EVs. Upon being taken up by less invasive PC cells, EV releases miR-222, leading to a cascade of effects. This includes the downregulation, phosphorylation, and translocation of p27 to the cell nucleus via the PPP2R2A/Akt pathway. Eventually, this molecular process encourages the proliferation and invasion of cancer cells.¹²⁸ There is a pressing demand for a non-invasive and precise biomarker to detect individuals at risk of developing chemoresistance, a condition where cancer cells become resistant to the effects of chemotherapy.¹²⁹ EVs are a rich source of miRNAs that exhibit consistent expression patterns in various cancers, including PC. AFs promote chemoresistance in PC cells following GEM treatment by releasing exosomes and maintaining communication with the cancer cells. The underlying mechanism involves miR-3173-5p contained in CAF exosomes, which inhibits ferroptosis and ACSL4 in the cancer cells. This study highlights a new way that PC develops resistance to treatment and suggests that targeting the miR-3173-5p/ACSL4 pathway could be a promising approach for treating GEM-resistant PC.⁸² Recently, it has come to light that PC stem cells, which have developed resistance to gemcitabine treatment, release EVs. EVs have a pivotal role in reducing chemosensitivity in gemcitabine-sensitive PC cells through the transport of miR-210. Notably, miR-210 antagonizes the impact of gemcitabine, inhibiting cell cycle arrest and apoptosis, while promoting activities such as tumor cell migration. Consequently, this phenomenon culminates in an EV-mediated escalation of the invasive and metastatic capabilities of gemcitabine-treated cells¹³⁰ (Fig 2).

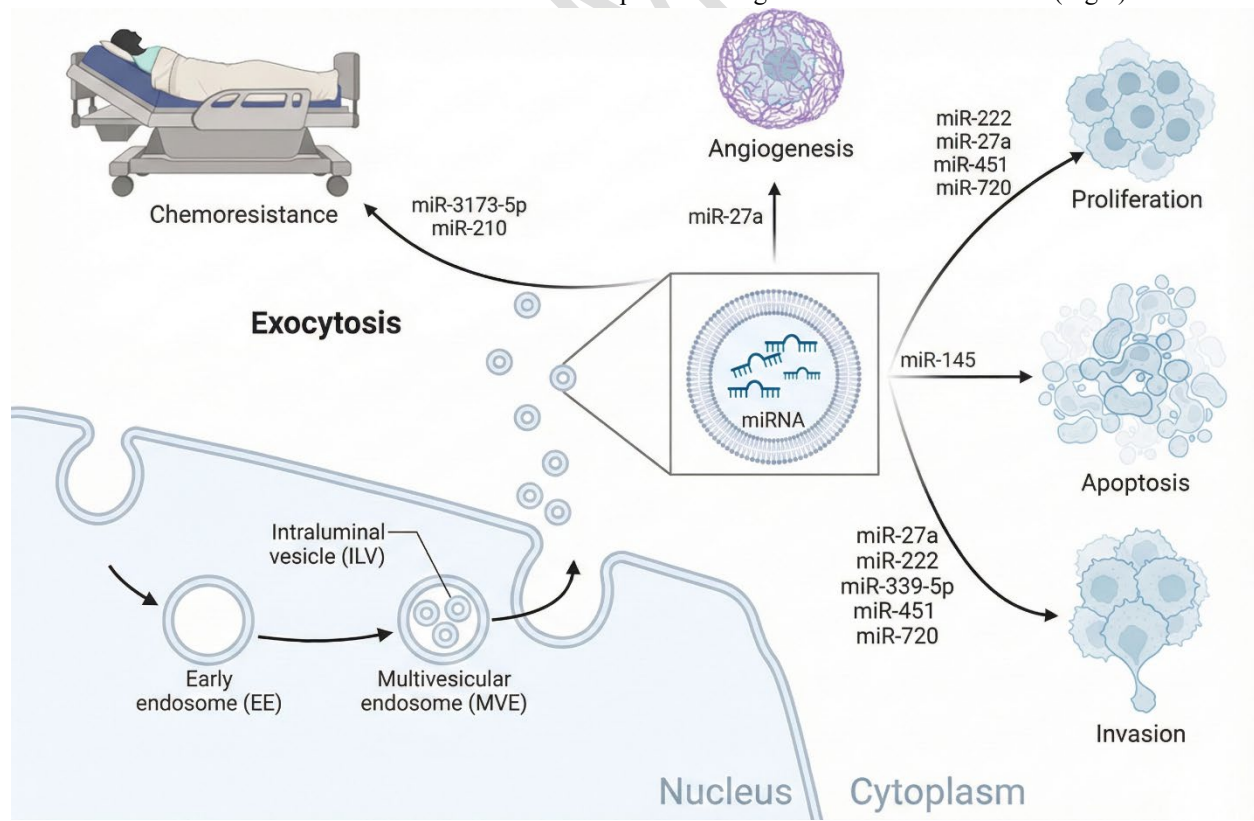


Fig. 2 Representation of extracellular vesicle (EV)-derived miRNAs in pancreatic cancer progression. EV biogenesis begins with the formation of early endosomes (EE), which mature into multivesicular endosomes (MVE) containing intraluminal vesicles (ILVs). Upon exocytosis, these vesicles release microRNAs (miRNAs) into the extracellular space. Once secreted, EV-associated miRNAs modulate several hallmarks of pancreatic cancer. Specific miRNAs such as miR-3173-5p and miR-210 contribute to chemoresistance, while miR-27a promotes angiogenesis. Other miRNAs—including miR-222, miR-27a, miR-451, and miR-720—drive cell proliferation, whereas miR-145 enhances apoptosis. Additional EV-miRNAs, including miR-27a, miR-222, miR-339-5p, miR-451, and miR-720, facilitate invasion and metastatic spread. Together, these EV-miRNAs orchestrate the interplay between tumor cells and their microenvironment, underscoring their dual role as biomarkers and therapeutic targets in pancreatic cancer.

Clinical EV-miRNA Signatures in Pancreatic Cancer Patients

EV-derived microRNAs are emerging as promising non-invasive biomarkers for PC, with particular value in early diagnosis and in distinguishing malignant from benign disease. The clinical application of these signatures paved the way for better and less invasive diagnosis in PC patients. A thorough meta-analysis of over 2,000 patients with pancreatic cancer highlighted significant markers for the detection of this cancer within EVs, with miR-10b, miR-21, and GPC1 emerging as notable candidates. When analyzing these biomarkers individually, they demonstrated good sensitivity and specificity. Combining RNA and protein markers further improved diagnostic accuracy, especially for early-stage pancreatic cancer.¹³¹ Early investigations demonstrated that plasma exosomal miR-196a and miR-1246 are selectively enriched in pancreatic cancer cells and elevated in circulation among patients with localized disease (stage I–IIA). In a cohort of 15 patients and matched controls, both miRNAs were significantly upregulated in plasma EVs from cancer patients, with ROC analyses showing AUCs of 0.81 for miR-196a and 0.73 for miR-1246, respectively. These values indicate fair diagnostic power, particularly in early-stage disease where clinical detection remains most challenging. Subgroup analyses further revealed that miR-196a better indicated PDAC, while miR-1246 was especially elevated in IPMN. Notably, these markers were not significantly altered in neuroendocrine tumors, underscoring their histotype specificity.¹³² More recently, a large multicentric prospective study identified the EV-miR-200 family (miR-200a, miR-200b, miR-200c, miR-141, miR-429) as a robust diagnostic signature. In validation cohorts, combined EV-miR-200 expression achieved an AUC of 0.823 in distinguishing PDAC from benign pancreaticobiliary disease, with individual family members reaching AUCs between 0.70 and 0.78. Importantly, in an independent cohort the model's performance improved to an AUC of 0.987, with sensitivity of 100% and specificity of 88%. When EV-miR-200 signatures were combined with CA19-9, diagnostic accuracy approached perfection (AUC 0.997–1.00), clearly outperforming CA19-9 alone (AUC ~0.86–0.92).¹³³ A recent multiethnic radiogenomic study identified a three-EV-miRNA panel (miR-1260b, miR-151a-3p, miR-5695) that robustly discriminated pancreatic cancer (PC) from benign lesions. In machine learning models, this signature achieved AUCs of 0.978 (training), 0.919 and 0.857 (validation), with pooled external validation confirming high accuracy (AUC 0.897). By contrast, CA19-9 performed lower (AUC 0.843) in the same cohort. Beyond diagnosis, this EV-miRNA signature stratified PC into two molecular subtypes: one linked to aggressive features and poor survival, and another associated with favorable immune profiles and longer survival. These results highlight that EV-miRNA signatures not only outperform CA19-9 for early detection but also provide clinically meaningful subtype classification, supporting their integration into precision oncology strategies.¹³⁴ A multicenter study validated a urinary EV-miRNA assay for pancreatic cancer detection across all stages. The panel achieved AUCs of 0.972 (training) and 0.963 (testing), with sensitivities of 93.9% and 77.8%, and specificities above 91%. Importantly, it detected early-stage disease (I/IIA) with AUCs near 0.98 and sensitivities up to 97%, far exceeding CA19-9, which identified only 37.5% of early cases. These results highlight urinary EV-miRNAs as a noninvasive tool that outperforms CA19-9, especially for early detection.¹³⁵ In IPMN, a precursor of pancreatic ductal adenocarcinoma, distinguishing low-risk from high-risk lesions remains clinically challenging. A recent study profiled serum from over 300 IPMN patients and identified a panel of seven miRNAs that, when applied through machine learning, could differentiate high- from low-risk IPMN with an AUC of 0.94. Protein biomarkers alone reached similar accuracy (AUC ~0.95), but a combined panel of five proteins and three miRNAs achieved AUC 0.97, far outperforming guideline-based clinical criteria (AUC ~0.81). Importantly, these EV-miRNA-based signatures exceeded the performance of CA19-9, whose reported accuracy for IPMN risk stratification is much lower (AUC 0.62–0.78). Thus, blood-based miRNA panels provide a robust noninvasive tool not only for

pancreatic cancer detection but also for risk stratification of premalignant lesions, directly informing surgical decision-making.¹³⁶ A multicenter study evaluated a multianalyte plasma panel consisting of tumor-associated EV-miRNAs and mRNAs, circulating free DNA (cfDNA) concentration, KRAS mutations, and CA19-9. In blinded testing (n=136), this five-marker panel (EV-CK18 mRNA, EV-CD63 mRNA, EV-miR-409, cfDNA concentration, and CA19-9) distinguished PDAC from controls with 92% accuracy (AUC 0.95; sensitivity 88%, specificity 95%), outperforming CA19-9 alone (accuracy 84%). Importantly, the panel also improved disease staging: when combined with imaging, it identified occult metastases with 84% accuracy (AUC 0.85) compared with only 64% for imaging alone. These findings demonstrate that EV-miRNA/mRNA signatures, especially when combined with cfDNA and CA19-9, provide greater sensitivity and specificity than traditional biomarkers or imaging alone, offering both diagnostic and prognostic value.¹³⁷

The role of miRNAs in pancreatic cancer metastasis

Metastasis is a critical hallmark of PC, contributing significantly to its aggressiveness and poor prognosis.⁹⁴ miRNAs have been implicated in the regulation of various processes within cancer cells, including metastasis. miR-143, known for its downregulation in PC, plays a pivotal role in suppressing autophagy and the metastasis of PC. Autophagy, a cellular self-cannibalization process, has been linked to cancer progression and metastasis. The downregulation of miR-143 appears to facilitate metastasis by promoting autophagy, making it a significant player in the spread of PC.⁶² On the other hand, miR-155 shows an upregulation in PDAC, and its expression is associated with the promotion of lymph node metastasis. This miRNA's involvement in PDAC metastasis has been associated with the upregulation of NiCl2, indicating the complex molecular mechanisms at play.⁹⁴ Similarly, miR-199b-5p exhibits an upregulation and has been linked to the promotion of both tumor growth and metastasis of PC cells. This miRNA is believed to modulate the expression of LINC01133, thereby influencing the metastatic potential of PC.⁹⁴ MiR-200c-3p, when downregulated, has been associated with the promotion of cell proliferation and metastasis in PC. This effect is potentially mediated through its interaction with lncRNA MALAT-1.⁷² MiR-221, exhibiting upregulation in PDAC, plays a role in promoting migration, metastasis, and uncontrolled proliferation of PC cells. The presence of NiCl2 further supports the influence of miR-221 on the metastatic behavior of PDAC.⁶⁵ MiR-223-5p, though not explicitly associated with changes in expression, has been linked to the promotion of tumor growth and metastasis of PC cells, potentially through its interaction with LINC01705, a long non-coding RNA involved in cancer progression.⁷⁷ MiR-345 shows upregulation in PC and is implicated in tumor development, metastasis, and chemoresistance. This miRNA is believed to target BCL2 and CCL8, affecting the metastatic potential of PC.⁹⁴ MiR-532 exhibits downregulation and has been shown to inhibit proliferation and metastasis while promoting autophagy. This regulatory activity is partly attributed to its effect on TWIST1, a key transcription factor involved in cancer metastasis.⁸⁸ SERPINA4, or kallistatin, is a multifunctional protein with roles in anti-inflammatory responses, angiogenesis regulation, and endothelial function. It also influences blood pressure, possesses antioxidant properties, and exhibits anti-fibrotic effects, making it a crucial player in various physiological processes and a subject of ongoing research for its therapeutic potential.¹³⁸ MiR-665 demonstrates downregulation in PC and is associated with the promotion of proliferation, cell migration, invasion, and tumor metastasis. These effects are likely mediated through the hsa_circ_0006215, miR-378a-3p, and SERPINA4 signaling pathways.⁹⁴ DLX6-AS1 was shown to interact with miR-181b, and the suppression of miR-181b reversed the effects of DLX6-AS1 knockdown. MiR-181b was found to target the gene ZEB2 and influence EMT. In addition, in vivo, experiments demonstrated that DLX6-AS1 knockdown inhibited tumor growth and metastasis. This suggests that DLX6-AS1 promotes PC progression by regulating miR-181b and related processes.⁶⁷ LINP1 enhances PC cell proliferation and metastasis by modulating microRNA-491-3p, impacting the incidence of lymph node or distant metastasis and the prognosis of PC patients.⁵² It has been shown that Linc00261 expression was reduced in PC tissues and cell lines, and low expression was associated with poorer patient outcomes. Overexpression of Linc00261 inhibited PC cell migration and invasion in vitro, as well as reduced metastasis in an in vivo mouse model. Linc00261 directly interacted with miR-552-5p, leading to decreased miR-552-5p levels. Additionally, Linc00261 overexpression increased FOXO3 expression, a target of miR-552-5p, and inhibited the Wnt signaling pathway. Conversely, overexpressing miR-552-5p in Linc00261-overexpressing PC cells increased migration and invasion, while decreasing FOXO3 and Wnt signaling pathway component expression.⁸⁹ A summary of miRNAs which play a role in PC metastasis is shown in Table 1.

The potential uses of miRNAs in the treatment of pancreatic cancer: Focus on novel approaches

Oncolytic viruses have shown promise as a novel therapeutic strategy. However, the intricate interplay between viral vectors and tumor cells can pose challenges for successful viral replication.¹³⁹ Researchers have discovered two miRNAs, miR-99b and miR-485, which enhance oncolytic adenovirus activity by boosting viral replication. By targeting repressors of viral protein expression (including ELF4, MDM2, and KLF8), these miRNAs improve the virus's efficacy.¹⁴⁰ Additionally, the transformation of cancer cells during tumorigenesis results in the deregulation of numerous miRNAs, some of which can affect the replication of oncolytic adenoviruses.¹⁴¹ Notably, miR-222 has been identified as a limiting factor in this context. Researchers have developed a therapeutic adenovirus, AdNuPAR-E-miR222-S, which incorporates miR-222 sponges to reduce the levels of this miRNA. This modification enhances the fitness of the adenovirus, increases its cytotoxicity, and effectively controls tumor growth in xenograft models.¹⁴² Sicard et al.¹⁴³ developed a lentivirus vector (LV) incorporating anti-miRNA (anti-miR-21) and substantiated its ability to dose-dependently restrain the proliferation of PC cells in murine models. In a separate investigation, Chaudhary et al.¹⁴⁴ documented that the LV-mediated overexpression of miR-205 heightened the responsiveness of PC stem cells to chemotherapy and suppressed the proliferation of tumor cells. Kent and colleagues provided evidence that the introduction of tumor suppressor miRNA, specifically miR-143/145, via viral-mediated transduction, effectively impeded the growth of PC cells.¹⁴⁵

Antagomirs have emerged as a promising strategy in the challenging landscape of cancer.¹⁴⁶ The discovery of a distinctive side population (SP) with stem cell-like attributes within PC cells has ignited significant interest. This SP exhibited elevated expression of microRNA-21 and microRNA-221, contributing to aggressive tumor formation in mouse models. The application of antagomirs targeting miR-21 and miR-221 resulted in a reduction in the SP cell fraction, decreased proliferation, and increased sensitivity to chemotherapeutic agents, notably gemcitabine. Additionally, the combined therapy of antagomirs displayed synergistic effects, leading to a notable inhibition of primary tumor growth and metastasis. These findings highlight the potential of antagomirs as an innovative therapeutic approach for addressing the stem-like subpopulations and their role in PC progression, offering valuable insights into the future of PC therapy.^{147,148} In a study, researchers combined the use of miR-21 antisense oligonucleotides (ASO-miR-21) and the drug gemcitabine (Gem) delivered via specialized nanoparticles, to enhance treatment outcome. These nanoparticles, coated with an anti-CD44v6 single-chain variable fragment (scFvCD44v6), were designed for precise drug delivery. The study demonstrated that ASO-miR-21 downregulated the cancer-promoting miR-21, resulting in the upregulation of tumor-suppressor genes PDCD4 and PTEN. This, in turn, inhibited the cancer cells' ability to spread, proliferate, migrate, and invade in vitro, and inhibited the tumor growth and metastasis in vivo.¹⁴⁹ CRISPR-Cas9, a revolutionary genome-editing tool, has gained immense attention in the field of cancer research.^{29,150} It allows precise modification of the DNA in a highly specific manner. This technology has the potential to disrupt the expression of oncogenic miRNAs.¹⁵¹ In a study conducted by Vorvis and their team,¹⁵² they delved into miRNA-profiling investigations, revealing a significant reduction in the presence of the transcription factor forkhead box protein A2 (FOXA2) in PDAC compared to healthy pancreatic tissues. Notably, the researchers established that miR-199a plays a direct role in controlling FOXA2 expression. Intriguingly, the suppression of FOXA2 expression through the application of CRISPR/Cas9 technology resulted in heightened tumor growth in pancreatic tumor xenografts. These findings underscore the remarkable capability of the CRISPR/Cas9 system to achieve the lasting silencing of FOXA2 within a PC cell line, shedding light on FOXA2's in vivo function and providing further evidence of its role as a tumor suppressor in PC, regulated by miR-199a.

In a study exploring the use of nanoparticles for delivering tumor-suppressing miRNAs, Chen and colleagues introduced a novel chimeric peptide called PL-1. Their research demonstrated the efficient delivery of miR-212 into PDAC cells using miR-212/PL-1 nanoparticles. Furthermore, these nanoparticles significantly enhanced the responsiveness of tumor cells to doxorubicin and concurrently reduced USP9X, a protein involved in deubiquitination processes, ultimately promoting apoptosis in these cancer cells.¹⁵³ A nanoformulation based on PLGA was employed to deliver the tumor-suppressing miR-150 into PC cells. This nanoformulation effectively reduced the expression of the MUC4 gene and HER2, resulting in the inhibition of PC cell growth and invasion.¹⁵⁴ The application of nanocomplexes to deliver miR-34a as a potential treatment for PC was investigated. It was shown that these nanocomplexes are equipped with a tumor-targeting peptide known as CC9, which enhances their uptake by PC cells

and elevates the expression of miR-34a. This increased miR-34a level leads to the arrest of the cell cycle, induction of apoptosis, and the suppression of genes associated with cancer progression. Notably, *in vivo* experiments using these miR-34a delivery systems in a PC model reveal a substantial reduction in tumor growth and an increase in cancer cell apoptosis.¹⁵⁵ Su and colleagues designed a study to investigate how exosomes facilitate communication between human PC cells (Panc-1) and macrophages. They altered the exosome content by transfecting Panc-1 cells with microRNA-155 and microRNA-125b-2, and used a nanoparticle vectors consisting of hyaluronic acid plus polyethylene imine or polyethylene glycol to deliver the exosome contents. The results showed that reprogramming cells via exosomes leads to changes in communication and macrophage polarization.¹⁵⁶ MiR-192 is identified as an epigenetically regulated suppressor gene in PC. Its downregulation, linked to promoter methylation, was associated with cell proliferation, invasion, and early metastatic behavior. Overexpressing miR-192 reduced cell proliferation and invasion, and its target gene SERPINE1 (PAI-1) was implicated in these effects.¹⁵⁷ The reduced expression of miR-449a in both cancer tissues and cell lines correlated with heightened cell proliferation and invasion. MiR-449a directly interacted with the ataxia-telangiectasia group D complementing (ATDC) gene and influenced the Wnt signaling pathway, implying its role as a suppressor of PC. The miR-449a/ATDC relationship might play a crucial part in the development of PC and offer promising targets for therapy¹⁵⁸ (Fig 3).

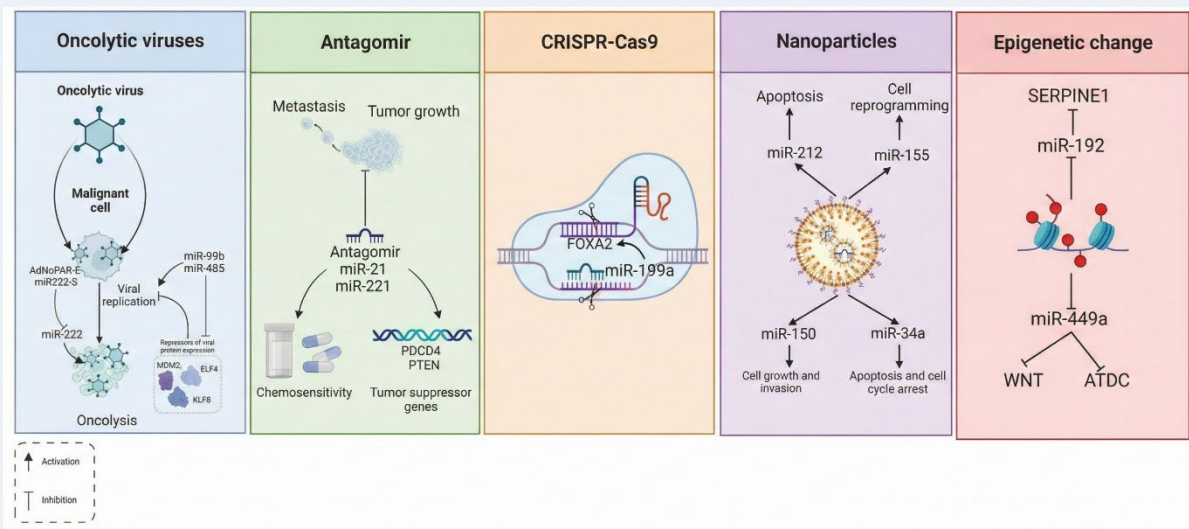


Fig. 3 Therapeutic strategies targeting microRNAs (miRNAs) in cancer. Different approaches are being developed to modulate miRNA activity for therapeutic purposes. Oncolytic viruses exploit viral replication within malignant cells, promoting oncolysis and repression of oncogenic miRNAs such as miR-222, while restoring tumor suppressor networks. Antagomirs, chemically modified antisense oligonucleotides, silence oncogenic miRNAs (e.g., miR-21, miR-221) to reduce tumor growth and metastasis, restore tumor suppressor genes (PDCD4, PTEN), and enhance chemosensitivity. CRISPR-Cas9–based editing enables direct targeting of miRNA loci, such as the suppression of miR-199a to restore expression of transcription factors like FOXA2. Nanoparticle delivery systems allow efficient transport of miRNA mimics or inhibitors; for example, miR-212 and miR-34a promote apoptosis and cell cycle arrest, while miR-155 and miR-150 regulate cell reprogramming and invasion. Epigenetic modulation of miRNAs, such as SERPINE1-induced changes in miR-192 and miR-449a, alters downstream signaling pathways (WNT, ATDC), affecting cancer progression. Together, these strategies highlight diverse methods of harnessing miRNA biology for anticancer therapy.

The first clinical evaluation of miRNA mimic therapy was the Phase I trial of MRX34 (NCT01829971), a liposomal formulation of the tumor suppressor miR-34a. This study enrolled patients with advanced solid tumors, including pancreatic cancer, to determine safety and dosing. MRX34 administration resulted in successful delivery of miR-34a and dose-dependent modulation of target gene expression, with partial responses observed in a few patients and stable disease in others. However, despite evidence of biological activity, the trial was terminated early due to severe

immune-mediated adverse events, including fatalities, underscoring both the therapeutic potential and the current safety challenges of miRNA mimic-based strategies in oncology.¹⁵⁹

Emerging RNA-Binding Protein Regulators of miRNA Processing in Pancreatic Cancer

In addition to canonical miRNA biogenesis, RNA-binding proteins (RBPs) have emerged as critical modulators of miRNA maturation and function in PDAC. A prominent RBP is LIN28, which exists as two homologues, LIN28A and LIN28B, and functions as an oncofetal regulator of let7 miRNA biogenesis. LIN28B acts in the nucleus by binding to the terminal loop of prelet7, blocking microprocessor complex activity and preventing maturation into functional let7 (inhibiting tumor-suppressive functions).¹⁶⁰ Meanwhile, LIN28A exerts its effect in the cytoplasm through recruitment of TUT4/7 to uridylylate prelet7, triggering its degradation rather than Dicer processing; this post-transcriptional blockade occurs via uridylation-mediated destabilization and involves the exoribonuclease DIS3L2. This suppression of the let7 family derepresses a range of oncogenic targets, including KRAS, c-MYC, HMGA1/2, VEGF, IL6, IGF1R, and IGF2BP2 leading to phenotypes such as enhanced proliferation, angiogenesis, invasion, metastasis, and tumor-promoting inflammation in various cancers.¹⁶¹ PDAC specifically, dysregulated LIN28B expression is linked to poor prognosis and increased metastatic potential; moreover, LIN28 knockdown has been shown to restore let7 expression and sensitize tumors to chemotherapeutic agents such as gemcitabine by repressing downstream genes like RRM2, a factor implicated in chemoresistance.¹⁶²

Conclusion, limitations, and perspectives

The intricate roles of miRNAs in PC have been increasingly recognized as pivotal factors in its pathogenesis, diagnosis, prognosis, and treatment. MiRNAs have emerged as versatile molecules that can either promote or suppress tumor progression, depending on their specific functions. They hold promise as diagnostic and prognostic biomarkers, and their potential for therapeutic interventions is rapidly expanding. MiRNA-based therapies, in combination with innovative techniques such as nanoparticle delivery and CRISPR-Cas9 technology, are paving the way for more effective and targeted treatments. As our understanding of miRNAs continues to evolve, they are likely to play an increasingly central role in the comprehensive management of PC, offering hope for improved outcomes and enhanced patient care in the fight against this challenging disease. One of the primary challenges with miRNAs in cancer is achieving a balance between specificity and sensitivity. miRNAs can have multiple target genes, and their expression can vary in different cancer subtypes. This complexity makes it challenging to pinpoint precise miRNA signatures for accurate diagnosis and prognosis.¹⁶³ Variability in miRNA expression between individuals and even within tumor samples can be significant. This variability can make it difficult to establish consistent and robust biomarkers for cancer.¹⁶⁴ The source of miRNA samples, such as blood, tissue, or other body fluids, can greatly impact the results. Standardization in sample collection and processing is essential for reliable and reproducible miRNA-based diagnostics and therapies.¹⁶⁴ miRNA research has the potential to contribute to the era of precision medicine. By identifying patient-specific miRNA profiles, treatment strategies can be personalized to target the unique molecular characteristics of an individual's cancer.¹⁶⁵ The future likely holds the development of combination therapies that incorporate miRNA-based treatments with other established cancer therapies, such as chemotherapy, immunotherapy, and targeted therapies.¹⁶⁶ Advances in technology will enable more precise miRNA detection and manipulation. This includes the use of CRISPR/Cas9 for targeted miRNA regulation and improved nanoparticle-based delivery systems.¹⁶⁷ The shift of miRNA-based therapies from preclinical research to clinical trials is crucial for assessing their real-world safety and efficacy. The ASCEND-PANCREATIC study, involving 7,062 participants, aims to enhance early pancreatic cancer detection through a combination of assessments, including cfDNA methylation, ctDNA mutations, serum proteins, and blood miRNAs. The model's development and validation will target those with early-stage cancers, benign conditions, and healthy individuals, with a focus on evaluating the detection test in high-risk individuals.¹⁶⁸

Despite encouraging findings on the diagnostic and prognostic roles of miRNAs in PC, several obstacles hinder their translation into routine clinical use. One major challenge is biomarker variability. Reported circulating miRNA signatures often lack reproducibility across studies due to differences in sample type (serum, plasma, whole blood, or exosomal fractions), pre-analytical handling, and detection platforms (qPCR, microarrays, RNA sequencing, droplet digital PCR). Inconsistent normalization strategies and variability in endogenous controls further complicate data interpretation, making cross-study comparisons difficult and limiting clinical validation.¹⁶⁹ Moreover, population

heterogeneity, including genetic background, comorbidities, and lifestyle factors, influences circulating miRNA expression and reduces generalizability of proposed panels. Another critical barrier is regulatory and translational feasibility. For diagnostic use, regulatory agencies such as the FDA and EMA require robust validation in large, multicenter, prospective cohorts with standardized pipelines. However, most current studies are retrospective, small in scale, and lack independent validation.

While liquid biopsy has emerged as a promising tool for minimally invasive diagnosis and monitoring of pancreatic cancer, several limitations constrain its clinical translation. Pre-analytic variability, including differences in EV/miRNA isolation techniques, normalization strategies, and biofluid sources (serum, plasma, exosomes) can lead to inconsistent results across studies. Furthermore, many investigations rely on relatively small and ethnically homogeneous cohorts, limiting the generalizability of proposed biomarker panels. Another critical issue is the risk of overfitting in machine learning-based models, where predictive accuracy may appear artificially high in training sets but fail to replicate in independent validation cohorts. Addressing these challenges will require large, multi-ethnic, prospective studies with standardized pipelines for sample handling, data analysis, and validation before liquid biopsy can be reliably adopted into routine pancreatic cancer care.

In addition, therapeutic applications face unique challenges. Combination strategies, such as pairing miRNA antagonists with gemcitabine have demonstrated synergistic effects in preclinical pancreatic cancer models but raise concerns about systemic toxicity. The early termination of the MRX34 trial, due to severe immune-related adverse events, highlights the importance of safety considerations. Future directions must therefore prioritize the development of tumor-specific delivery platforms, including exosome-mimetic nanovesicles, to minimize off-target accumulation. Moreover, emerging CRISPR-Cas9-based strategies for editing oncogenic or tumor-suppressive miRNAs require careful evaluation of potential off-target edits and unintended gene regulation. Addressing these issues through more refined delivery technologies and rigorous preclinical validation will be essential to advance miRNA therapeutics safely into the clinic.

Conflict of interest

Authors declare that there is no conflict of interest.

Authors' contribution

AP, RH, QB, and AA conceived and designed the study; MAZ, MM, AHKO, AD, RS, HG, and AI collected and organized the literature data; MB, SHFS, RKD, and MHP analyzed and interpreted the findings; AP and RH drafted the manuscript and prepared visualizations; QB, AA, and TAK critically revised and edited the article; QB, AA, and TAK supervised the study and managed correspondence with the journal; all authors (AP, RH, MB, MAZ, MM, AHKO, AD, RS, HG, AI, SHFS, RKD, MHP, QB, AA, TAK) reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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ChatGPT (OpenAI, San Francisco, CA, USA) was used to identify grammatical issues and improve the academic language and clarity of the manuscript. The authors reviewed and verified all AI-assisted edits to ensure accuracy and integrity of the final content.

Data Availability

Not applicable. This article is a review and does not contain any new data. All data supporting the findings of this study are available within the cited references.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent to publish

Not applicable

References

1. Yonemori K, Kurahara H, Maemura K, Natsugoe S. MicroRNA in pancreatic cancer. *J Hum Genet* 2017;62(1):33-40. doi:<https://doi.org/10.1038/jhg.2016.59>
2. Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. *CA Cancer J Clin* 2025;75(1):10-45. doi:<https://doi.org/10.3322/caac.21871>
3. Peduzzi G, Archibugi L, Farinella R, Ponz de Leon Pisani R, Vodickova L, Vodicka P, et al. The exposome and pancreatic cancer, lifestyle and environmental risk factors for PDAC. *Semin Cancer Biol* 2025;113:100-29. doi:<https://doi.org/10.1016/j.semcancer.2025.05.004>
4. Mishan MA, Khazeei Tabari MA, Parnian J, Fallahi J, Mahrooz A, Bagheri A. Functional mechanisms of miR-192 family in cancer. *Genes Chromosomes Cancer* 2020;59(12):722-35. doi:<https://doi.org/10.1002/gcc.22889>
5. Joulani M, Aghajamal N, Nouri M, Rahmani Khajeh F, Sharifi N, Saghafi D, et al. Non-coding RNAs and Hippo signaling in non-small cell lung cancer: emerging roles as biomarkers and therapeutic targets. *Discov Oncol* 2025;16(1):1365. doi:<https://doi.org/10.1007/s12672-025-03099-6>
6. Yehia R, Schaalan M, Abdallah DM, Saad AS, Sarhan N, Saleh S. Impact of TNF- α gene polymorphisms on pancreatic and non-small cell lung cancer-induced cachexia in adult Egyptian patients: a focus on pathogenic trajectories. *Front Oncol* 2021;11:783231. doi:<https://doi.org/10.3389/fonc.2021.783231>
7. Mortoglou M, Miralles F, Arisan ED, Dart A, Jurcevic S, Lange S, et al. microRNA-21 regulates stemness in pancreatic ductal adenocarcinoma cells. *Int J Mol Sci* 2022;23(3):1275. doi:<https://doi.org/10.3390/ijms23031275>
8. Han H, Wang L, Xu J, Wang A. miR-128 induces pancreas cancer cell apoptosis by targeting MDM4. *Exp Ther Med* 2018;15(6):5017-22. doi:<https://doi.org/10.3892/etm.2018.6047>
9. Si H, Zhang N, Shi C, Luo Z, Hou S. Tumor-suppressive miR-29c binds to MAPK1 inhibiting the ERK/MAPK pathway in pancreatic cancer. *Clin Transl Oncol* 2023;25(3):803-16. doi:<https://doi.org/10.1007/s12094-022-02991-9>
10. Chen C, Demirkhanyan L, Gondi CS. The multifaceted role of miR-21 in pancreatic cancers. *Cells* 2024;13(11):948. doi:<https://doi.org/10.3390/cells13110948>
11. Liu F, Mao H, Chai S, Mao H. Meta-analysis of the diagnostic value of exosomal miR-21 as a biomarker for the prediction of cancer. *J Clin Lab Anal* 2021;35(10):e23956. doi:<https://doi.org/10.1002/jcla.23956>
12. Yu Y, Tong Y, Zhong A, Wang Y, Lu R, Guo L. Identification of serum microRNA-25 as a novel biomarker for pancreatic cancer. *Medicine (Baltimore)* 2020;99(52):e23863. doi:<https://doi.org/10.1097/md.00000000000023863>

13. Romano R, Picca A, Eusebi LHU, Marzetti E, Calvani R, Moro L, et al. Extracellular vesicles and pancreatic cancer: insights on the roles of miRNA, lncRNA, and protein cargos in cancer progression. *Cells* 2021;10(6):1361. doi:<https://doi.org/10.3390/cells10061361>
14. Abels ER, Breakefield XO. Introduction to extracellular vesicles: biogenesis, RNA cargo selection, content, release, and uptake. *Cell Mol Neurobiol* 2016;36(3):301-12. doi:<https://doi.org/10.1007/s10571-016-0366-z>
15. Wang J, Rong Y, Ji C, Lv C, Jiang D, Ge X, et al. MicroRNA-421-3p-abundant small extracellular vesicles derived from M2 bone marrow-derived macrophages attenuate apoptosis and promote motor function recovery via inhibition of mTOR in spinal cord injury. *J Nanobiotechnology* 2020;18(1):72. doi:<https://doi.org/10.1186/s12951-020-00630-5>
16. Zeöld A, Sándor GO, Kiss A, Soós A, Tölgyes T, Bursics A, et al. Shared extracellular vesicle miRNA profiles of matched ductal pancreatic adenocarcinoma organoids and blood plasma samples show the power of organoid technology. *Cell Mol Life Sci* 2021;78(6):3005-20. doi:<https://doi.org/10.1007/s00018-020-03703-8>
17. Yu H, Xin C, Zhou Y, Ding X. Advances in the application of extracellular vesicles in precise diagnosis of pancreatic cancer. *Eur J Med Res* 2025;30(1):478. doi:<https://doi.org/10.1186/s40001-025-02739-5>
18. Xu D, Di K, Fan B, Wu J, Gu X, Sun Y, et al. MicroRNAs in extracellular vesicles: Sorting mechanisms, diagnostic value, isolation, and detection technology. *Front Bioeng Biotechnol* 2022;10:948959. doi:<https://doi.org/10.3389/fbioe.2022.948959>
19. Giatromanolaki A, Koukourakis MI, Koutsopoulos A, Mendrinou S, Sivridis E. The metabolic interactions between tumor cells and tumor-associated stroma (TAS) in prostatic cancer. *Cancer Biol Ther* 2012;13(13):1284-9. doi:<https://doi.org/10.4161/cbt.21785>
20. Zhou Q, Chen D, Zhang J, Xiang J, Zhang T, Wang H, et al. Pancreatic ductal adenocarcinoma holds unique features to form an immunosuppressive microenvironment: a narrative review. *J Pancreatol* 2022;5(4):174-85. doi:<https://doi.org/10.1097/JP9.000000000000109>
21. Murphy KJ, Chambers CR, Herrmann D, Timpson P, Pereira BA. Dynamic stromal alterations influence tumor-stroma crosstalk to promote pancreatic cancer and treatment resistance. *Cancers (Basel)* 2021;13(14):3481. doi:<https://doi.org/10.3390/cancers13143481>
22. Halbrook CJ, Lyssiotis CA, Pasca di Magliano M, Maitra A. Pancreatic cancer: advances and challenges. *Cell* 2023;186(8):1729-54. doi:<https://doi.org/10.1016/j.cell.2023.02.014>
23. Yang J, Wen C, Guo H, Chai Y, Sun G, Cheng H. Targeting early diagnosis and treatment of pancreatic cancer among the diabetic population: a comprehensive review of biomarker screening strategies. *Diabetol Metab Syndr* 2025;17(1):176. doi:<https://doi.org/10.1186/s13098-025-01750-4>
24. Zheng Z, Lu Z, Yan F, Song Y. The role of novel biomarkers in the early diagnosis of pancreatic cancer: a systematic review and meta-analysis. *PLoS One* 2025;20(5):e0322720. doi:<https://doi.org/10.1371/journal.pone.0322720>
25. Xu X, Long C, Li M, Shen C, Ye Q, Li Y, et al. Systematic review and meta-analysis: diagnostic accuracy of exosomes in pancreatic cancer. *World J Surg Oncol* 2025;23(1):51. doi:<https://doi.org/10.1186/s12957-025-03666-9>
26. Kawai M, Fukuda A, Otomo R, Obata S, Minaga K, Asada M, et al. Early detection of pancreatic cancer by comprehensive serum miRNA sequencing with automated machine learning. *Br J Cancer* 2024;131(7):1158-68. doi:<https://doi.org/10.1038/s41416-024-02794-5>
27. City of Hope Medical Center. Early Detection of Pancreatic Cancer: Prospective Study [Internet]. 2024. Available from: <https://clinicaltrials.gov/study/NCT06388967>.

28. Hasheminasabgorji E, Mishan MA, Khazeei Tabari MA, Bagheri A. miR-638: a promising cancer biomarker with therapeutic potential. *Curr Mol Med* 2023;23(5):377-89. doi:<https://doi.org/10.2174/1566524022666220405125900>
29. Azani A, Sharafi M, Doachi R, Akbarzadeh S, Lorestani P, Haji Kamanaj Olia A, et al. Applications of CRISPR-Cas9 in mitigating cellular senescence and age-related disease progression. *Clin Exp Med* 2025;25(1):237. doi:<https://doi.org/10.1007/s10238-025-01771-3>
30. Habibi B, Gholami S, Bagheri A, Fakhar M, Moradi A, Khazeei Tabari MA. Cystic echinococcosis microRNAs as potential noninvasive biomarkers: current insights and upcoming perspective. *Expert Rev Mol Diagn* 2023;23(10):885-94. doi:<https://doi.org/10.1080/14737159.2023.2246367>
31. Akbari Kordkheyli V, Khonakdar Tarsi A, Mishan MA, Tafazoli A, Bardania H, Zarpou S, et al. Effects of quercetin on microRNAs: a mechanistic review. *J Cell Biochem* 2019;120(8):12141-55. doi:<https://doi.org/10.1002/jcb.28663>
32. Oliveto S, Mancino M, Manfrini N, Biffo S. Role of microRNAs in translation regulation and cancer. *World J Biol Chem* 2017;8(1):45-56. doi:<https://doi.org/10.4331/wjbc.v8.i1.45>
33. Han X, Medeiros LJ, Zhang YH, You MJ, Andreeff M, Konopleva M, et al. High expression of human homologue of murine double minute 4 and the short splicing variant, HDM4-S, in bone marrow in patients with acute myeloid leukemia or myelodysplastic syndrome. *Clin Lymphoma Myeloma Leuk* 2016;16 Suppl:S30-8. doi:<https://doi.org/10.1016/j.clml.2016.03.012>
34. Haupt S, Mejía-Hernández JO, Vijayakumaran R, Keam SP, Haupt Y. The long and the short of it: the MDM4 tail so far. *J Mol Cell Biol* 2019;11(3):231-44. doi:<https://doi.org/10.1093/jmcb/mjz007>
35. Ghafouri-Fard S, Oskoei VK, Azari I, Taheri M. Suppressor of cytokine signaling (SOCS) genes are downregulated in breast cancer. *World J Surg Oncol* 2018;16(1):226. doi:<https://doi.org/10.1186/s12957-018-1529-9>
36. Wang X, Lang M, Zhao T, Feng X, Zheng C, Huang C, et al. Cancer-FOXP3 directly activated CCL5 to recruit FOXP3(+)Treg cells in pancreatic ductal adenocarcinoma. *Oncogene* 2017;36(21):3048-58. doi:<https://doi.org/10.1038/onc.2016.458>
37. Kim CH. FOXP3 and its role in the immune system. *Adv Exp Med Biol* 2009;665:17-29. doi:https://doi.org/10.1007/978-1-4419-1599-3_2
38. Roshani Asl E, Amini M, Najafi S, Mansoori B, Mokhtarzadeh A, Mohammadi A, et al. Interplay between MAPK/ERK signaling pathway and microRNAs: a crucial mechanism regulating cancer cell metabolism and tumor progression. *Life Sci* 2021;278:119499. doi:<https://doi.org/10.1016/j.lfs.2021.119499>
39. Ahmad S, Abbas M, Ullah MF, Aziz MH, Beylerli O, Alam MA, et al. Long non-coding RNAs regulated NF-κB signaling in cancer metastasis: micromanaging by not so small non-coding RNAs. *Semin Cancer Biol* 2022;85:155-63. doi:<https://doi.org/10.1016/j.semcancer.2021.07.015>
40. Khurana N, Dodhiawala PB, Bulle A, Lim KH. Deciphering the role of innate immune NF-κB pathway in pancreatic cancer. *Cancers (Basel)* 2020;12(9):2675. doi:<https://doi.org/10.3390/cancers12092675>
41. Ta N, Huang X, Zheng K, Zhang Y, Gao Y, Deng L, et al. miRNA-1290 promotes aggressiveness in pancreatic ductal adenocarcinoma by targeting IKK1. *Cell Physiol Biochem* 2018;51(2):711-28. doi:<https://doi.org/10.1159/000495328>
42. Lefler JE, MarElia-Bennett CB, Thies KA, Hildreth BE 3rd, Sharma SM, Pitarresi JR, et al. STAT3 in tumor fibroblasts promotes an immunosuppressive microenvironment in pancreatic cancer. *Life Sci Alliance* 2022;5(11):e202201460. doi:<https://doi.org/10.26508/lsa.202201460>

43. Li X, Jiang W, Li W, Dong S, Du Y, Zhang H, et al. Betulinic acid-mediated miRNA-365 inhibited the progression of pancreatic cancer. *Oncol Res* 2023;31(4):505-14. doi:<https://doi.org/10.32604/or.2023.026959>
44. Ardito CM, Grüner BM, Takeuchi KK, Lubeseder-Martellato C, Teichmann N, Mazur PK, et al. EGF receptor is required for KRAS-induced pancreatic tumorigenesis. *Cancer Cell* 2012;22(3):304-17. doi:<https://doi.org/10.1016/j.ccr.2012.07.024>
45. Liu J, Ye L, Lin K, Zhong T, Luo J, Wang T, et al. miR-4299 inhibits tumor progression in pancreatic cancer through targeting ADAM17. *Mol Cell Biochem* 2023;478(8):1727-42. doi:<https://doi.org/10.1007/s11010-022-04617-8>
46. Aiello NM, Brabletz T, Kang Y, Nieto MA, Weinberg RA, Stanger BZ. Upholding a role for EMT in pancreatic cancer metastasis. *Nature* 2017;547(7661):E7-8. doi:<https://doi.org/10.1038/nature22963>
47. Liu S, He X, Di Y, Li Q, Li F, Ma Y, et al. NamiRNA-enhancer network of miR-492 activates the NR2C1-TGF- β /Smad3 pathway to promote epithelial-mesenchymal transition of pancreatic cancer. *Carcinogenesis* 2023;44(2):153-65. doi:<https://doi.org/10.1093/carcin/bgac102>
48. Jafarzadeh A, Paknahad MH, Nemati M, Jafarzadeh S, Mahjoubin-Tehran M, Rajabi A, et al. Dysregulated expression and functions of microRNA-330 in cancers: a potential therapeutic target. *Biomed Pharmacother* 2022;146:112600. doi:<https://doi.org/10.1016/j.biopha.2021.112600>
49. Song F, Zhang L, Ji P, Zheng H, Zhao Y, Zhang W, et al. Altered expression and loss of heterozygosity of the migration and invasion inhibitory protein (MIIP) gene in breast cancer. *Oncol Rep* 2015;33(6):2771-8. doi:<https://doi.org/10.3892/or.2015.3905>
50. Niu Y, Jin Y, Deng SC, Deng SJ, Zhu S, Liu Y, et al. MiRNA-646-mediated reciprocal repression between HIF-1 α and MIIP contributes to tumorigenesis of pancreatic cancer. *Oncogene* 2018;37(13):1743-58. doi:<https://doi.org/10.1038/s41388-017-0082-2>
51. Han C, Zheng H, Hu D, Wang M, Wang H, Zhang L. Hsa_circ_0007401 regulates gemcitabine resistance of pancreatic cancer through the hsa-miR-6509-3p/fli1 axis. *Medicine (Baltimore)* 2023;102(21):e33775. doi:<https://doi.org/10.1097/md.00000000000033775>
52. Chen AY, Zhang K, Liu GQ. LncRNA LINP1 promotes malignant progression of pancreatic cancer by adsorbing microRNA-491-3p. *Eur Rev Med Pharmacol Sci* 2020;24(18):9315-24. doi:https://doi.org/10.26355/eurrev_202009_23013
53. Ye H, Zhou Q, Zheng S, Li G, Lin Q, Ye L, et al. FEZF1-AS1/miR-107/ZNF312B axis facilitates progression and Warburg effect in pancreatic ductal adenocarcinoma. *Cell Death Dis* 2018;9(2):34. doi:<https://doi.org/10.1038/s41419-017-0052-1>
54. Liu B, Wang W, Sun S, Ding H, Lan L, Li X, et al. Knockdown of lncRNA ABHD11-AS1 suppresses the tumorigenesis of pancreatic cancer via sponging miR-1231. *Onco Targets Ther* 2020;13:11347-58. doi:<https://doi.org/10.2147/ott.S259598>
55. Meng D, Li C, Wu C. Effects of LINC02532 targeting miR-145 on proliferation, migration, invasion and apoptosis of pancreatic cancer stem cells. *Chin J Tissue Eng Res* 2022;26(1):52.
56. Chen B, Li Q, Zhou Y, Wang X, Zhang Q, Wang Y, et al. The long coding RNA AFAP1-AS1 promotes tumor cell growth and invasion in pancreatic cancer through upregulating the IGF1R oncogene via sequestration of miR-133a. *Cell Cycle* 2018;17(16):1949-66. doi:<https://doi.org/10.1080/15384101.2018.1496741>
57. Liu PJ, Pan YH, Wang DW, You D. Long non-coding RNA XIST promotes cell proliferation of pancreatic cancer through miR-137 and Notch1 pathway. *Eur Rev Med Pharmacol Sci* 2020;24(23):12161-70. doi:https://doi.org/10.26355/eurrev_202012_24005

58. Yang M, Sun S, Guo Y, Qin J, Liu G. Long non-coding RNA MCM3AP-AS1 promotes growth and migration through modulating FOXK1 by sponging miR-138-5p in pancreatic cancer. *Mol Med* 2019;25(1):55. doi:<https://doi.org/10.1186/s10020-019-0121-2>
59. Zhang M, Ma S, Li X, Yu H, Tan Y, He J, et al. Long non-coding RNA CTBP1-AS2 upregulates USP22 to promote pancreatic carcinoma progression by sponging miR-141-3p. *Mol Med Rep* 2022;25(3):86. doi:<https://doi.org/10.3892/mmr.2022.12602>
60. Sun J, Zhang Y. LncRNA XIST enhanced TGF- β 2 expression by targeting miR-141-3p to promote pancreatic cancer cells invasion. *Biosci Rep* 2019;39(7):BSR20190332. doi:<https://doi.org/10.1042/bsr20190332>
61. Cui XP, Wang CX, Wang ZY, Li J, Tan YW, Gu ST, et al. LncRNA TP73-AS1 sponges miR-141-3p to promote the migration and invasion of pancreatic cancer cells through the up-regulation of BDH2. *Biosci Rep* 2019;39(3):BSR20181937. doi:<https://doi.org/10.1042/bsr20181937>
62. Liu YF, Luo D, Li X, Li ZQ, Yu X, Zhu HW. PVT1 knockdown inhibits autophagy and improves gemcitabine sensitivity by regulating the miR-143/HIF-1 α /VMP1 axis in pancreatic cancer. *Pancreas* 2021;50(2):227-34. doi:<https://doi.org/10.1097/mpa.0000000000001747>
63. Fu X, Sun G, Tu S, Fang K, Xiong Y, Tu Y, et al. Hsa_circ_0046523 mediates an immunosuppressive tumor microenvironment by regulating miR-148a-3p/PD-L1 axis in pancreatic cancer. *Front Oncol* 2022;12:877376. doi:<https://doi.org/10.3389/fonc.2022.877376>
64. Yuan ZJ, Yu C, Hu XF, He Y, Chen P, Ouyang SX. LINC00152 promotes pancreatic cancer cell proliferation, migration and invasion via targeting miR-150. *Am J Transl Res* 2020;12(5):2241-56.
65. Mortoglou M, Manić L, Buha Djordjevic A, Bulat Z, Đorđević V, Manis K, et al. Nickel's role in pancreatic ductal adenocarcinoma: potential involvement of microRNAs. *Toxics* 2022;10(3):148. doi:<https://doi.org/10.3390/toxics10030148>
66. Fernandez-Castañer E, Vila-Casadesus M, Vila-Navarro E, Parra C, Lozano JJ, Castells A, et al. MicroRNAs deregulated in intraductal papillary mucinous neoplasm converge on actin cytoskeleton-related pathways that are maintained in pancreatic ductal adenocarcinoma. *Cancers (Basel)* 2021;13(10):2369. doi:<https://doi.org/10.3390/cancers13102369>
67. An Y, Chen XM, Yang Y, Mo F, Jiang Y, Sun DL, et al. LncRNA DLX6-AS1 promoted cancer cell proliferation and invasion by attenuating the endogenous function of miR-181b in pancreatic cancer. *Cancer Cell Int* 2018;18:143. doi:<https://doi.org/10.1186/s12935-018-0643-7>
68. Gao ZQ, Wang JF, Chen DH, Ma XS, Yang W, Zhe T, et al. Long non-coding RNA GAS5 antagonizes the chemoresistance of pancreatic cancer cells through down-regulation of miR-181c-5p. *Biomed Pharmacother* 2018;97:809-17. doi:<https://doi.org/10.1016/j.biopha.2017.10.157>
69. Ghafouri-Fard S, Khoshbakht T, Taheri M, Ebrahimzadeh K. A review on the role of PCAT6 lncRNA in tumorigenesis. *Biomed Pharmacother* 2021;142:112010. doi:<https://doi.org/10.1016/j.biopha.2021.112010>
70. Fang Z, Ruan B, Zhong M, Xiong J, Jiang Y, Song Z. Silencing LINC00491 inhibits pancreatic cancer progression through miR-188-5p-induced inhibition of ZFP91. *J Cancer* 2022;13(6):1808-19. doi:<https://doi.org/10.7150/jca.65071>
71. Yang X, Wang L, Zhou F, Ye S, Sun Q. Yin Yang 1-induced activation of LINC01133 facilitates the progression of pancreatic cancer by sponging miR-199b-5p to upregulate myelin regulatory factor expression. *Bioengineered* 2022;13(5):13352-65. doi:<https://doi.org/10.1080/21655979.2022.2038900>
72. Zhuo M, Yuan C, Han T, Cui J, Jiao F, Wang L. A novel feedback loop between high MALAT-1 and low miR-200c-3p promotes cell migration and invasion in pancreatic ductal adenocarcinoma and is predictive of poor prognosis. *BMC Cancer* 2018;18(1):1032. doi:<https://doi.org/10.1186/s12885-018-4954-9>

73. Zhang H, Feng X, Zhang M, Liu A, Tian L, Bo W, et al. Long non-coding RNA CASC2 upregulates PTEN to suppress pancreatic carcinoma cell metastasis by downregulating miR-21. *Cancer Cell Int* 2019;19:18. doi:<https://doi.org/10.1186/s12935-019-0728-y>
74. Zhang J, Shen Y, Ma D, Li Z, Zhang Z, Jin W. SLCO4A1-AS1 mediates pancreatic cancer development via miR-4673/KIF21B axis. *Open Med (Wars)* 2022;17(1):253-65. doi:<https://doi.org/10.1515/med-2022-0418>
75. Li L, Wang N, Wang J, Li J. Hsa_circRNA_001859 regulates pancreatic cancer progression and epithelial-mesenchymal transition through the miR-21-5p/SLC38A2 pathway. *Cancer Biomark* 2023;37(1):39-52. doi:<https://doi.org/10.3233/cbm-220229>
76. Xu C, Ye Q, Ye C, Liu S. circACTR2 attenuates gemcitabine chemoresistance in pancreatic cancer through PTEN mediated PI3K/AKT signaling pathway. *Biol Direct* 2023;18(1):14. doi:<https://doi.org/10.1186/s13062-023-00368-8>
77. Li J, Zhang J, Tao S, Hong J, Zhang Y, Chen W. Prognostication of pancreatic cancer using the cancer genome atlas based ferroptosis-related long non-coding RNAs. *Front Genet* 2022;13:838021. doi:<https://doi.org/10.3389/fgene.2022.838021>
78. Li X, Zhou S, Fan T, Feng X. lncRNA DGCR 5/miR-27a-3p/BNIP3 promotes cell apoptosis in pancreatic cancer by regulating the p38 MAPK pathway. *Int J Mol Med* 2020;46(2):729-39. doi:<https://doi.org/10.3892/ijmm.2020.4632>
79. Zhao X, Liu Y, Li Z, Zheng S, Wang Z, Li W, et al. Linc00511 acts as a competing endogenous RNA to regulate VEGFA expression through sponging hsa-miR-29b-3p in pancreatic ductal adenocarcinoma. *J Cell Mol Med* 2018;22(1):655-67. doi:<https://doi.org/10.1111/jcmm.13351>
80. Zhu X, Niu X, Ge C. Inhibition of LINC00994 represses malignant behaviors of pancreatic cancer cells: interacting with miR-765-3p/RUNX2 axis. *Cancer Biol Ther* 2019;20(6):799-811. doi:<https://doi.org/10.1080/15384047.2018.1564566>
81. Chen G, Xu L, Ye G, Lin J, Meng Z, Shen Y. Overexpression of a long non-coding RNA BC037916 is associated with pancreatic tumorigenesis and poor prognosis. *Onco Targets Ther* 2020;13:13451-63. doi:<https://doi.org/10.2147/ott.S282350>
82. Qi R, Bai Y, Li K, Liu N, Xu Y, Dal E, et al. Cancer-associated fibroblasts suppress ferroptosis and induce gemcitabine resistance in pancreatic cancer cells by secreting exosome-derived ACSL4-targeting miRNAs. *Drug Resist Updat* 2023;68:100960. doi:<https://doi.org/10.1016/j.drug.2023.100960>
83. Natesh NS, White BM, Bennett MMC, Uz M, Kalari Kandy RR, Batra SK, et al. Emerging role of miR-345 and its effective delivery as a potential therapeutic candidate in pancreatic cancer and other cancers. *Pharmaceutics* 2021;13(12):1987. doi:<https://doi.org/10.3390/pharmaceutics13121987>
84. Sun Z, Zhang B, Cui T. Long non-coding RNA XIST exerts oncogenic functions in pancreatic cancer via miR-34a-5p. *Oncol Rep* 2018;39(4):1591-600. doi:<https://doi.org/10.3892/or.2018.6245>
85. Zhu P, Ge N, Liu D, Yang F, Zhang K, Guo J, et al. Preliminary investigation of the function of hsa_circ_0006215 in pancreatic cancer. *Oncol Lett* 2018;16(1):603-11. doi:<https://doi.org/10.3892/ol.2018.8652>
86. Zhao L, Kong H, Sun H, Chen Z, Chen B, Zhou M. LncRNA-PVT1 promotes pancreatic cancer cells proliferation and migration through acting as a molecular sponge to regulate miR-448. *J Cell Physiol* 2018;233(5):4044-55. doi:<https://doi.org/10.1002/jcp.26072>
87. Gong Y, Dai HS, Shu JJ, Liu W, Bie P, Zhang LD. LNC00673 suppresses proliferation and metastasis of pancreatic cancer via target miR-504/HNF1A. *J Cancer* 2020;11(4):940-8. doi:<https://doi.org/10.7150/jca.32855>

88. Wu H, Li A, Zheng Q, Gu J, Zhou W. LncRNA LZTS1-AS1 induces proliferation, metastasis and inhibits autophagy of pancreatic cancer cells through the miR-532 /TWIST1 signaling pathway. *Cancer Cell Int* 2023;23(1):130. doi:<https://doi.org/10.1186/s12935-023-02979-7>
89. Chen T, Lei S, Zeng Z, Zhang J, Xue Y, Sun Y, et al. Linc00261 inhibits metastasis and the WNT signaling pathway of pancreatic cancer by regulating a miR-552-5p/FOXO3 axis. *Oncol Rep* 2020;43(3):930-42. doi:<https://doi.org/10.3892/or.2020.7480>
90. Zhong M, Fang Z, Ruan B, Xiong J, Li J, Song Z. LINC01128 facilitates the progression of pancreatic cancer through up-regulation of LDHA by targeting miR-561-5p. *Cancer Cell Int* 2022;22(1):93. doi:<https://doi.org/10.1186/s12935-022-02490-5>
91. Zhang WT, Zhang JJ, Shao Q, Wang YK, Jia JP, Qian B, et al. FGD5-AS1 is an oncogenic lncRNA in pancreatic cancer and regulates the Wnt/ β -catenin signaling pathway via miR-577. *Oncol Rep* 2022;47(1):21. doi:<https://doi.org/10.3892/or.2021.8232>
92. Deng PC, Chen WB, Cai HH, An Y, Wu XQ, Chen XM, et al. LncRNA SNHG14 potentiates pancreatic cancer progression via modulation of annexin A2 expression by acting as a competing endogenous RNA for miR-613. *J Cell Mol Med* 2019;23(11):7222-32. doi:<https://doi.org/10.1111/jcmm.14467>
93. Ge JN, Yan D, Ge CL, Wei MJ. LncRNA C9orf139 can regulate the growth of pancreatic cancer by mediating the miR-663a/Sox12 axis. *World J Gastrointest Oncol* 2020;12(11):1272-87. doi:<https://doi.org/10.4251/wjgo.v12.i11.1272>
94. Safa AR. Epithelial-mesenchymal transition: a hallmark in pancreatic cancer stem cell migration, metastasis formation, and drug resistance. *J Cancer Metastasis Treat* 2020;6:40. doi:<https://doi.org/10.20517/2394-4722.2020.55>
95. Cao W, Zhou G. LncRNA SNHG12 contributes proliferation, invasion and epithelial-mesenchymal transition of pancreatic cancer cells by absorbing miRNA-320b. *Biosci Rep* 2020;40(6):BSR20200805. doi:<https://doi.org/10.1042/bsr20200805>
96. Fernandez-Castañer E, Vila-Casadesus M, Vila-Navarro E, Parra C, Lozano JJ, Castells A, et al. MicroRNAs deregulated in intraductal papillary mucinous neoplasm converge on actin cytoskeleton-related pathways that are maintained in pancreatic ductal adenocarcinoma. *Cancers (Basel)* 2021;13(10):2369. doi:<https://doi.org/10.3390/cancers13102369>
97. Abue M, Yokoyama M, Shibuya R, Tamai K, Yamaguchi K, Sato I, et al. Circulating miR-483-3p and miR-21 is highly expressed in plasma of pancreatic cancer. *Int J Oncol* 2015;46(2):539-47. doi:<https://doi.org/10.3892/ijo.2014.2743>
98. Akamatsu M, Makino N, Ikeda Y, Matsuda A, Ito M, Kakizaki Y, et al. Specific MAPK-associated microRNAs in serum differentiate pancreatic cancer from autoimmune pancreatitis. *PLoS One* 2016;11(7):e0158669. doi:<https://doi.org/10.1371/journal.pone.0158669>
99. Panda AC. Circular RNAs act as miRNA sponges. In: Xiao J, ed. *Circular RNAs: Biogenesis and Functions*. Singapore: Springer; 2018. p. 67-79. doi:https://doi.org/10.1007/978-981-13-1426-1_6
100. Parker SJ, Amendola CR, Hollinshead KER, Yu Q, Yamamoto K, Encarnación-Rosado J, et al. Selective alanine transporter utilization creates a targetable metabolic niche in pancreatic cancer. *Cancer Discov* 2020;10(7):1018-37. doi:<https://doi.org/10.1158/2159-8290.Cd-19-0959>
101. Sun HM, Mi YS, Yu FD, Han Y, Liu XS, Lu S, et al. SERPINA4 is a novel independent prognostic indicator and a potential therapeutic target for colorectal cancer. *Am J Cancer Res* 2016;6(8):1636-49.

102. Qi R, Bai Y, Li K, Liu N, Xu Y, Dal E, et al. Cancer-associated fibroblasts suppress ferroptosis and induce gemcitabine resistance in pancreatic cancer cells by secreting exosome-derived ACSL4-targeting miRNAs. *Drug Resist Updat* 2023;68:100960. doi:<https://doi.org/10.1016/j.drup.2023.100960>
103. Martin L, Chang HY. Uncovering the role of genomic "dark matter" in human disease. *J Clin Invest* 2012;122(5):1589-95. doi:<https://doi.org/10.1172/jci60020>
104. Li J, Hou S, Ye Z, Wang W, Hu X, Hang Q. Long non-coding RNAs in pancreatic cancer: biologic functions, mechanisms, and clinical significance. *Cancers (Basel)* 2022;14(9):2115. doi:<https://doi.org/10.3390/cancers14092115>
105. Xia R, Hu C, Ye Y, Zhang X, Li T, He R, et al. HNF1A regulates oxaliplatin resistance in pancreatic cancer by targeting 53BP1. *Int J Oncol* 2023;62(4):45. doi:<https://doi.org/10.3892/ijo.2023.5493>
106. Luo Z, Li Y, Wang H, Fleming J, Li M, Kang Y, et al. Hepatocyte nuclear factor 1A (HNF1A) as a possible tumor suppressor in pancreatic cancer. *PLoS One* 2015;10(3):e0121082. doi:<https://doi.org/10.1371/journal.pone.0121082>
107. Zhang Z, Ji S, Zhang B, Liu J, Qin Y, Xu J, et al. Role of angiogenesis in pancreatic cancer biology and therapy. *Biomed Pharmacother* 2018;108:1135-40. doi:<https://doi.org/10.1016/j.biopha.2018.09.136>
108. Lin TC. RUNX2 and cancer. *Int J Mol Sci* 2023;24(8):7001. doi:<https://doi.org/10.3390/ijms24087001>
109. McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: a review of clinical diagnosis, epidemiology, treatment and outcomes. *World J Gastroenterol* 2018;24(43):4846-61. doi:<https://doi.org/10.3748/wjg.v24.i43.4846>
110. Shams R, Saberi S, Zali M, Sadeghi A, Ghafouri-Fard S, Asadzadeh Aghdaei H. Identification of potential microRNA panels for pancreatic cancer diagnosis using microarray datasets and bioinformatics methods. *Sci Rep* 2020;10(1):7559. doi:<https://doi.org/10.1038/s41598-020-64569-1>
111. Condrat CE, Thompson DC, Barbu MG, Bugnar OL, Boboc A, Cretoiu D, et al. miRNAs as biomarkers in disease: latest findings regarding their role in diagnosis and prognosis. *Cells* 2020;9(2):276. doi:<https://doi.org/10.3390/cells9020276>
112. Valihrach L, Androvic P, Kubista M. Circulating miRNA analysis for cancer diagnostics and therapy. *Mol Aspects Med* 2020;72:100825. doi:<https://doi.org/10.1016/j.mam.2019.10.002>
113. Aita A, Millino C, Sperti C, Pacchioni B, Plebani M, De Pittà C, et al. Serum miRNA profiling for early PDAC diagnosis and prognosis: a retrospective study. *Biomedicines* 2021;9(7):845. doi:<https://doi.org/10.3390/biomedicines9070845>
114. Seyed Salehi A, Parsa-Nikoo N, Roshan-Farзад F, Shams R, Fathi M, Asadzadeh Aghdaei H, et al. MicroRNA-125a-3p, -4530, and -92a as a potential circulating microRNA panel for noninvasive pancreatic cancer diagnosis. *Dis Markers* 2022;2022:8040419. doi:<https://doi.org/10.1155/2022/8040419>
115. Álvarez-Hilario LG, Salmerón-Bárceñas EG, Ávila-López PA, Hernández-Montes G, Aréchaga-Ocampo E, Herrera-Goepfert R, et al. Circulating miRNAs as noninvasive biomarkers for PDAC diagnosis and prognosis in Mexico. *Int J Mol Sci* 2023;24(20):15193. doi:<https://doi.org/10.3390/ijms242015193>
116. Cui Z, Du L, Wang J, Li Z, Xu J, Ou S, et al. Overexpression of CENPL mRNA potentially regulated by miR-340-3p predicts the prognosis of pancreatic cancer patients. *BMC Cancer* 2022;22(1):1354. doi:<https://doi.org/10.1186/s12885-022-10450-5>
117. Li Y, Wang Z, Zhao F, Zeng J, Yang X. MicroRNA-190b expression predicts a good prognosis and attenuates the malignant progression of pancreatic cancer by targeting MEF2C and TCF4. *Oncol Rep* 2022;47(1):12. doi:<https://doi.org/10.3892/or.2021.8223>

118. Hirabayashi K, Miyazawa M, Takanashi Y, Morimachi M, Kawanishi A, Saika T, et al. miR-4653-3p overexpression is associated with a poor prognosis of pancreatic ductal adenocarcinoma via HIPK2 downregulation. *Sci Rep* 2022;12(1):17927. doi:<https://doi.org/10.1038/s41598-022-22950-2>
119. Shi W, Wartmann T, Accuffi S, Al-Madhi S, Perrakis A, Kahlert C, et al. Integrating a microRNA signature as a liquid biopsy-based tool for the early diagnosis and prediction of potential therapeutic targets in pancreatic cancer. *Br J Cancer* 2024;130(1):125-34. doi:<https://doi.org/10.1038/s41416-023-02488-4>
120. Baba S, Kawasaki T, Hirano S, Nakamura T, Asano T, Okazaki R, et al. A noninvasive urinary microRNA-based assay for the detection of pancreatic cancer from early to late stages: a case control study. *EClinicalMedicine* 2024;78:102936. doi:<https://doi.org/10.1016/j.eclinm.2024.102936>
121. Treekitkarnmongkol W, Dai J, Liu S, Sankaran D, Nguyen T, Balasenthil S, et al. Blood-based microRNA biomarker signature of early-stage pancreatic ductal adenocarcinoma with lead-time trajectory in prediagnostic samples. *Gastro Hep Adv* 2024;3(8):1098-115. doi:<https://doi.org/10.1016/j.gastha.2024.08.002>
122. Chakraborty A, Patton DJ, Smith BF, Agarwal P. miRNAs: potential as biomarkers and therapeutic targets for cancer. *Genes (Basel)* 2023;14(7):1375. doi:<https://doi.org/10.3390/genes14071375>
123. Krauss T, Heisz S, Honecker J, Prokopchuk O, Martignoni M, Janssen KP, et al. Specific miRNAs are associated with human cancer cachexia in an organ-specific manner. *J Cachexia Sarcopenia Muscle* 2023;14(3):1381-94. doi:<https://doi.org/10.1002/jcsm.13224>
124. Han S, Gonzalo DH, Feely M, Rinaldi C, Belsare S, Zhai H, et al. Stroma-derived extracellular vesicles deliver tumor-suppressive miRNAs to pancreatic cancer cells. *Oncotarget* 2018;9(5):5764-77. doi:<https://doi.org/10.18632/oncotarget.23532>
125. Verel-Yilmaz Y, Fernández JP, Schäfer A, Nevermann S, Cook L, Gercke N, et al. Extracellular vesicle-based detection of pancreatic cancer. *Front Cell Dev Biol* 2021;9:697939. doi:<https://doi.org/10.3389/fcell.2021.697939>
126. Shang D, Xie C, Hu J, Tan J, Yuan Y, Liu Z, et al. Pancreatic cancer cell-derived exosomal microRNA-27a promotes angiogenesis of human microvascular endothelial cells in pancreatic cancer via BTG2. *J Cell Mol Med* 2020;24(1):588-604. doi:<https://doi.org/10.1111/jcmm.14766>
127. Ma Y, Yu S, Zhao W, Lu Z, Chen J. miR-27a regulates the growth, colony formation and migration of pancreatic cancer cells by targeting Sprouty2. *Cancer Lett* 2010;298(2):150-8. doi:<https://doi.org/10.1016/j.canlet.2010.06.012>
128. Yu Z, Zhao S, Wang L, Wang J, Zhou J. miRNA-339-5p Plays an Important role in invasion and migration of pancreatic cancer cells. *Med Sci Monit* 2019;25:7509-17. doi:<https://doi.org/10.12659/msm.917038>
129. Li C, Zhou T, Chen J, Li R, Chen H, Luo S, et al. The role of exosomal miRNAs in cancer. *J Transl Med* 2022;20(1):6. doi:<https://doi.org/10.1186/s12967-021-03215-4>
130. Yang Z, Zhao N, Cui J, Wu H, Xiong J, Peng T. Exosomes derived from cancer stem cells of gemcitabine-resistant pancreatic cancer cells enhance drug resistance by delivering miR-210. *Cell Oncol (Dordr)* 2020;43(1):123-36. doi:<https://doi.org/10.1007/s13402-019-00476-6>
131. Jia E, Ren N, Shi X, Zhang R, Yu H, Yu F, et al. Extracellular vesicle biomarkers for pancreatic cancer diagnosis: a systematic review and meta-analysis. *BMC Cancer* 2022;22(1):573. doi:<https://doi.org/10.1186/s12885-022-09463-x>
132. Xu YF, Hannafon BN, Zhao YD, Postier RG, Ding WQ. Plasma exosome miR-196a and miR-1246 are potential indicators of localized pancreatic cancer. *Oncotarget* 2017;8(44):77028-40. doi:<https://doi.org/10.18632/oncotarget.20332>

133. Liu DSK, Puik JR, Patel BY, Venø MT, Vahabi M, Prado MM, et al. Unlocking the diagnostic power of plasma extracellular vesicle miR-200 family in pancreatic ductal adenocarcinoma. *J Exp Clin Cancer Res* 2024;43(1):189. doi:<https://doi.org/10.1186/s13046-024-03090-z>
134. Xu J, Shi W, Zhu Y, Zhang C, Nagelschmitz J, Doelling M, et al. Human multiethnic radiogenomics reveals low-abundance microRNA signature in plasma-derived extracellular vesicles for early diagnosis and molecular subtyping of pancreatic cancer. *Elife* 2025;14:RP103737. doi:<https://doi.org/10.7554/eLife.103737>
135. Baba S, Kawasaki T, Hirano S, Nakamura T, Asano T, Okazaki R, et al. A noninvasive urinary microRNA-based assay for the detection of pancreatic cancer from early to late stages: a case control study. *EClinicalMedicine* 2024;78:102936. doi:<https://doi.org/10.1016/j.eclinm.2024.102936>
136. Zhang C, Al-Shaheri FN, Alhamdani MSS, Bauer AS, Hoheisel JD, Schenk M, et al. Blood-based diagnosis and risk stratification of patients with pancreatic intraductal papillary mucinous neoplasm (IPMN). *Clin Cancer Res* 2023;29(8):1535-45. doi:<https://doi.org/10.1158/1078-0432.Ccr-22-2531>
137. Yang Z, LaRiviere MJ, Ko J, Till JE, Christensen T, Yee SS, et al. A multianalyte panel consisting of extracellular vesicle miRNAs and mRNAs, cfDNA, and CA19-9 shows utility for diagnosis and staging of pancreatic ductal adenocarcinoma. *Clin Cancer Res* 2020;26(13):3248-58. doi:<https://doi.org/10.1158/1078-0432.Ccr-19-3313>
138. He Y, Han Y, Xing J, Zhai X, Wang S, Xin S, et al. Kallistatin correlates with inflammation in abdominal aortic aneurysm and suppresses its formation in mice. *Cardiovasc Diagn Ther* 2020;10(2):107-23. doi:<https://doi.org/10.21037/cdt.2019.12.08>
139. Martinez-Quintanilla J, Seah I, Chua M, Shah K. Oncolytic viruses: overcoming translational challenges. *J Clin Invest* 2019;129(4):1407-18. doi:<https://doi.org/10.1172/jci122287>
140. Rovira-Rigau M, Raimondi G, Marín M, Gironella M, Alemany R, Fillat C. Bioselection reveals miR-99b and miR-485 as enhancers of adenoviral oncolysis in pancreatic cancer. *Mol Ther* 2019;27(1):230-43. doi:<https://doi.org/10.1016/j.ymthe.2018.09.016>
141. Brachtlova T, van Beusechem VW. Unleashing the full potential of oncolytic adenoviruses against cancer by applying RNA interference: the force awakens. *Cells* 2018;7(12):228. doi:<https://doi.org/10.3390/cells7120228>
142. Raimondi G, Gea-Sorlí S, Otero-Mateo M, Fillat C. Inhibition of miR-222 by oncolytic adenovirus-encoded miRNA sponges promotes viral oncolysis and elicits antitumor effects in pancreatic cancer models. *Cancers (Basel)* 2021;13(13):3233. doi:<https://doi.org/10.3390/cancers13133233>
143. Sicard F, Gayral M, Lulka H, Buscail L, Cordelier P. Targeting miR-21 for the therapy of pancreatic cancer. *Mol Ther* 2013;21(5):986-94. doi:<https://doi.org/10.1038/mt.2013.35>
144. Chaudhary AK, Mondal G, Kumar V, Kattel K, Mahato RI. Chemosensitization and inhibition of pancreatic cancer stem cell proliferation by overexpression of microRNA-205. *Cancer Lett* 2017;402:1-8. doi:<https://doi.org/10.1016/j.canlet.2017.05.007>
145. Kent OA, Chivukula RR, Mullendore M, Wentzel EA, Feldmann G, Lee KH, et al. Repression of the miR-143/145 cluster by oncogenic Ras initiates a tumor-promoting feed-forward pathway. *Genes Dev* 2010;24(24):2754-9. doi:<https://doi.org/10.1101/gad.1950610>
146. Garzon R, Marcucci G, Croce CM. Targeting microRNAs in cancer: rationale, strategies and challenges. *Nat Rev Drug Discov* 2010;9(10):775-89. doi:<https://doi.org/10.1038/nrd3179>
147. Park JK, Lee EJ, Esau C, Schmittgen TD. Antisense inhibition of microRNA-21 or -221 arrests cell cycle, induces apoptosis, and sensitizes the effects of gemcitabine in pancreatic adenocarcinoma. *Pancreas* 2009;38(7):e190-9. doi:<https://doi.org/10.1097/MPA.0b013e3181ba82e1>

148. Zhao Y, Zhao L, Ischenko I, Bao Q, Schwarz B, Nieß H, et al. Antisense inhibition of microRNA-21 and microRNA-221 in tumor-initiating stem-like cells modulates tumorigenesis, metastasis, and chemotherapy resistance in pancreatic cancer. *Target Oncol* 2015;10(4):535-48. doi:<https://doi.org/10.1007/s11523-015-0360-2>
149. Li Y, Chen Y, Li J, Zhang Z, Huang C, Lian G, et al. Co-delivery of microRNA-21 antisense oligonucleotides and gemcitabine using nanomedicine for pancreatic cancer therapy. *Cancer Sci* 2017;108(7):1493-503. doi:<https://doi.org/10.1111/cas.13267>
150. Akram F, Haq IU, Sahreen S, Nasir N, Naseem W, Imtiaz M, et al. CRISPR/Cas9: a revolutionary genome editing tool for human cancers treatment. *Technol Cancer Res Treat* 2022;21:15330338221132078. doi:<https://doi.org/10.1177/15330338221132078>
151. Aquino-Jarquín G. Emerging role of CRISPR/Cas9 technology for microRNAs editing in cancer research. *Cancer Res* 2017;77(24):6812-7. doi:<https://doi.org/10.1158/0008-5472.Can-17-2142>
152. Vorvis C, Hatziaepostolou M, Mahurkar-Joshi S, Koutsioumpa M, Williams J, Donahue TR, et al. Transcriptomic and CRISPR/Cas9 technologies reveal FOXA2 as a tumor suppressor gene in pancreatic cancer. *Am J Physiol Gastrointest Liver Physiol* 2016;310(11):G1124-37. doi:<https://doi.org/10.1152/ajpgi.00035.2016>
153. Chen W, Zhou Y, Zhi X, Ma T, Liu H, Chen BW, et al. Delivery of miR-212 by chimeric peptide-condensed supramolecular nanoparticles enhances the sensitivity of pancreatic ductal adenocarcinoma to doxorubicin. *Biomaterials* 2019;192:590-600. doi:<https://doi.org/10.1016/j.biomaterials.2018.11.035>
154. Arora S, Swaminathan SK, Kirtane A, Srivastava SK, Bhardwaj A, Singh S, et al. Synthesis, characterization, and evaluation of poly (D,L-lactide-co-glycolide)-based nanoformulation of miRNA-150: potential implications for pancreatic cancer therapy. *Int J Nanomedicine* 2014;9:2933-42. doi:<https://doi.org/10.2147/ijn.S61949>
155. Hu QL, Jiang QY, Jin X, Shen J, Wang K, Li YB, et al. Cationic microRNA-delivering nanovectors with bifunctional peptides for efficient treatment of PANC-1 xenograft model. *Biomaterials* 2013;34(9):2265-76. doi:<https://doi.org/10.1016/j.biomaterials.2012.12.016>
156. Su MJ, Aldawsari H, Amiji M. Pancreatic cancer cell exosome-mediated macrophage reprogramming and the role of microRNAs 155 and 125b2 transfection using nanoparticle delivery systems. *Sci Rep* 2016;6:30110. doi:<https://doi.org/10.1038/srep30110>
157. Botla SK, Savant S, Jandaghi P, Bauer AS, Mücke O, Moskalev EA, et al. Early epigenetic downregulation of microRNA-192 expression promotes pancreatic cancer progression. *Cancer Res* 2016;76(14):4149-59. doi:<https://doi.org/10.1158/0008-5472.Can-15-0390>
158. Li F, Liang J, Bai L. MicroRNA-449a functions as a tumor suppressor in pancreatic cancer by the epigenetic regulation of ATDC expression. *Biomed Pharmacother* 2018;103:782-9. doi:<https://doi.org/10.1016/j.biopha.2018.04.101>
159. Hong DS, Kang YK, Borad M, Sachdev J, Ejadi S, Lim HY, et al. Phase 1 study of MRX34, a liposomal miR-34a mimic, in patients with advanced solid tumours. *Br J Cancer* 2020;122(11):1630-7. doi:<https://doi.org/10.1038/s41416-020-0802-1>
160. Liu Y, Wang D, Zhou M, Chen H, Wang H, Min J, et al. The KRAS/Lin28B axis maintains stemness of pancreatic cancer cells via the let-7i/TET3 pathway. *Mol Oncol* 2021;15(1):262-78. doi:<https://doi.org/10.1002/1878-0261.12836>
161. Kang D, Lee Y, Lee JS. RNA-binding proteins in cancer: functional and therapeutic perspectives. *Cancers (Basel)* 2020;12(9):2699. doi:<https://doi.org/10.3390/cancers12092699>
162. Bhutia YD, Hung SW, Krentz M, Patel D, Lovin D, Manoharan R, et al. Differential processing of let-7a precursors influences RRM2 expression and chemosensitivity in pancreatic cancer: role of LIN-28 and SET oncoprotein. *PLoS One* 2013;8(1):e53436. doi:<https://doi.org/10.1371/journal.pone.0053436>

163. Sharifi Z, Talkhabi M, Taleahmad S. Identification of potential microRNA diagnostic panels and uncovering regulatory mechanisms in breast cancer pathogenesis. *Sci Rep* 2022;12(1):20135. doi:<https://doi.org/10.1038/s41598-022-24347-7>
164. Wu J, Cai H, Xiang YB, Matthews CE, Ye F, Zheng W, et al. Intra-individual variation of miRNA expression levels in human plasma samples. *Biomarkers* 2018;23(4):339-46. doi:<https://doi.org/10.1080/1354750x.2018.1427794>
165. Sindhu KJ, Venkatesan N, Karunakaran D. MicroRNA interactome multiomics characterization for cancer research and personalized medicine: an expert review. *Omics* 2021;25(9):545-66. doi:<https://doi.org/10.1089/omi.2021.0087>
166. He B, Zhao Z, Cai Q, Zhang Y, Zhang P, Shi S, et al. miRNA-based biomarkers, therapies, and resistance in Cancer. *Int J Biol Sci* 2020;16(14):2628-47. doi:<https://doi.org/10.7150/ijbs.47203>
167. To KKW, Fong W, Tong CWS, Wu M, Yan W, Cho WCS. Advances in the discovery of microRNA-based anticancer therapeutics: latest tools and developments. *Expert Opin Drug Discov* 2020;15(1):63-83. doi:<https://doi.org/10.1080/17460441.2020.1690449>
168. Casotti MC, Meira DD, Alves LNR, de Oliveira Bessa BG, Campanharo CV, Vicente CR, et al. Translational bioinformatics applied to the study of complex diseases. *Genes (Basel)* 2023;14(2):419. doi:<https://doi.org/10.3390/genes14020419>
169. Lee I, Baxter D, Lee MY, Scherler K, Wang K. The importance of standardization on analyzing circulating RNA. *Mol Diagn Ther* 2017;21(3):259-68. doi:<https://doi.org/10.1007/s40291-016-0251-y>