

Advances in MicroRNA-Based Approaches for Early Detection, Targeted Treatment, and Prognostic Prediction 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, indicating the urgent need for innovative diagnostic and therapeutic strategies. Micro ribonucleic acid (miRNAs) are small non-coding RNAs that regulate gene expression post-transcriptionally. Moreover, they have emerged as the critical modulators of PC pathogenesis and influence key oncogenic and tumor-suppressive pathways, including KRAS, NF- κ B, and AKT/STAT3. Dysregulated miRNAs (e.g., miR-21 and miR-155) drive tumor proliferation, epithelial-mesenchymal transition, and chemoresistance. Conversely, tumor-suppressive miRNAs (e.g., 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. In addition, 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, such as 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. Overall, 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

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 Moreover, this type of cancer is associated with various risk factors, encompassing environmental and genetic triggers. However, the relative contribution of some factors (e.g., obesity) remains

debated, with cohort studies reporting inconsistent associations depending on population and methodological design.³ Micro ribonucleic acid (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} Additionally, 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 as well as the downregulation of miR-128⁸ and miR-29c,⁹ which influence critical signaling

pathways, including extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK), protein kinase B/signal transducer and activator of transcription 3 (AKT/STAT3), and nuclear factor kappa B (NF- κ B). In particular, miR-21 has a multifaceted role; it is implicated in proliferation, epithelial-mesenchymal transition (EMT), anti-apoptosis, and angiogenesis via targets like phosphatase and tensin homolog (PTEN) and vascular endothelial growth factor (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 apoptosis, proliferation, invasion, and metastasis processes.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 that are released by virtually all cell types.¹³ They 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} The noninvasive prediction of outcomes is a critical objective in medicine, as it can facilitate early diagnosis, prognosis, and therapeutic decision-making. It is noteworthy that 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 (e.g., blood, urine, and saliva) can provide valuable insights into cancer development and progression. Further, altered miRNA profiles within EVs have been linked to specific cancer types, making them potential noninvasive biomarkers for early detection and prognosis.¹⁸ Furthermore, tumor-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 essential effect on pancreatic ductal adenocarcinoma (PDAC) progression.²⁰ Crucially, emerging evidence indicates 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 nearly 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 According to recent meta-analytic data, miRNA-only biomarker panels achieve high diagnostic accuracy with a pooled sensitivity of 88%, a specificity of 91% and an area under the curve (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 a sensitivity of 96% and a specificity of 90%.²⁵ By contrast, combining CA19-9 with circulating miRNAs has shown substantially 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 display superior diagnostic performance compared to single miRNAs, especially when combined with established markers, including CA19-9.²⁶ Similarly, translational momentum is building through ongoing prospective clinical studies, such as the PANXEON trial, which aims to validate an exosome-based miRNA signature for the 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. It is noteworthy that miRNAs have risen to prominence as pivotal molecules governing the pathobiology of PC. Therefore, this review aims to consolidate the current understanding of miRNAs 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, the study seeks to shed light on the promise and challenges of harnessing miRNAs in the fight against PC.

Micro Ribonucleic Acid Biogenesis and Activity

MiRNAs are small non-coding RNA molecules that are crucial for gene regulation. Their formation involves a complex, tightly regulated process from nuclear transcription to functional miRNA maturation, indicating 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. Then, exportin-5, along with Ran-GTP, 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, which are essential for miRNA function. The passenger strand is usually degraded. Additionally, the mature miRNA in RISC directs the complex to its target messenger RNA (mRNA), leading to gene silencing.³¹ Moreover, miRNAs bind to target mRNAs, typically in the 3' UTR, through partial sequence complementarity. This binding can cause translational repression or degradation of the mRNA, resulting in reduced expression of the target gene (Figure 1).³²

Role of Micro Ribonucleic Acids in Pancreatic Cancer

Role of Micro Ribonucleic Acids in the Pathogenesis of Pancreatic Cancer

The downregulation of miR-128, which promotes apoptosis, is closely associated with the protein MDM4 (MDMX), which is a key regulator of the tumor suppressor p53. MDM4 binds to p53, inhibiting its activity and preventing it from performing tumor-suppressive functions (e.g., regulating the cell cycle and inducing apoptosis).⁸ In addition, the balance of p53 activity is crucial for proper cellular responses to stress and damage. The dysregulation or overexpression of MDM4 can lead to p53 inactivation, contributing to the development and progression of PC.^{33,34} Further, the upregulation of miR-155, leading to structural and metabolic changes in pancreatic cells, is mediated through the suppressors of cytokine signaling 1 (SOCS1) and forkhead box P3 (FOXP3) pathway, with reduced SOCS1 and Foxp3 levels associated with the severity

of cachexia in PC patients.⁶ The protein family known as SOCS1 is characterized as the direct controller 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, the elevated expression levels of Foxp3 have shown a notable association with tumor invasion in PDAC.^{36,37} Likewise, 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, which is a signaling cascade that holds profound relevance for PC progression.⁹ This pathway has a key role in transducing extracellular signals and regulating essential cellular processes, such as proliferation, differentiation, and survival. In PC, the dysregulated activation of this pathway is frequently 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 the 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

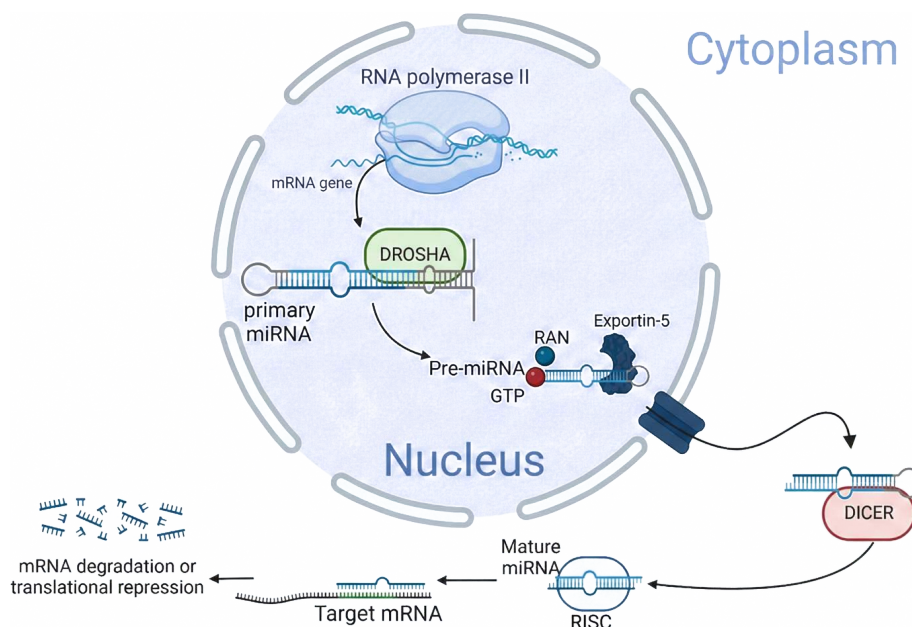


Figure 1. Schematic Representation of the MicroRNA Biogenesis and Gene Silencing Pathway

Note. MiRNA: Micro ribonucleic acid; RISC: Ribonucleic acid-induced silencing complex; pri-miRNAs: Primary micro ribonucleic acids; pre-miRNAs: Precursor micro ribonucleic acids. pri-miRNAs are transcribed in the nucleus by RNA polymerase II from miRNA genes and form hairpin structures. In addition, pri-miRNAs are cleaved by the microprocessor complex containing the RNase III enzyme DROSHA, generating 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 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.

being significantly influenced by the presence and activity of IKK1.⁴¹ Similarly, the AKT/STAT3 axis is crucial in PC, driving disease progression and treatment resistance. The 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 Thus, 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 A disintegrin and metalloproteinase 17 (ADAM17) plays a vital 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 The downregulation of miR-4299d inhibits cell proliferation and 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 In addition, miR-492 has 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 transforming growth factor beta (TGF- β)/Smad3 pathway, promoting EMT in PC.⁴⁷ Furthermore, miR-561-5p, when upregulated, is associated with the promotion of cell proliferation, migration, invasion, EMT, and cell growth.⁴⁸ Further, migration and invasion inhibitory protein (MIIP) is a protein that plays a role in regulating cell migration and invasion.⁴⁹ Hypoxia-inducible factor 1 alpha (HIF-1 α) is also 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 Mortoglou et al explored the role of miRNAs in EMT and found that knocking out miR-21 in PDAC cells reversed EMT, resulting in decreased cell proliferation and invasion (Table 1).⁷

Role of Micro Ribonucleic Acid in Differentiating Pancreatic Neoplasms

Pancreatic neoplasms, including PDAC, intraductal papillary mucinous neoplasms (IPMNs), and pancreatic neuroendocrine tumors, 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. Some studies have identified distinct miRNA expression profiles between PDAC and IPMNs. For instance, Fernandez-Castañer et al 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. Their findings revealed that miRNA alterations contribute to the structural and metabolic changes observed 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 alterations 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 It is noteworthy that the integration of miRNA profiling into clinical practices 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. Such biomarkers can improve specificity while reducing misdiagnosis in clinical practice.⁹⁸

Targeting Micro Ribonucleic Acids by Other Non-Coding Ribonucleic Acids 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 long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and even protein-coding mRNAs, which compete for shared miRNAs in order 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 (GEM) 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. Additionally, *FLI1* expression was significantly reduced in GEM-resistant PC patients.⁵¹

A similar study on GEM resistance in PC cells demonstrated 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 its significant implications in cancer. Moreover, separate investigations have underscored the pivotal role of SLC38A2 in the context of PC.¹⁰⁰ Likewise, 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 Similarly, 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 the upregulation of SERPINA4.⁸⁵

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 inhibition of 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 and 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
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 the 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, and 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 pancreatic cancer (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
miR-21-5p	Upregulation	Promotion of cell proliferation, migration, invasion, and epithelial-mesenchymal transition (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 and inhibition of ferroptosis	ACSL4	82
miR-345	Upregulation	Tumor development, metastasis, and chemoresistance	BCL2 and CCL8	83
miR-34a-5p	Downregulation	Promotion of migration, invasion, and proliferation	XIST	84

Table 1. Continued.

MiRNA (Biomarker)	Alteration	Cellular Function	Target	References
miR-365	Downregulation	Inhibition of proliferation and invasion and promotion of apoptosis	AKT/STAT3	43
miR-378a-3p	Downregulation	Promotion of cell migration/ <i>hsa_circ_0006215</i> , <i>miR-378a-3p</i> , and <i>SERPINA4</i> signaling pathways	<i>SERPINA4</i>	85
miR-4299d	Downregulation	Inhibition of PC cell proliferation, invasion, promotion of apoptosis, reduction of PC tumor growth, and regulation of immune escape	<i>ADAM17</i>	45
miR-448	Downregulation	Promotion of proliferation and migration	<i>SERBP1</i>	86
miR-4673/miR-876-3p	Downregulation	Promotion of cell growth, migration, invasion, and induced cell apoptosis	<i>SLCO4A1-AS1</i>	74
miR-492	Upregulation	Promotion of cell proliferation, migration, and invasion, activation of <i>NR2C1/NDUFA12/TMCC3</i> genes, activation of the <i>TGF-β/Smad3</i> pathway, and promotion of EMT	<i>NR2C1</i> , <i>NDUFA12</i> , <i>TMCC3</i> , and <i>TGF-β/Smad3</i>	47
miR-497-5p	Downregulation	Promotion of cell proliferation, invasion, and migration	<i>IGF1R</i>	73
miR-504	Upregulation	Promotion of cell apoptosis, viability, and migration	<i>HNF1A</i>	87
miR-532	Downregulation	Inhibition of proliferation, metastasis, and promotion of autophagy	<i>TWIST1</i>	88
miR-552-5p	Upregulation	Promotion of migration and invasion	<i>FOXO3</i>	89
miR-561-5p	Upregulation	Promotion of cell proliferation, migration and invasion and epithelial-mesenchymal transition and cell growth	<i>LINC01128</i>	90
miR-577	Downregulation	Promotion of cell proliferation, migration, and invasion	<i>FGD5-AS1</i>	91
miR-613	Downregulation	Promotion of cell proliferation, growth, and invasion	<i>ANXA2</i>	92
miR-646	Upregulation	Promotion of proliferation and invasion	<i>MIIP/(HIF-1α)</i>	50
miR-663a	Downregulation	Promotion of proliferation, invasion, and migration	<i>Sox12</i>	93
miR-665	Downregulation	Promotion of proliferation, cell migration, invasion, and tumor metastasis	<i>hsa_circ_0006215</i> , <i>miR-378a-3p</i> , and <i>SERPINA4</i> signaling pathways	94
miR-765-3p	Downregulation	Inhibition of growth, migration, invasion, promotion of G1 cell cycle arrest, and apoptosis	<i>RUNX2</i>	80
miRNA-320b	Downregulation	Promotion of proliferation, invasion and epithelial–mesenchymal transition	<i>SNHG12</i>	95

Note. MiRNA: Micro ribonucleic acid; PDAC: Pancreatic ductal adenocarcinoma.

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} Further, *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 miRNAs, lncRNAs can influence the expression of key genes and signal transduction pathways, thereby impacting the development and progression of PC.¹⁰⁴ Studies indicate that lncRNA *XIST* promotes PC cell proliferation by interacting with *miR-137* and reducing its expression. Furthermore, *XIST* 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 confirmed 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 demonstrated that there is a direct interaction between *miR-141-3p* and *XIST*, and *miR-141-3p* negatively

regulates *TGF-β2* expression.⁶⁰ *XIST* promotes PC cell proliferation, migration, invasion, inhibiting apoptosis. Moreover, *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 et al 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 In addition, lncRNA *ABHD11-AS1* is another non-coding RNA that 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 PC by modulating the *miR-504/HNF1A* pathway. Additionally, *miR-504* has been identified as a target of *LINC00673* in PC.⁸⁷ The overexpression of *LINC02532* and underexpression of *miR-145* are associated with increased cancer stem cell aggressiveness, while downregulating *LINC02532* and upregulating *miR-145* inhibit proliferation, migration, and invasion, and induce 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 insulin-like growth factor 1 receptor (IGF1R) and the MEK/ERK pathway. Accordingly, AFAP1-AS1 has promise as both a diagnostic marker and a therapeutic focus for PC.⁵⁶ In PC, the upregulated lncRNA SNHG14 accelerates tumor progression by acting as a ceRNA for miR-613, modulating Annexin A2 expression.⁹² Silencing LINC00491 inhibits PC cell migration, invasion, proliferation, and tumor growth. Further, LINC00491 interacts with miR-188-5p, which targets ZFP91. Inhibiting miR-188-5p restores 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. Moreover, 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 Additionally, lncRNA CASC2 was identified as a direct regulator of miR-21, and the overexpression of miR-21 reversed the antimetastatic effects of CASC2. The 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. Likewise, 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. Similarly, DGCR5 influences the BNIP3 and p38 MAPK pathways through miR-27a-3p, promoting apoptosis and attenuating PC development. Therefore, 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 PC. This hallmark is frequently associated with the development of poor vascular networks and dense stromal tissue in tumors.¹⁰⁷ Linc00511 is upregulated in PDAC tissues and cell lines, correlating with poor prognosis. The depletion of Linc00511 in PDAC cells inhibits proliferation, migration, invasion, and endothelial tube formation. Mechanistically, Linc00511 upregulates vascular endothelial growth factor A (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. It should be noted that 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 In addition, lncRNA BC037916 correlates with the clinical stage, primary tumor size, and regional lymph node invasion,

making it an independent prognostic marker for PC. The inhibition of BC037916 suppresses the JAK2/STAT3 and TGF- β pathways. It also positively regulates Twist expression via miR-3145-3p, enhancing proliferation and invasion, reducing apoptosis.⁸¹ In a study, Zhao et al 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, and invasion, promoting apoptosis. Further, 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 PC correlates with poor patient prognosis. Silencing LINC01128 inhibits tumor progression, including proliferation, migration, and invasion, both in vitro and in vivo. Furthermore, LINC01128 acts as a sponge for miR-561-5p, with its downstream target being lactate dehydrogenase A. MiR-561-5p is reduced in PC, demonstrating a negative correlation with LINC01128.⁹⁰ Table 1 presents a summary of miRNAs that are involved in PC pathogenesis and their targets.

Significance of Micro Ribonucleic Acids in the Diagnosis of Pancreatic Cancer

MiRNAs show significant promise in the diagnosis of PC, a disease that is 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 (e.g., 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 revealed 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. However, 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, thereby 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 PC, surpassing the diagnostic accuracy of individual miRNAs.¹¹⁴ Álvarez-Hilario et al identified a novel diagnostic panel comprising serum miR-222-3p and miR-221-3p for the detection of

PDAC and observed that the elevated expression of miR-221-3p and miR-222-3p was associated with reduced survival rates.¹¹⁵ The elevated levels of tissue miR-552-5p are related to enhanced cell migration and invasion while concurrently leading to reduced expression of FOXO3 and components of the Wnt signaling pathway.⁸⁹ miR-340-3p is another tissue miRNA with potential for PC detection. Cui et al reported that miR-340-3p is upregulated in pancreatic adenocarcinoma and targets CENPL, which is associated with decreased overall survival.¹¹⁶ Table 2 provides a summary of the miRNAs associated with the diagnosis of PC.

Important Role of miRNAs in the Detection of Early-Stage Pancreatic Cancer

The early detection of PC 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 PC patients and 213 healthy controls demonstrated the diagnostic potential of a panel of 100 highly expressed miRNAs. When combined with CA19-9, these miRNAs achieved an AUC of 0.99, with a sensitivity of 90% and a specificity of 98%. Remarkably, the model maintained high diagnostic accuracy for early-stage PC (stage 0-I) in an independent cohort, achieving an AUC of 0.97, a sensitivity of 67%, and a specificity of 98%. This indicates 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 PC. The diagnostic model incorporating these miRNAs

achieved accuracy values exceeding 94% in test datasets. Furthermore, the 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 PC early but also in distinguishing it from pancreatitis and assessing disease progression.¹¹⁹ An innovative approach involved using urinary EV-derived miRNAs for PC detection. A study evaluated samples from 153 PC patients and 309 healthy controls, identifying miRNA patterns that mirrored tumor and microenvironmental signals. The diagnostic model displayed 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% and 77.8% in the training and test sets, respectively. 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 (i.e., 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 PC from chronic pancreatitis, with AUC values exceeding 0.93. Validation in a separate cohort confirmed 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. Moreover, miRNAs can be indicative of

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, and 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

Note. MiRNA: Micro ribonucleic acid; OS: Overall survival.

treatment response and disease recurrence, offering a means to monitor a patient's progress over time.¹¹¹ Aita et al 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, can 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 et al 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 acceptable prognostic outcomes in PC. For instance, the expression of miRNA-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} The overexpression of CENPL mRNA, potentially regulated by miR-340-3p, serves as a prognostic marker, while miR-4653-3p upregulation represents an adverse outcome due to its negative regulation of HIPK2 in pancreatic ductal adenocarcinoma.¹¹⁸ Additionally, the lncRNA LINP1 has been implicated in the promotion of PC cell proliferation and metastasis by modulating miRNA-491-3p, thereby influencing the incidence of the 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 Ultimately, LINC01128 functions as a miRNA 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

According to research, miR-145 is differently expressed 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 can have therapeutic implications for inoperable PDAC.¹²⁴ Verel-Yilmaz et al¹²⁵ designed a study to address the urgent need for reliable early detection of PDAC. They 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 their findings revealed 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 is intriguing is that EVs derived from PC, which carry miR-27a, can stimulate the proliferation, invasion, and angiogenesis of human microvascular endothelial cells. This effect occurs by inhibiting the expression of B-cell translocation gene 2, 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 the animal models of PC. Likewise, the levels of EV-associated miR-339-5p are diminished in metastatic PC cells, and the external introduction of miR-339-5p results in the 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, including 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, which is 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 cancer-associated fibroblast 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 can 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 GEM treatment, release EVs. EVs have a pivotal role in reducing chemosensitivity in GEM-sensitive PC cells through the transport of miR-210. Remarkably, miR-210 antagonizes the impact of GEM, 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 GEM-treated cells¹³⁰ (Figure 2).

Clinical Extracellular Vesicle-miRNA Signatures in Pancreatic Cancer Patients

EV-derived miRNAs are emerging as promising non-invasive biomarkers for PC, with particular values in the

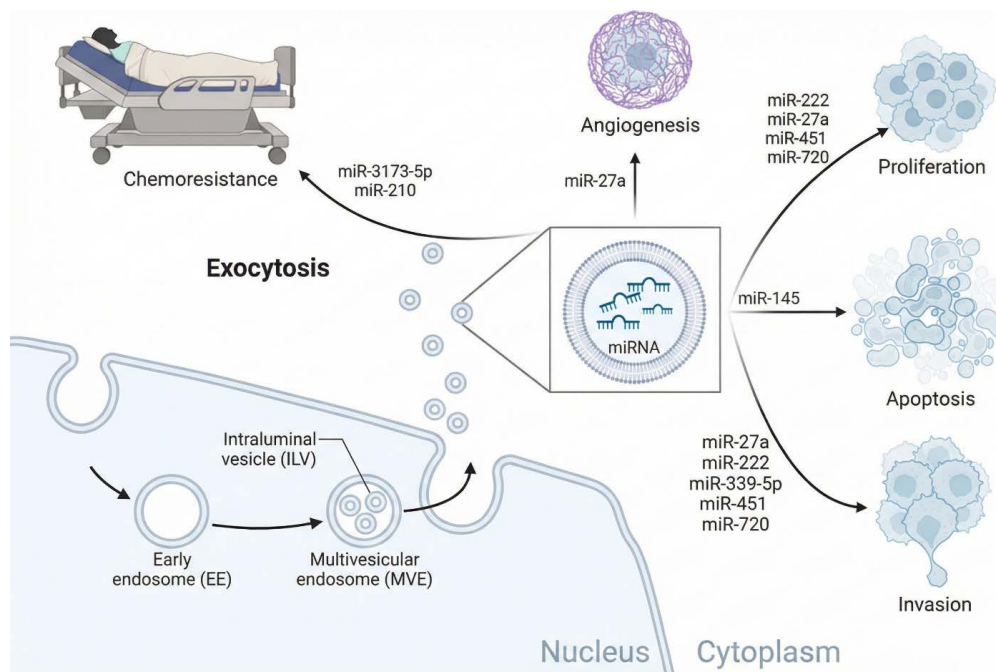


Figure 2. Representation of Extracellular Vesicle-Derived miRNAs in Pancreatic Cancer Progression

Note. miRNA: Micro ribonucleic acid; EV: Extracellular vesicle. EV biogenesis begins with the formation of early endosomes, which mature into multivesicular endosomes containing intraluminal vesicles. Upon exocytosis, these vesicles release 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. Overall, these EV-miRNAs orchestrate the interplay between tumor cells and their microenvironment, underscoring their dual role as biomarkers and therapeutic targets in pancreatic cancer.

early diagnosis and differentiation between malignant and 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 PC 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 acceptable sensitivity and specificity. Combining RNA and protein markers further improved diagnostic accuracy, especially for early-stage PC.¹³¹ Early investigations confirmed that plasma exosomal miR-196a and miR-1246 are selectively enriched in PC 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 receiver operating characteristic analyses showing AUCs of 0.81 and 0.73 for miR-196a and 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 considerably 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, and 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 a sensitivity of 100% and a 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, and miR-5695) that robustly discriminated 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). Conversely, 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 emphasize 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 PC 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%. More 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-miRNA 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-risk 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 an AUC of 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 was much lower (AUC: 0.62–0.78). Thus, blood-based miRNA panels provide a robust noninvasive tool not only for PC detection but also for the 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%). More 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 demonstrated 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

Role of Micro Ribonucleic Acids in Pancreatic Cancer Metastasis

Metastasis is a critical hallmark of PC, significantly contributing 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. Additionally, 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 involvement of miRNA in PDAC metastasis has been related to 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 Moreover, 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 Additionally, miR-223-5p, though not explicitly related to changes in expression, has been linked to the promotion of tumor growth and metastasis of PC cells, potentially through its interaction with LINC01705, which is a lncRNA that is involved in cancer progression.⁷⁷ In addition, 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 Furthermore, 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 that is involved in cancer metastasis.⁸⁸ SERPINA4, or kallistatin, is a multifunctional protein that has a role in anti-inflammatory responses, angiogenesis regulation, and endothelial function. Similarly, it 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 Moreover, 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. Likewise, miR-181b was found to target the gene *ZEB2* and influence EMT. In addition, in vivo experiments revealed that DLX6-AS1 knockdown inhibited tumor growth and metastasis, suggesting that DLX6-AS1 promotes PC progression by regulating miR-181b and related processes.⁶⁷ LINP1 enhances PC cell proliferation and metastasis by modulating miRNA-491-3p, thereby impacting the incidence of the lymph node or distant metastasis and the prognosis of PC patients.⁵² It has been reported that Linc00261 expression was reduced in PC tissues and cell lines, and low expression was related to poorer patient outcomes. The overexpression of Linc00261 inhibited PC cell migration and invasion in vitro, as well as reduced metastasis in an in vivo mouse model. More precisely, Linc00261 directly interacted with miR-552-5p, leading to decreased miR-552-5p levels. Additionally, the overexpression of Linc00261 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 Table 1 summarizes miRNAs that play a role in PC metastasis.

Potential Uses of Micro Ribonucleic Acids in the Treatment of Pancreatic Cancer: A 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 Some researchers have discovered two miRNAs (i.e., miR-99b and miR-485) that enhance oncolytic adenovirus activity by boosting viral replication. By targeting the 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. Scholars 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 al¹⁴³ developed a lentivirus vector 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 al¹⁴⁴ documented that the lentivirus vector-mediated overexpression of miR-205 heightened the responsiveness of PC stem cells to chemotherapy and suppressed the proliferation of tumor cells. Similarly, Kent et al 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 miRNA-21 and miRNA-221, contributing to aggressive tumor formation in mouse models. The application of antagomirs targeting miR-21 and miR-221 reduced the SP cell fraction, decreased proliferation, and increased sensitivity to chemotherapeutic agents, remarkably GEM. Additionally, the combined therapy of antagomirs had synergistic effects, leading to the 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 used both miR-21 antisense oligonucleotides (ASO-miR-21) and the drug GEM delivered via specialized nanoparticles

(NPs) in order to enhance treatment outcomes. These NPs, 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

Vorvis et al¹⁵² 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 concluded 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 lights on the in vivo function of FOXA2 and providing further evidence of its role as a tumor suppressor in PC, regulated by miR-199a.

Chen et al, exploring the use of NPs for delivering tumor-suppressing miRNAs, introduced a novel chimeric peptide called PL-1. Their findings demonstrated the efficient delivery of miR-212 into PDAC cells using miR-212/PL-1 NPs. Furthermore, these NPs 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 PLGA-based nanoformulation was employed to deliver the tumor-suppressing miR-150 into PC cells. This nanoformulation could effectively reduce 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 underwent investigation. It was found 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, the induction of apoptosis, and the suppression of genes associated with cancer progression. Noticeably, in vivo experiments using these miR-34a delivery systems in a PC model revealed a sharp reduction in tumor growth but an increase in cancer cell apoptosis.¹⁵⁵ Su et al investigated how exosomes facilitate communication between human PC cells (Panc-1) and macrophages. They altered the exosome content by transfecting Panc-1 cells with miRNA-155 and miRNA-125b-2 and used a NP vectors consisting of hyaluronic

acid plus polyethylene imine or polyethylene glycol to deliver exosome content. Their results confirmed 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. Moreover, 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 was correlated with heightened cell proliferation and invasion. Additionally, 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. Thus, the miR-449a/*ATDC* relationship might play a crucial part in the development of PC and offer promising targets for therapy (Figure 3).¹⁵⁸

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 PC, 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. Despite evidence of biological activities, the trial was terminated early due to severe immune-mediated adverse events, including fatalities, underscoring the therapeutic potential and the current safety challenges of miRNA mimic-based

strategies in oncology.¹⁵⁹

Emerging Ribonucleic Acid-Binding Protein Regulators of Micro Ribonucleic Acids Processing in Pancreatic Cancer

In addition to canonical miRNA biogenesis, RBPs have emerged as the 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 the recruitment of TUT4/7 to uridylate 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 a number of phenotypes, such as enhanced proliferation, angiogenesis, invasion, metastasis, and tumor-promoting inflammation in various cancers.¹⁶¹ PDAC specifically dysregulated LIN28B expression which 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 (e.g., GEM) by repressing downstream genes like *RRM2*, a factor that is implicated in chemoresistance.¹⁶²

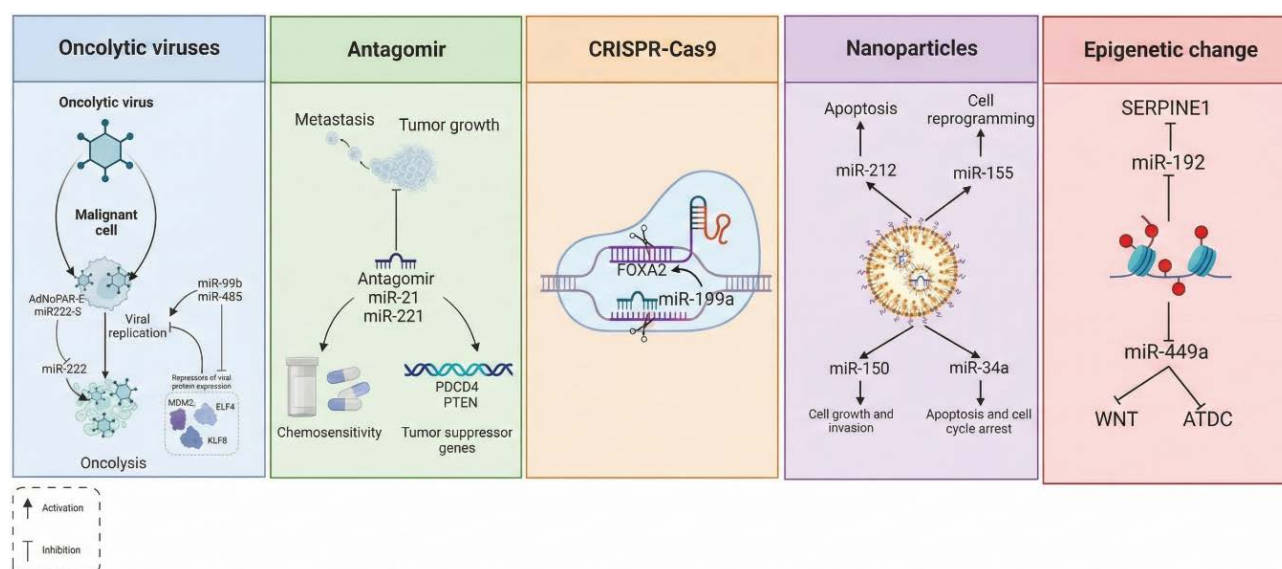


Figure 3. Therapeutic Strategies Targeting MiRNAs in Cancer

Note. MiRNA: Micro ribonucleic acid. 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 (e.g., miR-222) while restoring tumor suppressor networks. Antagomirs, chemically modified antisense oligonucleotides, silence oncogenic miRNAs (e.g., miR-21 and miR-221) to reduce tumor growth and metastasis, restore tumor suppressor genes (*PDCD4* and *PTEN*), and enhance chemosensitivity. CRISPR-Cas9-based editing enables direct targeting of miRNA loci (e.g., the suppression of miR-199a to restore the expression of transcription factors, including 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. The epigenetic modulation of miRNAs (e.g., SERPINE1-induced changes in miR-192 and miR-449a) alters downstream signaling pathways (Wnt and ATDC), affecting cancer progression. In general, these strategies highlight diverse methods of harnessing miRNA biology for anticancer therapy.

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. In addition, 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 (e.g., NP 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. Achieving a balance between specificity and sensitivity is one of the primary challenges with miRNAs in cancer. 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 (e.g., blood, tissue, or other body fluids) can greatly impact the results. Additionally, standardization in sample collection and processing is essential for reliable and reproducible miRNA-based diagnostics and therapies.¹⁶⁴ Further, 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 (e.g., chemotherapy, immunotherapy, and targeted therapies).¹⁶⁶ Advances in technology will enable more precise miRNA detection and manipulation, including the use of CRISPR/Cas9 for targeted miRNA regulation and improved NP-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 PC detection through a combination of assessments, including cfDNA methylation, ctDNA mutations, serum proteins, and blood miRNAs. In addition, 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 were found to hinder their translation into routine clinical use. One major challenge was 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 (quantitative polymerase chain reaction, microarrays, RNA sequencing, droplet digital polymerase chain reaction). 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, could influence circulating miRNA expression and reduce generalizability of the proposed panels. Another critical barrier was regulatory and translational feasibility. For diagnostic use, regulatory agencies, such as the U.S. Food and Drug Administration and European Medicines Agency, 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 PC, several limitations constrain its clinical translation. Pre-analytic variability, including differences in EV/miRNA isolation techniques, normalization strategies, and biofluid sources (serum, plasma, and exosomes) can lead to inconsistent results across studies. Furthermore, many investigations rely on relatively small and ethnically homogeneous cohorts, limiting the generalizability of the proposed biomarker panels. Another critical issue was 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. Accordingly 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 PC care.

In addition, therapeutic applications face unique challenges. Combination strategies (e.g., pairing miRNA antagonists with GEM) have demonstrated synergistic effects in preclinical PC 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, in order 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.

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Competing Interests

The authors declare that there is no conflict of interests.

Consent to Participate

Not applicable.

Consent to Publish

Not applicable

Declaration

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 the accuracy and integrity of the final content.

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This article is a review and contains no new data. All data supporting the findings of this study are available within the cited references.

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References

- Yonemori K, Kurahara H, Maemura K, Natsugoe S. MicroRNA in pancreatic cancer. *J Hum Genet* 2017;62(1):33-40. doi:10.1038/jhg.2016.59
- Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. *CA Cancer J Clin* 2025;75(1):10-45. doi:10.3322/caac.21871
- 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:10.1016/j.semcancer.2025.05.004
- 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:10.1002/gcc.22889
- 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:10.1007/s12672-025-03099-6
- Yehia R, Schaalán 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:10.3389/fonc.2021.783231
- 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:10.3390/ijms23031275
- 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:10.3892/etm.2018.6047
- 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:10.1007/s12094-022-02991-9
- Chen C, Demirkhanyan L, Gondi CS. The multifaceted role of miR-21 in pancreatic cancers. *Cells* 2024;13(11):948. doi:10.3390/cells13110948
- 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:10.1002/jcla.23956
- 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:10.1097/md.00000000000023863
- 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:10.3390/cells10061361
- 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:10.1007/s10571-016-0366-z
- 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:10.1186/s12951-020-00630-5
- 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:10.1007/s00018-020-03703-8
- 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:10.1186/s40001-025-02739-5
- 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:10.3389/fbioe.2022.948959
- 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:10.4161/cbt.21785
- 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:10.1097/JP9.0000000000000109
- 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: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: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: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: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: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: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: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: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: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: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: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: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: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: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: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: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: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: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: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: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:10.26508/lsa.202201460
 43. Li X, Jiang W, Li W, Dong S, Du Y, Zhang H, et al. Betulinic acid-mediating miRNA-365 inhibited the progression of pancreatic cancer. *Oncol Res* 2023;31(4):505-14. doi: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: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: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: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: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: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: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-1α and MIIP contributes to tumorigenesis of pancreatic cancer. *Oncogene* 2018;37(13):1743-58. doi: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: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: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: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:[10.2147/ott.S259598](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:[10.1080/15384101.2018.1496741](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:[10.26355/eurrev_202012_24005](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:[10.1186/s10020-019-0121-2](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:[10.3892/mmr.2022.12602](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:[10.1042/bsr20190332](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:[10.1042/bsr20181937](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 /VAMP1 axis in pancreatic cancer. *Pancreas* 2021;50(2):227-34. doi:[10.1097/mpa.0000000000001747](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:[10.3389/fonc.2022.877376](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, Dorđević V, Manis K, et al. Nickel's role in pancreatic ductal adenocarcinoma: potential involvement of microRNAs. *Toxics* 2022;10(3):148. doi:[10.3390/toxics10030148](https://doi.org/10.3390/toxics10030148)
 66. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA A Cancer J Clin* 2021;71:7-33. doi:[10.3322/caac.21654](https://doi.org/10.3322/caac.21654)
 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:[10.1186/s12935-018-0643-7](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:[10.1016/j.biopha.2017.10.157](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:[10.1016/j.biopha.2021.112010](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:[10.7150/jca.65071](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:[10.1080/21655979.2022.2038900](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:[10.1186/s12885-018-4954-9](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:[10.1186/s12935-019-0728-y](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:[10.1515/med-2022-0418](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:[10.3233/cbm-220229](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:[10.1186/s13062-023-00368-8](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:[10.3389/fgene.2022.838021](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:[10.3892/ijmm.2020.4632](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:[10.1111/jcmm.13351](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:[10.1080/15384047.2018.1564566](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:[10.2147/ott.S282350](https://doi.org/10.2147/ott.S282350)
 82. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209-249. doi:[10.3322/caac.21660](https://doi.org/10.3322/caac.21660)
 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:[10.3390/pharmaceutics13121987](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:[10.3892/or.2018.6245](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:[10.3892/ol.2018.8652](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: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: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: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: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: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: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: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: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: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: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: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: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: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: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: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:10.1016/j.drug.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: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: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: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: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:10.1016/j.biopha.2018.09.136
 108. Lin TC. RUNX2 and cancer. *Int J Mol Sci* 2023;24(8):7001. doi: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:10.3748/wjg.v24.i43.4846
 110. Shams R, Saberi S, Zali M, Sadeghi A, Ghafouri-Fard S, Asadzadeh Aghdai H. Identification of potential microRNA panels for pancreatic cancer diagnosis using microarray datasets and bioinformatics methods. *Sci Rep* 2020;10(1):7559. doi: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: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: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:10.3390/biomedicines9070845
 114. Seyed Salehi A, Parsa-Nikoo N, Roshan-Farзад F, Shams R, Fathi M, Asadzadeh Aghdai 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:10.1155/2022/8040419
 115. Álvarez-Hilario LG, Salmerón-Bárcenas 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: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: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: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: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:10.1038/s41416-023-02488-4
120. Singhi AD, Koay EJ, Chari ST, Maitra A. Early Detection of Pancreatic Cancer: Opportunities and Challenges. *Gastroenterology* 2019;156:2024–2040. doi:10.1053/j.gastro.2019.01.259
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: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: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: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: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: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: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: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: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: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: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: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: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: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: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:10.1016/j.eclinm.2024.102936
136. Zhang C, Al-Shaheri FN, Alhamedani 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: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: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: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: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: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: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: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: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: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: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: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: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: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:10.1111/cas.13267
150. Akram F, Haq IU, Sahreen S, Nasir N, Naseem W, Imitaz M, et al. CRISPR/Cas9: a revolutionary genome editing tool for human cancers treatment. *Technol*

- Cancer Res Treat 2022;21:15330338221132078. doi:[10.1177/15330338221132078](https://doi.org/10.1177/15330338221132078)
151. Aquino-Jarquin G. Emerging role of CRISPR/Cas9 technology for microRNAs editing in cancer research. *Cancer Res* 2017;77(24):6812-7. doi:[10.1158/0008-5472.Can-17-2142](https://doi.org/10.1158/0008-5472.Can-17-2142)
 152. Vorvis C, Hatzia Apostolou M, Mahurkar-Joshi S, Koutsoumpa 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:[10.1152/ajpgi.00035.2016](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:[10.1016/j.biomaterials.2018.11.035](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:[10.2147/ijn.S61949](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:[10.1016/j.biomaterials.2012.12.016](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:[10.1038/srep30110](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:[10.1158/0008-5472.Can-15-0390](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:[10.1016/j.biopha.2018.04.101](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:[10.1038/s41416-020-0802-1](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:[10.1002/1878-0261.12836](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:[10.3390/cancers12092699](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:[10.1371/journal.pone.0053436](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:[10.1038/s41598-022-24347-7](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:[10.1080/1354750x.2018.1427794](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:[10.1089/omi.2021.0087](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:[10.7150/ijbs.47203](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:[10.1080/17460441.2020.1690449](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:[10.3390/genes14020419](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:[10.1007/s40291-016-0251-y](https://doi.org/10.1007/s40291-016-0251-y)