Crosstalk between KRAS and miRNAs in pancreatic cancer: Opportunities for its diagnosis, prognosis and therapeutic intervention (Review)

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Abstract. Pancreatic cancer, predominantly manifested as pancreatic ductal adenocarcinoma (PDAC), is a highly aggressive malignancy in which the dysregulated crosstalk between Kirsten rat sarcoma viral oncogene homolog (KRAS) and microRNAs (miRNAs) plays a critical role. It is one of the leading causes of cancer-related mortality worldwide, with its global incidence more than doubling over the past 25 years. PDAC is characterized by rapid progression, invasiveness and profound resistance to conventional therapies, resulting in dismal prognosis. Its genetic profile is characterized by activating KRAS mutations, present in ~90% of cases. These mutations act as molecular switches that activate multiple intracellular signaling cascades and transcription factors, promoting uncontrolled proliferation, survival, migration and transformation. In addition to direct KRAS alterations, dysregulation of KRAS-targeting miRNAs further amplify aberrant RAS signaling. Emerging evidences highlights the significant role of miRNAs in driving tumor initiation, progression and metastasis. Several tumor-suppressive miRNAs that regulate KRAS signaling have demonstrated the capacity to suppress pancreatic tumor development *in vitro* and in preclinical models. Despite these advances, miRNA-based therapies, including mimics or anti-miRNA oligonucleotides targeting KRAS, remain largely unexplored in patients with PDAC. Further, circulating miRNAs show promise as non-invasive biomarkers for disease detection, monitoring progression and assessment of tumor aggressiveness. The present review provided a concise overview of KRAS signaling and its frequent mutations in PDAC, examines strategies to target KRAS and discussed the crosstalk between KRAS and tumor-suppressive miRNAs in regulating pancreatic tumorigenesis. It further explored diagnostic and prognostic miRNAs in pancreatic cancer. Collectively, these insights underscored the potential of miRNA-based interventions to improve early detection, prognosis and targeted therapy in this lethal disease.

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Contents

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is highly lethal, contributing to >400,000 mortalities across the globe each year. Epidemiological projections from North America and Europe suggest that PDAC is poised to become the second leading cause of cancer-related mortality within the next

decade. This trend is the lack of reliable early diagnostic tools, limited therapeutic options and the increasing incidence of the disease across all age groups and sexes (1,2). In United States alone, ~50,000 individuals are diagnosed annually and >45,000 of them succumb to the disease (3). The overall five-year survival rate for PDAC remains <10%, largely attributed to delayed diagnosis in >80% of cases (4). Despite advances in adjuvant therapies, the five-year disease-free survival rate remains low, at just 19-26% (5). Although the median overall survival of these patients has doubled over the past 15 years, from ~6 to 12 months, it remains unacceptably low. Long-term survival rate remains poor, with less than 3% of patients surviving beyond five years (6,7).

Pancreatic cancer has a significant genetic basis, with mutations in the Kirsten rat sarcoma viral oncogene homolog (KRAS) found in >80% of patients. These alterations are consistently associated with reduced overall survival and independent of stage of the disease (8,9). KRAS mutation testing is already part of clinical practice for several epithelial malignancies, including lung and colorectal cancers, where it guides therapeutic decision-making and eligibility for targeted therapy trials (10,11). Due to its clinical significance, KRAS mutation analysis is increasingly incorporated into PDAC diagnostic workflows, particularly through endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) in specialized settings (12).

Current treatment strategies for PDAC encompass surgical resection, chemotherapy, radiation therapy and emerging targeted or immunotherapeutic approaches. Translational research has revealed that PDAC is characterized by profound molecular and cellular heterogeneity, which likely contributes to its pronounced resistance to conventional therapies (13). Consequently, molecular biomarkers are increasingly recognized as predictive and prognostic tools for guiding personalized management of PDAC. However, the molecular of tumor progression and chemoresistance remain poorly elucidated, underscoring the urgent need for additional mechanistic and translational investigations.

Beyond identifying gene expression signatures in pancreatic cancer, elucidating the genetic and epigenetic mechanisms that regulate transcription and translation may unveil novel prognostic biomarkers. In recent years, microRNAs (miRNAs) have been recognized as key post-transcriptional modulators of gene expression, controlling the stability and translation of multiple target mRNAs. This has established miRNAs as promising biomarkers for predicting disease prognosis and therapeutic response (14,15).

Notably, despite the prevalence of KRAS activation through oncogenic mutations in the vast majority of PDAC cases, several miRNAs are capable of directly targeting KRAS, including miR-96, miR-217 and miR-126 and are consistently downregulated (16). Enforced expression of miR-96 and miR-217 have been shown to reduce KRAS protein levels and consequent attenuation of downstream v-Akt murine thymoma viral oncogene homolog (AKT) signaling (17). As reduced expression of these miRNAs correlates with increased KRAS activity, their dysregulation likely contributes to the hyperactivation of RAS-driven signaling pathways. Furthermore, several miRNAs that normally suppress the expression of KRAS oncoproteins are usually downregulated in PDAC, promoting sustained RAS pathway activation irrespective of activating KRAS mutations (18).

Despite recent advances in diagnostic techniques, including high-resolution imaging and EUS-guided FNA and advances in therapy with regimens such as gemcitabine, nab-paclitaxel plus gemcitabine and folinic acid, 5-fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX), the overall prognosis of PDAC remains poor (19,20). The PRODIGE 24 analysis showed that FOLFIRINOX therapy, patient age, tumor grade, disease stage and care at high-volume centers, markedly influenced overall survival (7). However, to date, no specific molecular determinant has been conclusively linked to prognosis in patients undergoing surgical resection for PDAC (21).

The present review outlined the multifaceted role of oncogenic KRAS in pathobiology, diagnosis, prognosis and therapeutic management of pancreatic cancer. It also explored the spectrum of RAS mutations across malignancies, with a particular emphasis on KRAS aberrations in PDAC and elucidated the molecular mechanisms by which miRNAs modulate KRAS-mediated signaling. Furthermore, the present review focused on some major modes of 'crosstalk' between KRAS and miRNAs in PDAC, including: i) Direct targeting of KRAS by specific miRNAs (e.g., miR-217, miR-216a-3p), ii) feedback effects whereby mutant KRAS alters the expression of miRNAs and iii) co-regulation of shared downstream effectors, forming feedback loops that shape cell signaling and tumor behavior.

2. KRAS-driven signaling in pancreatic ductal cells

Pancreatic cells rely on an intricate network of signaling cascades to coordinate their highly specialized exocrine and endocrine functions. Key regulatory pathways include Hippo, Wnt/β-catenin, phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin (PI3K-Akt-mTOR), nuclear factor-κB (NF-κB) and Janus kinase-signal transducer and activator of transcription (JAK-STAT). These signaling pathways control key cellular processes such as tissue development, differentiation, proliferation and maintenance of homeostatic (22-24). Perturbations in these signaling axes, whether through aberrant activation or dysregulation, profoundly affect pancreatic physiology (25). Oncogenic mutations in KRAS disrupt these pathways, driving pathological outcomes including uncontrolled cellular proliferation, dedifferentiation, inflammation and the eventual development of chronic pancreatitis and progression to PDAC (9).

The RAS superfamily comprises a set of small GTP-binding proteins that act as molecular switches within pancreatic ductal epithelial cells, orchestrating signal transduction from membrane-bound receptors to nuclear effectors. Among these, KRAS plays a pivotal role within the RAS-MAPK signaling cascade, a central regulatory network governing cell growth, survival and differentiation. Under physiological conditions, KRAS cycles between inactive GDP-bound and active GTP-bound states, thereby transmitting extracellular cues to intracellular effectors that maintain normal cellular behavior (26) (Fig. 1).

However, activating mutations in KRAS, which occur in the vast majority of PDAC cases, convert this tightly regulated molecular switch into a constitutively active oncoprotein.

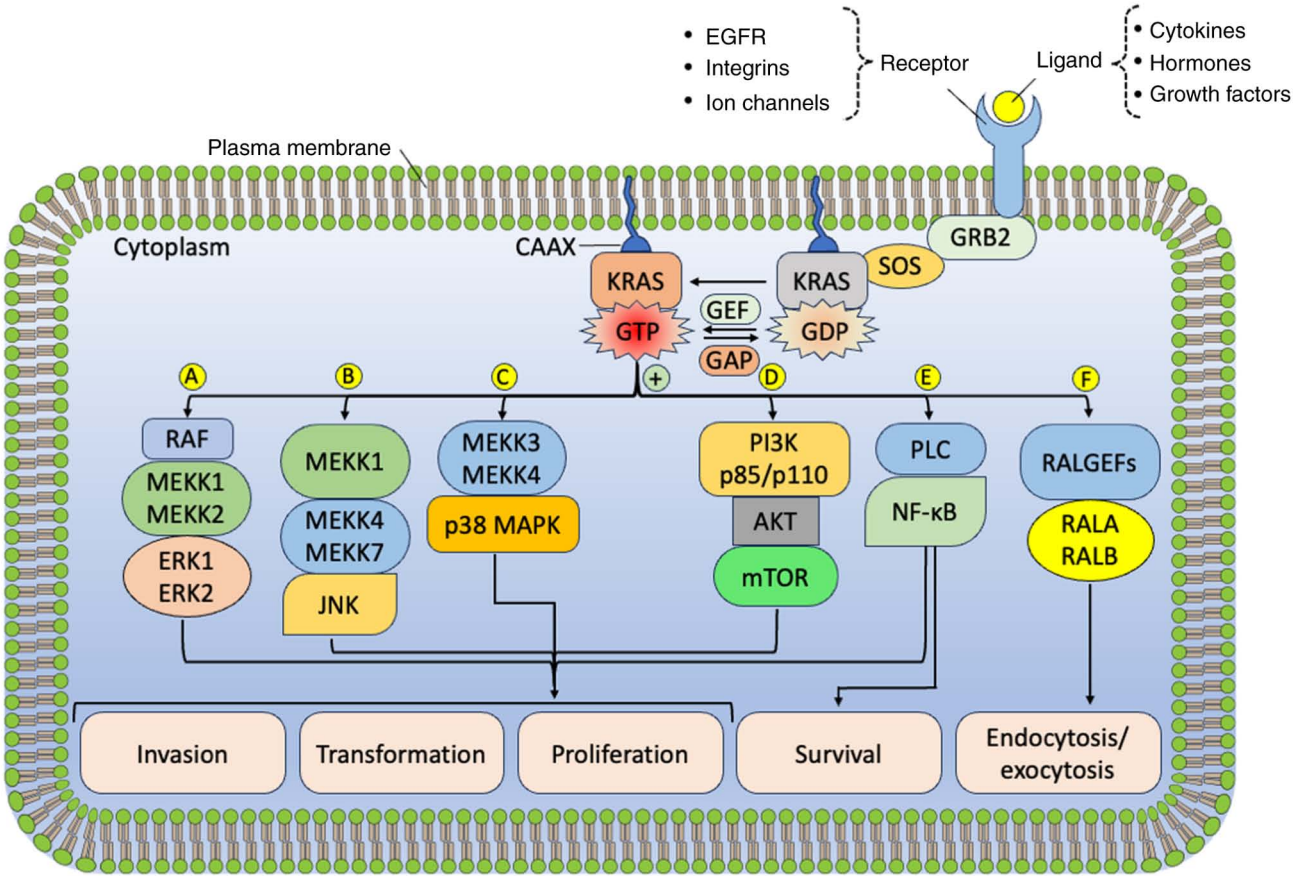

Figure 1. Stimulation of KRAS and the subsequent activation of intracellular key signaling networks. The major signaling pathways triggered by activated KRAS include (A) the MAPK/ERK pathway, (B) the JNK pathway, (C) the p38 MAPK pathway, (D) the PI3K pathway, (E) the NF-κB pathway and (F) The RALA-RALB pathway. JNK, c-Jun N-terminal Kinase; KRAS, Kirsten rat sarcoma viral oncogene homolog; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinase; NF-κB, nuclear factor-κB; PI3K, phosphoinositide 3-kinase; RALA, RAS-like proto-oncogene A; RALB, RAS-like proto-oncogene B.

Mutant KRAS chronically stimulates a range of downstream effector pathways, thereby orchestrating oncogenic signaling that sustains tumor cell proliferation, metabolic reprogramming, metastatic dissemination and therapeutic resistance. The principal downstream cascades driven by mutant KRAS include: i) The RAF-MEK-ERK (MAPK) pathway, the canonical and most extensively characterized effector route, which promotes cellular proliferation and survival (27); ii) MEKK1-4→MEKK4/MEKK7→JNK pathway, a pathway that is a part of the stress-activated MAP kinase (SAPK) network, also known as the JNK pathway; iii) MEKK3/MEKK4→p38 MAPK pathway, part of the SAPK system, parallel to JNK pathway; iv) the PI3K-Akt-mTOR pathway, which regulates metabolism, growth and anti-apoptotic signaling (28); v) PLC→NFκB pathway, this pathway links membrane receptor activation to inflammatory, immune and survival gene expression and vi) the Ras-like (RAL) Guanine Nucleotide Exchange Factor pathway (GEF) pathway (29), involved in cytoskeletal reorganization, vesicle trafficking and cell migration (Fig. 1). Besides these pathways, there can occur some other aberrantly activated pathways such as JAK-STAT, Wnt/β-catenin pathway, Hippo-YAP/TAZ Pathway, Notch pathway and FAK-SRC pathway. The Hedgehog (Hh) signaling pathway is aberrantly activated in the tumor microenvironment by oncogenic KRAS (30), facilitating reciprocal communication between cancer cells and the surrounding stroma to promote tumor progression. Collectively, these KRAS-mediated signaling networks highlight the pivotal role of this oncogene in orchestrating pancreatic cellular reprograming, positioning it as a master regulator of PDAC initiation and evolution (9).

KRAS and its interaction with associated proteins. The KRAS gene encrypts the KRAS protein, a small GTP-binding enzyme composed of ~189 amino acid residues having a molecular weight of ~21.6 kDa. Functionally, KRAS belongs to the RAS family of small GTPases, which act as molecular switches linking cell-surface growth factor receptors to a variety of intracellular signaling cascades and transcriptional networks that regulate cell survival, proliferation and differentiation (31). The human RAS protein family, comprising HRAS, NRAS and KRAS (KRAS4A and KRAS4B splice variants), shares a conserved structural organization with two major domains: The G domain (GTPase domain) and the hypervariable region, the membrane-targeting domain. The G domain (residues 1-164) encompasses the nucleotide-binding pocket responsible for GDP/GTP binding and hydrolysis, as well as regions essential for effector interactions. The C-terminal membrane-targeting domain (residues 165-188/189) contains the CAAX motif, where C denotes cysteine, A denotes aliphatic residues and X specifies the terminal amino acid (26).

Post-translational modifications of this motif are critical for proper membrane localization and function. Specifically, a 15-carbon farnesyl isoprenoid group is attached covalently to the cysteine residue by farnesyltransferase enzymes, enabling the protein to anchor to the inner leaflet of the plasma membrane, an essential step for its biological activity (32,33).

The dynamic cycle of active GTP and inactive GDP is tightly controlled by two classes of regulatory proteins: guanine nucleotide exchange factors (GEFs), which catalyze the exchange of GDP for GTP to activate KRAS and GTPase-activating proteins (GAPs), which accelerate GTP hydrolysis, thereby returning KRAS to its inactive state (34) (Fig. 1). Mutations in KRAS, particularly at codons 12, 13 and 61, impair intrinsic GTPase activity or GAP-mediated hydrolysis, effectively locking KRAS in its active, GTP-bound conformation and leading to constitutive signal transduction (35). Once activated, KRAS engages with a broad spectrum of downstream effectors, >80 proteins have been identified to date, initiating a multitude of signaling cascades. Upon activation of growth factor receptors, such as receptor tyrosine kinases or G-protein-coupled receptors, growth factor receptor-bound protein 2 associates with the guanine nucleotide exchange factor Son of Sevenless (SOS) and subsequently engages the KRAS protein (36).

For KRAS to become functionally active, it must localize to the plasma membrane. This membrane anchoring is mediated by the covalent attachment of a farnesyl isoprenoid group to a cysteine residue within the C-terminal CAAX motif of KRAS, a reaction catalyzed by farnesyltransferases. Once properly localized, KRAS attains its active configuration upon binding GTP. Mutations in KRAS typically diminish its GTPase activity, rendering it resistant to GAP-mediated inactivation and thus locking the protein in its GTP-bound, constitutively active state. This persistent activation drives multiple downstream signaling cascades and nuclear transcription programs that promote cell proliferation, survival and oncogenic transformation (37).

The prominent signal transduction pathways include RAF-MEK-ERK (MAPK) pathway, which governs cellular proliferation and differentiation; the PI3K-AKT-mTOR axis, which regulates cell metabolism, growth and survival; and the RAL-GEF and Tiam1-RAC pathways, which influence cytoskeletal remodeling, motility and vesicular trafficking (38). Through these signaling routes, activated KRAS orchestrates the transcriptional activation of several nuclear factors such as ETS-like gene 1 (ELK1), JUN and myelocytomatosis (MYC), which collectively promote cell cycle progression, transformation and resistance to apoptosis (39).

The precise localization and post-translational modifications of KRAS at the plasma membrane not only dictates its functional activation but also influences its selective engagement with specific effectors, thereby conferring signaling specificity. This precise spatial and temporal control of KRAS activity highlights its role as a master integrator of extracellular signals and intracellular responses, accounting for the potent oncogenicity and therapeutic intractability of mutant KRAS in PDAC. The stimulation of KRAS activity and its downstream molecular signaling routes is shown in Fig. 1.

3. KRAS driven signaling and the role of miRNAs

KRAS functions as a membrane-associated molecular integrator that transduces extracellular cues, such as growth factors, cytokines, or cellular stress signals, received through receptor tyrosine kinases, ion channels or integrins into intracellular signaling cascades, primarily the KRAS-ERK and PI3K-Akt pathways (40) (Fig. 1). In non-malignant cells with wild-type KRAS, this signaling axis is stringently synchronized through different layers of control. First, the equilibrium between active and inactive KRAS is governed by the opposing activities of GAPs and GEFs. Second, scaffold and adaptor proteins fine-tune the spatial and temporal fidelity of KRAS-MAPK signaling by ensuring the appropriate localization and assembly of pathway components. Proteins such as Sprouty Related EVH1 Domain Containing 1 (SPRED1) are essential for targeting GAPs to the membrane (41). Third, microRNAs (miRNAs) introduce an additional post-transcriptional regulatory layer by modulating the expression of RAS pathway constituents, scaffolds and modulators (42).

miRNAs have emerged as crucial regulators of oncogenic signaling networks, including the KRAS pathway and are being actively explored as therapeutic targets across multiple cancer types (43). In pancreatic cancer, oncogenic KRAS mutations result in constitutive activation of downstream pathways that drive malignant proliferation, metabolic adaptation and therapeutic resistance. Concurrently, several miRNAs function either as tumor suppressors, by directly repressing KRAS or its downstream effectors, or as oncogenic drivers that silence tumor-suppressive genes. The downregulation of tumor-suppressive miRNAs such as miR-96, miR-217 and the Let-7 family leads to enhanced KRAS expression and activity, thereby promoting tumor growth, invasiveness and survival. Conversely, certain miRNAs, including miR-31, are upregulated by oncogenic KRAS itself, further amplifying pro-metastatic signaling (17).

Extensive preclinical investigations have demonstrated that miRNA dysregulation profoundly influences PDAC initiation, progression and chemoresistance, highlighting the potential of miRNA-based therapeutics as a novel strategy to counteract KRAS-driven oncogenesis. By restoring tumor-suppressive miRNAs or inhibiting oncogenic ones, miRNA-directed interventions could redefine therapeutic paradigms in pancreatic cancer management (14).

The Let-7 family of miRNAs directly targets all major RAS isoforms, including KRAS, HRAS and NRAS. Negative regulators of the RAS-ERK cascade, such as RAS p21 protein activator 1 (RASA1) and Sprouty-related EVH1 domain-containing protein 1 (SPRED1), are jointly suppressed by miR-206 and miR-21. The GAP protein neurofibromin 1 (NF1) has been identified as a probable catalytic partner of SPRED1. Another inhibitor of the same pathway, Sprouty RTK signaling antagonist 1 (SPRY1), along with the PI3K-AKT pathway suppressor phosphatase and tensin homolog (PTEN), are uniquely targeted by miR-21. Furthermore, the downstream effector and tumor suppressor programmed cell death 4 (PDCD4) is co-regulated by miR-21 and miR-206 (44). The interplay between oncogenic RAS signaling and microRNAs targeting key components of the RAS pathway in cancer is diagrammatically represented in Fig. 2.

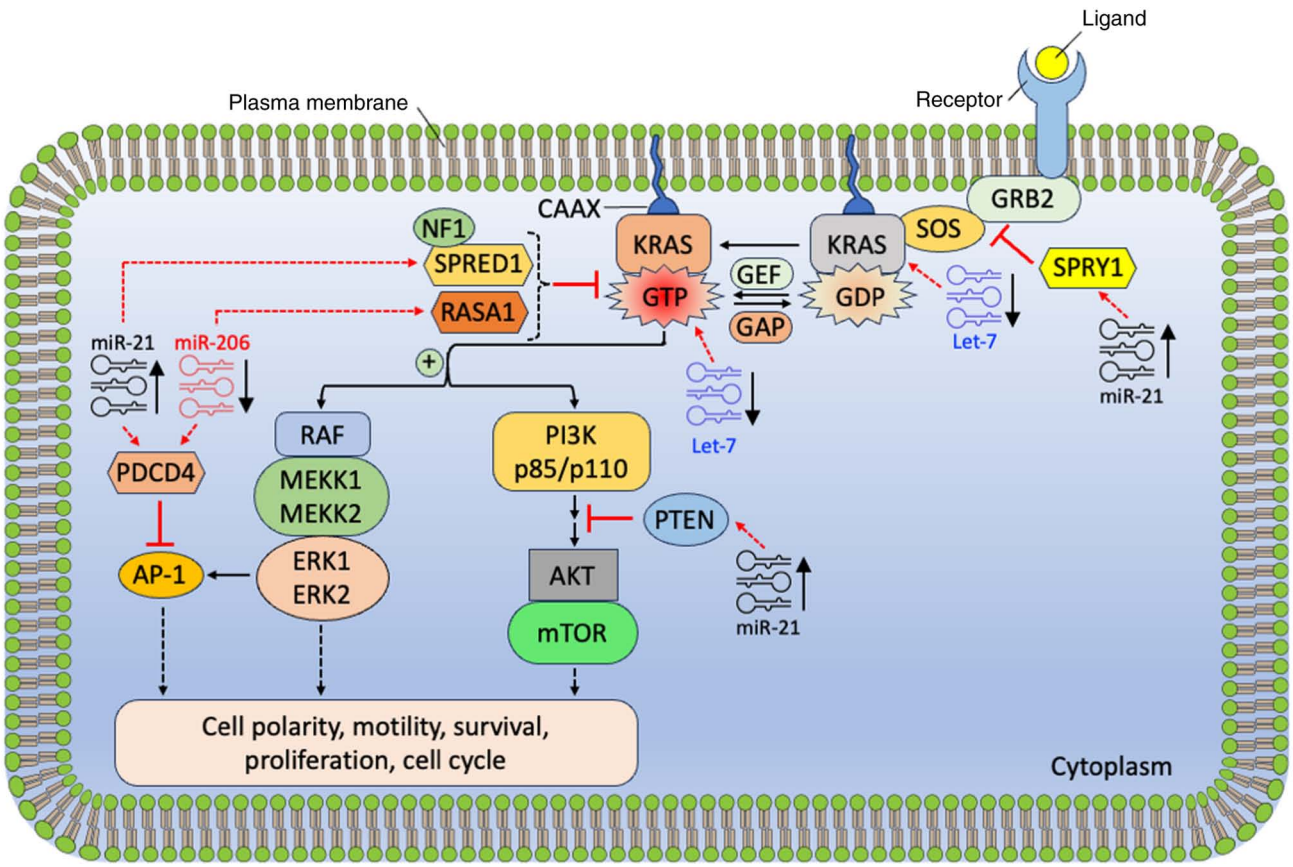

Figure 2. Interactions between oncogenic RAS signaling and miRNAs in cancer. RAS GTPases function as molecular switches, cycling between an inactive GDP-bound conformation and an active GTP-bound form. In cancer, RAS signaling frequently becomes constitutively active due to elevated RAS-GTP levels, which promote enhanced cell survival, proliferation and migration. miRNAs, such as Let-7 family and miR-206 are down regulated (↓), while miR-21 is upregulated (↑), capable of modulating multiple components of the RAS signaling network. GTPase, guanosine triphosphatase; miRNAs, microRNAs; RAS, rat sarcoma.

4. Feedback loops and reciprocal regulation between KRAS and miRNAs

Accumulating evidence indicates that the interaction between oncogenic KRAS signaling and miRNAs in PDAC is not unidirectional but instead organized into feedback loops and reciprocal regulatory circuits. These mechanisms contribute to the stabilization and amplification of KRAS-driven oncogenic programs and have important implications for tumor progression, therapeutic resistance and biomarker development (45,46).

One of the best-characterized examples is the KRAS-RREB1-miR-143/145 regulatory loop. Oncogenic KRAS activates the transcription factor Ras-responsive element binding protein 1 (RREB1), which directly represses the transcription of the tumor-suppressive miR-143/145 cluster. In turn, miR-143 and miR-145 directly target KRAS and RREB1, respectively. Loss of miR-143/145 expression in PDAC therefore leads to de-repression of KRAS signaling, creating a feed-forward loop that reinforces oncogenic KRAS activity. Disruption of this circuit has been shown to enhance cell proliferation, invasion and tumorigenicity, highlighting its functional importance in pancreatic cancer progression (47).

In addition to the miR-143/145 axis, several other KRAS-targeting miRNAs participate in reciprocal suppression loops. Members of the Let-7 family, as well as miR-127, miR-193a and miR-27b, directly bind the KRAS 3'-UTR and suppress its expression. However, sustained KRAS activation down-regulates these miRNAs through downstream MAPK and MYC-dependent transcriptional programs, thereby relieving inhibitory pressure on KRAS itself. Such reciprocal regulation ensures persistent KRAS pathway activation and contributes to the addiction of PDAC cells to KRAS signaling (42,48).

Conversely, oncogenic KRAS can induce the expression of certain oncogenic miRNAs that further enhance KRAS pathway output by targeting its negative regulators. For example, KRAS-driven up-regulation of miR-21, miR-31 and miR-155 has been reported to suppress tumor suppressors such as PTEN, RASA1 and NF1, thereby strengthening downstream MAPK and PI3K signaling. These miRNAs form positive feedback loops that indirectly amplify KRAS signaling and promote tumor growth, survival and chemoresistance (46).

Collectively, these findings underscore that KRAS-miRNA crosstalk in PDAC is governed by a network of interconnected feedback loops, rather than isolated regulatory events. A conceptual overview of these reciprocal mechanisms, including the KRAS→RREB1→miR-143/145 suppression→KRAS de-repression loop and additional KRAS-miRNA feedback circuits, is presented in Fig. 3. Understanding these regulatory architectures provides a framework for the rational design of therapeutic strategies aimed at restoring tumor-suppressive miRNAs or disrupting

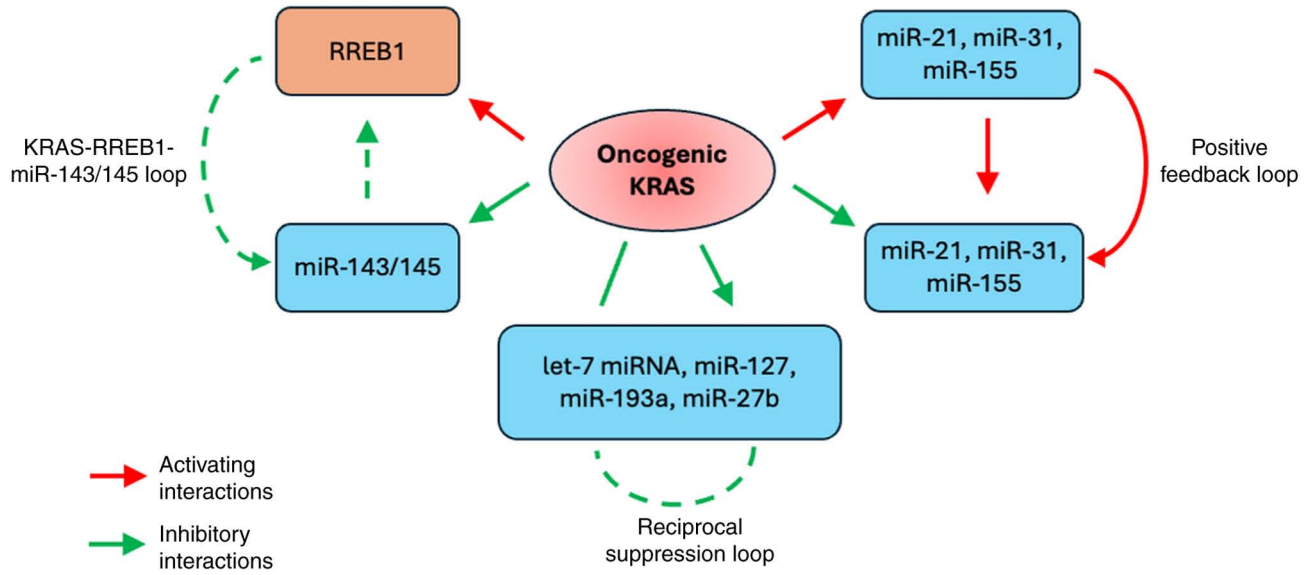

Figure 3. Feedback loops and reciprocal regulation between KRAS and miRNAs in PDAC. The diagram illustrates interconnected regulatory circuits between oncogenic KRAS signaling and miRNAs. KRAS → RREB1 → miR-143/145 suppression → KRAS de-repression forms a feed-forward loop that reinforces KRAS activity. Tumor-suppressive miRNAs (e.g., Let-7 family, miR-143/145) inhibit KRAS expression, but their levels are downregulated by KRAS-driven transcriptional programs. Oncogenic miRNAs (miR-21, miR-31, miR-155) are upregulated by KRAS and target negative regulators (PTEN, RASA1, NF1), amplifying downstream MAPK and PI3K signaling pathways. Collectively, these reciprocal circuits stabilize KRAS-driven oncogenic programs, promoting tumor growth, survival and chemoresistance. KRAS, Kirsten rat sarcoma viral oncogene homolog; KRAS, Kirsten rat sarcoma viral oncogene homolog; MAPK, mitogen activated protein kinase; miRNAs, microRNAs; NF1, neurofibromin 1; PDAC, pancreatic ductal adenocarcinoma; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; RASA1, RAS p21 protein activator 1; RREB1, Ras-responsive element-binding protein 1.

KRAS-reinforcing feedback loops. These approaches hold promises for improving diagnostic, prognostic and therapeutic strategies in pancreatic cancer.

5. Role of KRAS in pancreatic cancer

KRAS is the principal oncogenic driver in PDAC, harboring activating mutations, most notably $KRAS^{G12D}$ and $KRAS^{G12V}$, in >90% of tumors (49,50). Insights from genetically engineered mouse models, such as the Pdx1-Cre; LSL-$KRAS^{G12D}$ system, have been pivotal in delineating the stepwise transformation from normal pancreatic epithelium to pancreatic intraepithelial neoplasia (PanIN) and ultimately to invasive carcinoma. These models have underscored that sustained KRAS activation is sufficient to initiate neoplastic lesions and, in cooperation with additional genetic or epigenetic alterations, to drive full malignant progression (51).

Oncogenic KRAS engages a wide array of downstream effectors and signaling cascades, including the MAPK-ERK, PI3K-AKT-mTOR and RAL-GDS pathways, which collectively drive enhanced proliferation, altered metabolic programming, resistance to apoptosis and immune evasion. The magnitude and duration of KRAS signaling is directly associated with disease aggressiveness, metastatic potential and poor clinical outcomes, positioning KRAS mutation profiling as a valuable tool for early detection, prognosis and patient stratification (52).

From a therapeutic perspective, targeting KRAS remains a central focus of translational research. Emerging therapeutic modalities include direct pharmacological inhibition of KRAS (such as allele-specific inhibitors targeting $KRAS^{G12C}$), RNA interference-based silencing approaches and RAS-directed peptide or mRNA-based vaccines designed to elicit anti-tumor immunity (53,54). Moreover, mutant KRAS expression was markedly reduced by using CRISPR/Cas13a-mediated mRNA knockdown (55). In addition, inhibitors of downstream signaling nodes, including MEK, ERK and PI3K are being explored either as monotherapies or in rational combination regimens (Fig. 4). Although these approaches are still evolving, they represent promising avenues for overcoming the long-standing challenge of therapeutically targeting KRAS-driven pancreatic cancer (56).

KRAS mutations in PDAC and associated biological processes. A point mutation in KRAS oncogene, most commonly at codon 12, represents the initiating genetic alteration in most of the PDAC cases, occurring in 70-95% of cases (8,57). This single-nucleotide substitution alters the wild-type GGT codon (encoding glycine) to GAT or GTT, [encoding aspartic acid (G12D), or valine (G12V), GCT (alanine; G12A), or CGT (arginine; G12R)] (52). Less frequent mutations are also detected at codons 11, 13, 61 and 146, each conferring distinct biochemical properties and oncogenic potential (8,52,58).

These activating point mutations compromise the intrinsic GTPase activity of KRAS, rendering it resistant to regulation by GAPs. As a result, mutant KRAS remains constitutively locked in its GTP-bound, active state, persistently transmitting proliferative and pro-survival signals through downstream pathways such as RAF-MEK-ERK, PI3K-AKT-mTOR and RAL-GDS (38) (Fig. 1). Importantly, this aberrant activation of KRAS is frequently accompanied by the genetic inactivation of key tumor suppressor pathways, including inhibitor of cyclin-dependent kinase 4a/alternate reading frame (INK4a/ARF), tumor protein 53 (TP53) and deleted in pancreatic carcinoma locus 4/SMAD family

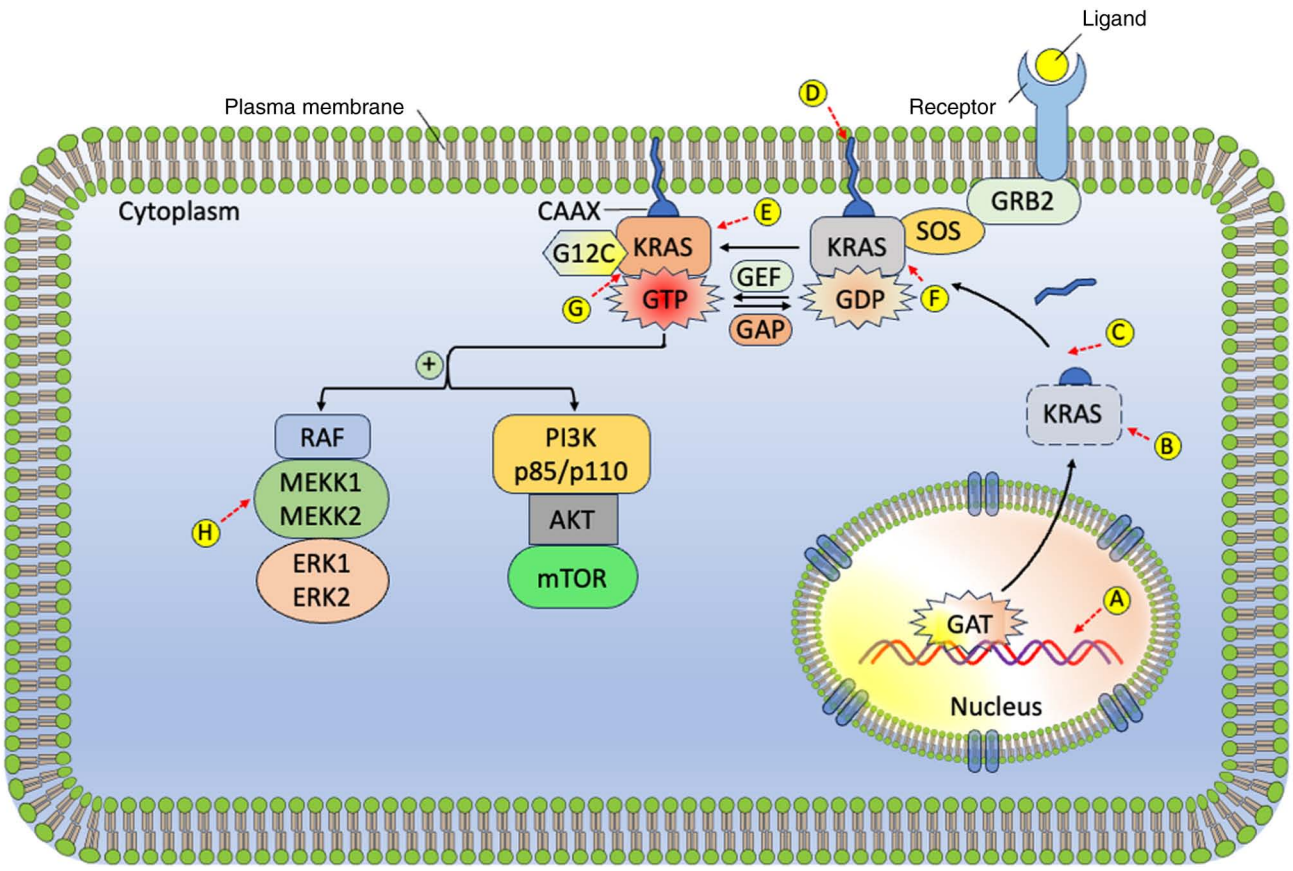

Figure 4. Various therapeutic approaches directed at the KRAS gene and KRAS protein: (A) RNAi strategies designed to suppress the expression of mutant KRAS, (B) FTIs that block the farnesylation of the KRAS protein, (C) Inhibition of PDEδ, (D) Disruption of RAS signaling by detaching farnesylated KRAS from the cell membrane, (E) KRAS-targeted vaccination, (F) Small-molecule inhibitors that bind to the RAS-GDP complex, (G) Blocking the KRAS-GTP interaction, (H) Targeting downstream signaling cascades, specifically the RAF-MEK-ERK and PI3K-AKT-mTOR pathways. FTIs, farnesyltransferase inhibitors; KRAS, Kirsten rat sarcoma viral oncogene homolog; RNAi, PDEδ, phosphodiesterase 6 delta; PI3K-AKT-mTOR, phosphoinositide 3-kinase-protein kinase B-mechanistic target of rapamycin; RAF-MEK-ERK, rapidly accelerated fibrosarcoma-mitogen-activated protein kinase-extracellular signal-regulated kinase; RAS, rat sarcoma; RNA interference.

member 4 (DPC4/SMAD4). Together, these alterations synergistically promote malignant transformation and drive tumor progression (8). Notably, KRAS mutations represent one of the earliest molecular events in pancreatic tumorigenesis and are detectable in preneoplastic lesions, including PanINs and intraductal papillary mucinous neoplasms (IPMNs), highlighting their central role in initiating the neoplastic cascade (59).

Extensive evidence highlights the critical role of KRAS mutations in driving multiple pancreatic cancer cell behaviors, including enhanced proliferation, survival, migration and invasion. Oncogenic KRAS extensively reprograms cellular metabolism, promoting increased glucose uptake, the Warburg effect and increased lactate and reactive oxygen species (ROS) production (38,60). Additionally, mutant KRAS stimulates macropino-cytosis and autophagy, supporting nutrient scavenging and tumor growth. Collectively, these metabolic and catabolic adaptations facilitate PDAC expansion and metastatic progression.

Beyond its cell-intrinsic functions, KRAS also coordinates dynamic interactions between tumor cells and the surrounding tumor microenvironment (61). These interactions are mediated largely through paracrine signaling. KRAS-mutant tumor cells secrete range of chemokines, including interleukin-6 (IL-6) and granulocyte-macrophage colony-stimulating factor (GM-CSF). These factors recruit and activate T cells, myeloid-derived suppressor cells, B cells and macrophages, thereby enhancing inflammation and tumor progression. Furthermore, KRAS is essential for communication with cancer-associated fibroblasts (CAFs), which are activated via tumor growth factor-β (TGF-β) and sonic hedgehog pathways. CAFs modulate the extracellular matrix, including hyaluronic acid and collagen, creating a supportive niche that enhances tumor cell proliferation (62).

Tumor aggressiveness associated with specific KRAS mutants. Although several studies have investigated the impact of distinct KRAS mutant alleles on tumor aggressiveness and phenotype across various cancer types, no definitive consensus has been reached. This uncertainty may arise from the lack of a single dominant signaling pathway that is consistently altered across different mutations. To date, no studies have directly compared the transforming efficiency of G12R, G12D and G12V alleles in pancreatic tumors. However, research in lung and colorectal cancer models, where KRAS is also frequently mutated, suggests that most KRAS variants have broadly similar effects on tumor growth and dissemination (63).

Subtle differences in downstream effector engagement are likely to influence the ultimate tumor phenotype. For example, in non-small cell lung carcinoma (NSCLC) cell lines, $KRAS^{G12D}$ preferentially activates PI3K and MEK pathways, whereas $KRAS^{G12V}$ predominantly engages RAL-GEFs and shows reduced AKT activation. Additionally, the G12R, G12D and G12V mutants exhibit lower affinity for RAF compared to wild-type KRAS (64). Molecular dynamics simulations further indicate that the conformational flexibility of KRAS mutants differs from wild type, with significant variation among mutants themselves, highlighting the complexity of allele-specific effects (65). Notably, the switch-I region, which mediates effector binding, is more accessible in mutant forms, particularly G12D bound to GDP, providing mechanistic insight into differential effector interactions (65).

Prognosis of KRAS mutations. Several studies have investigated whether the occurrence of KRAS mutations affects the PDAC prognosis (66). Analyses have been conducted on both resected tumor specimens and EUS-FNA-derived samples, in studies including more than 50 patients. The KRAS mutation were consistently associated with poorer survival, independent of surgical intervention (66,67). It should be noted that some study cohorts were heterogeneous, including resected PDAC, ampullary carcinomas, non-resectable tumors and recurrent lesions. Despite these variations, most investigations concluded that KRAS mutations adversely affect survival irrespective of curative surgery.

Emerging evidence suggests that specific KRAS mutational subtypes may further influence prognosis (52,57). For example, PDAC patients harboring $KRAS^{G12D}$ mutations exhibited considerably reduced overall survival (~6 months) compared with those with wild-type KRAS (~9 months), $KRAS^{G12V}$ (~9 months), or $KRAS^{G12R}$ (~14 months), independent of chemotherapy (57). Other similar studies indicate that $KRAS^{G12D}$, $KRAS^{G12R}$, or combinations of mutant alleles are linked to associated with poorer clinical outcomes (68). These differences may reflect allele-specific engagement of downstream signaling pathways (69).

To establish definitive prognostic correlations, multi-center studies with larger, homogeneous cohorts (>200 patients) are required. Nevertheless, KRAS mutation testing already provides a robust prognostic biomarker for PDAC. Integrating KRAS status with additional molecular markers, such as S100A2 expression, immune infiltration metrics, or microRNAs, may further refine risk stratification (70).

6. Targeting KRAS for treatment

In pancreatic cancer, therapeutic targeting of KRAS has been extensively investigated; however, two major challenges remain; its historical designation as the 'undruggable' and the emergence of bypass pathways despite KRAS inhibition. KRAS mutants exhibit high GTP-binding affinity and a sterically constrained active site and their signaling relies on protein-protein interactions that lack well-defined binding pockets, complicating direct inhibition. Conceptually, KRAS blockade should suppress the cancer growth and induce regression in KRAS-dependent PDAC. Indeed, KRAS inactivation in mouse models causes tumor shrinkage; however, spontaneous recurrence occurs, with ~1/3 of recurrent tumors lacking KRAS expression (71). In these KRAS-independent tumors, Yes associated protein 1 (YAP1) amplification collaborates with E2F for cell cycle activation and DNA repair, driving aggressive, quasi-mesenchymal phenotypes (72).

Despite these challenges, multiple approaches have been advanced for targeting KRAS mutants, including genetic approaches and small-molecule inhibitors identified through *in silic*o and *in vitro* screening platforms (73). Various therapeutic approaches have been tried that direct at the KRAS gene and its protein. These approaches include RNA interference (RNAi) strategies designed to overwhelm the expression of KRAS mutant (predominantly the $KRAS^{G12D}$ variant) (74,75). The other approach involved the use of farnesyltransferase inhibitors (FTIs) (such as lonafarnib or tipifarnib) that block the farnesylation of the KRAS protein at the C-terminal CAAX motif. This approach led to the prevention of its localization to the endoplasmic reticulum and Golgi apparatus (32,76). Moreover, inhibition of phosphodiesterase 6δ (PDEδ) with deltarasin was also employed, as it facilitates the transport of farnesylated KRAS to the plasma membrane (32,77).

In addition, disruption of RAS signaling by detaching farnesylated KRAS from the cell membrane (such as farnesyl thiosalicylic acid, also known as Salirasib) has also been attempted (32). Furthermore, KRAS-targeted vaccination has also been employed, utilizing mutant peptide antigens that contain amino acid substitutions characteristic of various KRAS mutations (78). In addition, small-molecule inhibitors that bind to the RAS-GDP complex, obstructing the interaction between KRAS and the SOS, thereby preventing SOS-mediated nucleotide exchange has been worked out (79-81).

Moreover, blocking the KRAS-GTP interaction prevents KRAS binding with RAF. This strategy includes covalent small molecules that selectively recognize and irreversibly bind to the $KRAS^{G12C}$ mutant, neutralizing its downstream signaling. Furthermore, targeting downstream signaling cascades, specifically the RAF-MEK-ERK and PI3K-AKT-mTOR pathways, using small-molecule inhibitors has also been routinely worked out (82,83). These approaches and their mechanisms of action are summarized in Fig. 3.

KRAS inhibition by RNAi. RNAi has emerged as a novel approach to suppress KRAS expression in mutant-driven cancers, including pancreatic cancer (75). *In vivo* and *in vitro* studies validate that RNAi-mediated knockdown of mutant KRAS in PDAC cells reduces proliferation, anchorage-independent growth and tumorigenicity (32). These findings suggest that KRAS-targeted small interfering RNAs (siRNAs) may represent a viable therapeutic approach (74). However, systemic delivery of siRNAs is limited by enzymatic degradation, renal clearance and challenges in achieving tumor-specific targeting. To overcome these barriers, siRNAs have been incorporated into Local Drug Eluter (LODER) implants, a decomposable polymeric matrix that protects siRNAs and enables its sustained, localized release within tumors over several months. In preclinical models, LODER-mediated delivery inhibited pancreatic tumor growth and improved survival (84,85). This approach was translated into a phase I-IIa clinical trial in combination with FOLFIRINOX chemotherapy, demonstrating encouraging efficacy, with a

median survival of almost15 months and the survival rate of 18-months (86).

Another innovative strategy employs human fibroblast-derived inhibitory exosomes (iExosomes) loaded with KRAS-specific siRNAs. These vesicles, expressing CD47 to evade uptake by the reticuloendothelial system, efficiently deliver siRNA via macropinocytosis and show robust antitumor activity in preclinical PDAC models (87). Clinical trials are currently underway to evaluate their safety and efficacy in metastatic PDAC. Additionally, systemic delivery of KRAS-targeting siRNAs using dioleoyl-phosphatidylcholine-based nanoliposomal platforms represents a promising approach for *in vivo* therapy (88).

KRAS-binding pocket targeting. Some small molecules have been found to directly bind KRAS hydrophobic pocket on the inactive KRAS-GDP complex, disrupting the interaction between KRAS and SOS, inhibiting nucleotide exchange (79,80). A second strategy involved compounds that obstruct the interface of GTP-bound KRAS and RAF or other downstream effectors, effectively blocking signal transduction. A third approach targets the KRAS-SOS complex, preventing activation of KRAS by small-molecule binding. While these approaches remain largely preclinical and have yet to be fully validated *in vivo*, they challenge the long-standing view of KRAS as an 'undruggable' oncogenic target.

Anti-KRAS vaccination. An alternative strategy to inhibit KRAS involves peptide-based vaccination using RAS peptides harboring specific amino acid mutations. To date, KRAS-targeted vaccination approaches in have not demonstrated clear clinical benefit, although novel peptide formulations are currently under clinical investigation (78,80). The first human trial of GI-4000, a recombinant heat-inactivated *Saccharomyces cerevisiae* vaccine expressing mutant KRAS, demonstrated a favorable safety profile and elicited measurable immune responses in most patients with pancreatic cancer (89).

KRAS membrane localization disruption. Another strategy to target KRAS focuses on disrupting its membrane localization, a critical step for its activation. KRAS undergoes farnesylation and is trafficked from the endoplasmic reticulum to the plasma membrane, where it attaches GTP and becomes active. Farnesyltransferase inhibitors (such as tipifarnib) were designed to block this farnesylation. However, clinical results have been largely disappointing as KRAS can undergo alternative prenylation via geranylgeranyl transferase 1, bypassing the blockade (32,76).

An alternative approach targets KRAS translocation by inhibiting phosphodiesterase 6δ (PDEδ), a chaperone that facilitates the membrane trafficking of farnesylated KRAS. Deltarasin, a high-affinity PDEδ inhibitor, disrupts KRAS membrane association and effectively reduces the proliferation in KRAS-dependent PDAC cell lines (32,90). A related strategy involves farnesyl-cysteine mimetics that compete with KRAS for membrane anchoring. Farnesyl thiosalicylic acid (FTS, Salirasib) displaces farnesylated KRAS from the membrane, induces its proteolytic degradation and inhibits downstream signaling (32). FTS has demonstrated preclinical and early clinical potential as a KRAS-targeted therapy in PDAC (91).

RAF-MEK-ERK pathway targeting. Beyond post-translational modifications and membrane localization of KRAS, its mutant-driven signaling networks constitute critical therapeutic targets (Fig. 1). Among these pathways, the RAF-MEK-ERK cascade is a major effector pathway, prompting the development of multiple MEK inhibitors. For instance, trametinib, an allosteric inhibitor of MEK1/2 blocks both its activation and kinase potential (92). Similarly, selumetinib, another oral MEK1/2 inhibitor, demonstrated limited clinical benefit, showing no significant survival advantage over capecitabine in gemcitabine-refractory PDAC (93,94). In addition, some trials are ongoing, evaluating other inhibitors of MEK such as refametinib and pimasertib, often in addition with gemcitabine, to enhance the therapeutic efficacy (80,82).

PI3K-AKT-mTOR targeting. A variety of inhibitors targeting PI3K, RAF, AKT and mTOR are under preclinical and clinical investigation (80). While early phase I trials occasionally observed partial tumor responses, most approaches targeting AKT, PI3K, or mTOR have yielded limited efficacy in KRAS-mutant tumors (95). Preclinical studies, however, demonstrate synergistic antitumor effects when PI3K pathway inhibitors are combined with RAF-MEK-ERK inhibitors in mouse models (79,96). Several clinical trials (phase I-III) have evaluated combinatorial approaches, including AKT inhibitors with MEK inhibitors (such as selumetinib), mTOR inhibitors (everolimus and temsirolimus), PI3K inhibitors (rigosertib), or multi-kinase inhibitors (sorafenib), with or without gemcitabine. Despite these efforts, most combinations have failed to achieve meaningful clinical benefit, often resulting in enhanced toxicity or treatment-related adverse effects (57).

Other inhibitors and targets. The downstream members of KRAS, the GTPases, Ras like proto-oncogene A (RALA) and RALB play crucial roles in PDAC cell transformation and invasion (66). Once activated, RALA and RALB regulate key cellular processes, including autophagy, cytokine signaling, endocytosis and transcriptional control. Dysregulation of these activities can promote cell propagation, apoptosis resistance and metastatic spread (32,38). Autophagy can be therapeutically targeted using inhibitors such as hydroxychloroquine, often in combination with MEK-ERK pathway inhibitors (97). Clinical trials evaluating the combination of trametinib (MEK1/2 inhibitor) and hydroxychloroquine are ongoing, highlighting the potential of such combinatorial strategies in PDAC.

Additional KRAS-pathway targets under investigation include ruxolitinib (a JAK1/2 inhibitor) and NF-κB inhibitors. Other approaches focus on agents affecting synthetic lethal interactions, transcriptional programs, survival signaling, cell cycle regulation, protein kinases, apoptosis and senescence (79,80). Beyond canonical effectors, KRAS-regulated metabolic pathways such as glucose and glutamine metabolism, macropinocytosis and autophagy present promising therapeutic targets (98).

Challenges and future directions of targeting the KRAS-miRNA axis in PDAC. Despite increasing evidence supporting miRNAs as regulators of KRAS signaling in PDAC, several challenges hinder their clinical translation (99,100). Efficient and tumor-specific delivery of miRNA-based therapeutics remains a major obstacle, largely due to the dense desmoplastic stroma and poor vascularization characteristic of PDAC (101). Although emerging delivery platforms, including lipid nanoparticles and exosome-based systems, have improved miRNA stability and uptake, further refinement is required to enhance tissue specificity and reduce systemic toxicity (102,103).

An additional challenge is the context-dependent nature of miRNA function (104). Individual miRNAs may exert divergent roles depending on tumor type, genetic background and oncogenic signaling, complicating therapeutic development (105,106). This highlights the need for PDAC-specific functional validation using relevant preclinical models (107). Moreover, because miRNAs regulate multiple downstream targets, off-target effects and unintended pathway modulation remain concerns, necessitating improved target prediction and transcriptomic profiling approaches (108).

Given these limitations, combination strategies are likely to be essential (109). Modulating KRAS-associated miRNAs may enhance responses to inhibitors of the MEK-ERK pathway, autophagy, or inflammatory signaling, thereby overcoming adaptive resistance to single-agent therapies (110). Importantly, the role of specific miRNAs must be interpreted within the PDAC context; for example, miR-96 promotes KRAS-driven tumor progression in PDAC but has been reported to function as a tumor suppressor in other cancers (111). Collectively, these considerations underscore the importance of context-aware and combinatorial approaches for translating KRAS-miRNA-targeted therapies into clinical applications (112).

7. Paradigm shift towards understanding the role of miRNA in PDAC

Recent innovations in high-throughput miRNA profiling have revolutionized our understanding of PDAC, uncovering robust miRNA signatures with clinical utility in diagnosis, prognosis and therapy. Recent computational studies have identified several dysregulated miRNAs inversely associated with KRAS expression, suggesting their potential as biomarkers and regulators of KRAS-driven oncogenesis in PDAC (113). A multicenter study reported a five-miRNA serum signature (hsa-miR-1343-5p, -4632-5p, -4665-5p, -665 and -6803-5p) capable of detecting early-stage pancreatobiliary tumors with >80% sensitivity and specificity, markedly outperforming CA19-9 (114).

A recent meta-analysis confirmed the diagnostic accuracy of miRNAs in pancreatic cancer, notably, miR-320, miR-1290, miR-93, miR-25, miR-451, miR-20, miR-21, miR-223 and miR-122. In addition, prognostically, miR-10, miR-21 and miR-221 associated strongly with survival (115). Furthermore, circulating and exosomal miRNAs (e.g., miR-21, miR-10b, miR-205-5p, miR-1246, miR-191-5p) have demonstrated utility in distinguishing PDAC from benign conditions such as pancreatitis, with diagnostic accuracy reaching 94% (116,117). These findings substantiate the paradigm shift: miRNAs are not peripheral players but central regulators of PDAC's molecular architecture, influencing KRAS-driven signaling, tumor progression and therapeutic response.

Therapeutic modulation of miRNAs is gaining traction. For instance, miR-665 has shown inhibitory effects on cancer cell growth, highlighting the potential of miRNA mimics and anti-miRNAs as precision therapeutics targeting tumor-specific molecular profiles (114). Integration of miRNA-based strategies into personalized medicine, tailoring interventions to individual tumor signatures. This may offer a promising avenue for improving outcomes in this aggressive disease.

8. Overview of miRNA structure, biogenesis and mechanism of action

miRNAs are small, single stranded (20-25 nucleotides), non-coding type RNAs that constitute one of the largest gene regulatory families, modulating gene expression via mRNA degradation or translational repression (14,118,119). Of miRNAs, ~50% are transcribed from non-coding genomic regions, while the rest are located within introns of protein-coding genes. The biogenesis of miRNA begins with transcription by RNA polymerase II, generating hairpin-shaped primary transcripts (pri-miRNAs) (14) (Fig. 5). These are processed by the Drosha-DGCR8 complex into ~60-70 nucleotide precursor (pre-)miRNAs. The pre-miRNAs are exported out of the nucleus by binding with Exportin-5 to the cytoplasm in a GTP-dependent manner (120,121). In the cytoplasm, Dicer cleaves pre-miRNAs into miRNA duplexes. One strand, known as the passenger strand, is degraded, while the other strand known as guide strand, is incorporated into the RNA-induced silencing complex (RISC) (122) (Fig. 5).

Argonaute (Ago) proteins, especially Ago2, are core RISC components, with Piwi-Argonaute-Zwille and P-element-Induced Wimpy testis domains facilitating binding to mature miRNAs and interaction with target mRNAs (123,124). miRNA binding typically occurs via the seed sequence (nucleotides 2-8) within the 3' untranslated region (3' UTR) of target mRNAs. Perfect complementarity usually triggers mRNA cleavage, while partial pairing results in translational repression, allowing a single miRNA to regulate multiple targets and vice versa (125).

Therapeutic applications include the use of miRNA mimics for replacement therapy and antisense oligonucleotides (ASOs) to suppress overexpressed miRNAs. ASOs can target pri-miRNAs, pre-miRNAs, or mature miRNAs, providing flexibility to modulate miRNA activity in diseases (126,127). Studies also reveal alternative mechanisms of miRNA action, highlighting the versatility and complexity of miRNA-mediated gene regulation (128,129).

9. Role of miRNAs in pancreatic cancer

In PDAC, miRNAs can function as either tumor suppressors or oncogenes and therapeutic strategies are accordingly categorized into miRNA replacement therapy and miRNA inhibition therapy (55). Profiling studies have shown that dysregulation of specific miRNAs correlates with poor

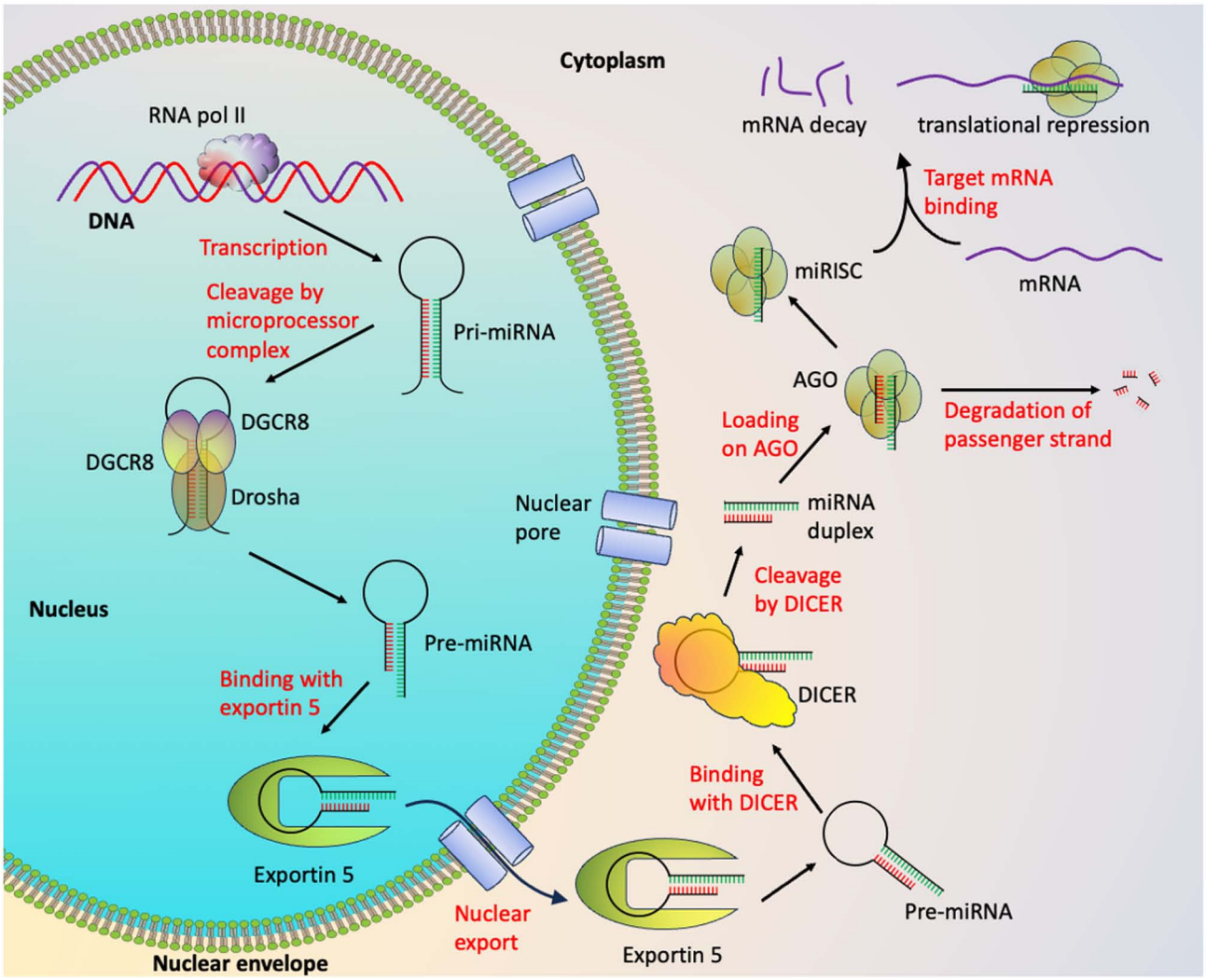

Figure 5. A diagrammatic overview of miRNA biogenesis. RNA polymerase II transcripts pri-miRNA, it is cleaved by Drosha-DGCR8 microprocessor unit to form pre-miRNA. Exportin 5 transports pre-miRNA out of the nucleus, followed by its cleavage by Dicer to yield miRNA duplex. AGO protein leads to the degradation of passenger strand of miRNA duplex and forms a mature miRNA. The miRNA guides the RISC to repress target RNA for translation, ultimately leading to mRNA decay. AGO, argonaute; Drosha-DGCR8, double-stranded RNA-specific ribonuclease III-DiGeorge syndrome critical region 8; miRNAs, microRNAs; pri-miRNA, primary microRNA; pre-miRNA, precursor microRNA; RISC, RNA-induced silencing complex.

prognosis, chemoresistance, invasion, metastasis and epithelial-mesenchymal transition (EMT). Several miRNAs implicated in PDAC development and progression include miR-21, miR-10b, miR-218, miR-205, miR-200c and Let-7 (130,131).

miRNA replacement therapy restores downregulated tumor-suppressive miRNAs, thereby reactivating normal cellular programs and suppressing oncogenic processes. For instance, the miR-200 family reduces cancer stemness by suppressing sex-determining region Y-box 2, Smad interacting protein 1 and zinc finger E-box binding homeobox 1, while the Let-7 family acts as a tumor suppressor across multiple cancers, including pancreatic, lung, ovarian and breast (132,133).

Conversely, oncogenic miRNAs such as miR-21, miR-210, miR-155 and miR-221 are often upregulated in PDAC, promoting tumor progression and correlating with reduced survival. These can be targeted through miRNA inhibition therapy approaches, using antisense oligonucleotides (AMOs) to degrade or block miRNA function (134). miRNAs are detectable via non-invasive samples including blood, saliva, urine and feces (135). For example, a study by Abue *et al* showed markedly elevated plasma levels of miR-483-3p and miR-21 in PDAC patients compared to healthy controls, highlighting their potential as diagnostic biomarkers (136).

Interactions between miRNAs and KRAS in PDAC. miRNAs serve as key regulators of KRAS expression. Several miRNAs, including the members of Let-7 and miR-143/145 families, bind directly to the 3'-UTR of KRAS mRNA, resulting in its degradation or translational repression. Loss or dysregulation of these miRNAs leads to aberrant KRAS activation, promoting uncontrolled proliferation, enhanced invasiveness and resistance to apoptosis. Consequently, the miRNA-KRAS network serves as a key regulatory axis in pancreatic tumor development and represents a promising avenue for targeted therapies.

10. Regulation of signaling via miRNAs

The coordinated interplay of miRNAs can modulate communication among multiple pathway components,

thereby influencing the key signaling networks such as the RAS-RAF-MAPK cascade (42,137). Key pathway members, including HRAS, KRAS and NRAS, are directly targeted by Let-7 (42) (Fig. 2). miRNAs also modulate essential regulatory proteins, including RASA1, SPRED1, SPRY1 and the tumor suppressor PTEN. For instance, miR-21 and miR-206 jointly target SPRED1, RASA1 and SPRY1, whereas miR-21 alone regulates PTEN (138,139).

Beyond direct pathway components, miRNAs can also regulate upstream activators and downstream effectors; miR-9-3p targets the integrin subunit β1 (140) and miR-206 and miR-21 targets tumor suppressor PDCD4 (141,142). Notably, a number of miRNAs exhibit dynamic expression patterns during the progression of pancreatic cancer, modulating signaling networks and contributing to PDAC pathogenesis (143).

11. miRNAs targeting KRAS

The first evidence of miRNA-mediated regulation of KRAS proteins was demonstrated by Johnson *et al* (144), who demonstrated that the Let-7 family directly targets KRAS mRNA in lung cancer. Subsequent studies have identified multiple miRNAs that modulate RAS expression across different malignancies. Given that oncogenic KRAS is a principal driver and lineage-survival gene in PDAC, understanding miRNA-mediated regulation of KRAS is of biological and therapeutic relevance (145,146).

Although the mutational activation of KRAS is nearly universal in PDAC, accumulating evidence indicates that post-transcriptional regulation by miRNAs markedly influences KRAS protein output and downstream signaling strength. Importantly, these regulatory relationships can be either unidirectional, where miRNAs suppress KRAS expression, or bidirectional, where KRAS signaling feeds back to repress miRNA expression, forming self-reinforcing oncogenic loops.

To date, miRNAs reported to directly target KRAS in PDAC, include miR-126, miR-96, miR-145, miR-143, miR-193b, miR-217, miR-206, miR-3923, Let-7a and Let-7b (Fig. 2; Table I) (147,148). Most of these miRNAs function as tumor suppressors and their downregulation contributes to sustained KRAS signaling, tumor progression and therapeutic resistance. Some of these miRNAs include:

Let-7. The human Let-7 miRNA family comprises at least 13 members, including Let-7a and Let-7b. These miRNAs are well-established regulators of cell proliferation, differentiation and apoptosis through the direct targeting of key oncogenes, MYC, RAS and high mobility group AT-hook 2 (149). Let-7 is widely regarded as a canonical tumor-suppressive miRNA family and its downregulation is frequently observed across multiple cancer types, including PDAC (150).

The interaction between Let-7 and KRAS in pancreatic cancer is predominantly unidirectional, with Let-7 directly binding to complementary sites within the 3'-UTR of KRAS mRNA and suppressing its translation. This interaction has been validated by luciferase reporter assays and KRAS protein analyses in PDAC cell models (151). However, emerging evidence also supports an indirect feedback component, whereby oncogenic KRAS signaling suppresses Let-7 biogenesis through upregulation of LIN28A/B, known inhibitors of Let-7 maturation. This KRAS-LIN28-Let-7 axis, described in PDAC and other KRAS-driven cancers, establishes a feed-forward oncogenic loop that reinforces KRAS expression at the post-transcriptional level (48,152).

Functionally, restoration of Let-7 expression *in vitro* reduces KRAS protein levels, inhibits PDAC cell proliferation and suppresses tumorigenicity. Nevertheless, *in vivo* studies have produced variable results, underscoring the importance of delivery efficiency and tumor microenvironmental context (153). Collectively, Let-7 functions as both a direct KRAS suppressor and a node within a broader regulatory loop sustaining KRAS signaling.

miR-96. miR-96 belongs to the miR-183-96-182 cluster, whose members display context-dependent oncogenic or tumor-suppressive functions (154). While miR-96 is upregulated in several epithelial cancers, its expression is notably reduced in PDAC (155). Current evidence supports a strictly unidirectional regulatory relationship between miR-96 and KRAS in PDAC. miR-96 directly binds to the KRAS 3'-UTR, leading to translational repression and attenuation of KRAS-driven MAPK and PI3K signaling pathways (156). Functional studies have not demonstrated reciprocal regulation of miR-96 by KRAS signaling, indicating that miR-96 acts primarily as an upstream suppressor rather than part of a feedback loop. Restoration of miR-96 expression inhibits PDAC cell growth, migration and tumor progression, highlighting its role as a tumor-suppressive regulator of KRAS output (155,156).

miR-126. miR-126 is encoded within intron 7 of the EGFL7 gene on chromosome 9 and plays key roles in angiogenesis, inflammation and tumor biology (157). In PDAC, miR-126 acts as a unidirectional suppressor of KRAS, directly targeting its 3'-UTR and reducing KRAS protein expression (158). Loss of miR-126 enhances downstream KRAS signaling, promoting tumor growth and invasion (158).

While KRAS-mediated repression of miR-126 has been observed indirectly via epigenetic silencing mechanisms in other cancers, direct evidence of a feedback loop in pancreatic cancer remains limited (157). Thus, current data support miR-126 as a primarily upstream regulator of KRAS rather than a reciprocal feedback component.

miR-143/145. The miR-143/145 cluster is one of the best-characterized miRNA systems involved in KRAS regulation. Its tumor-suppressive role was first identified in colorectal cancer, where miR-143 was shown to inhibit KRAS translation via binding to its 3'-UTR (159). In pancreatic cancer, the miR-143/145 cluster forms a well-defined negative feedback loop with KRAS. Kent *et al* (47) demonstrated that oncogenic KRAS represses miR-143/145 transcription through activation of RREB1, which binds the miR-143/145 promoter. In turn, both KRAS and RREB1 are direct targets of miR-143/145, creating a self-reinforcing feed-forward loop that sustains oncogenic KRAS signaling when miR-143/145 is lost (47). Loss of this cluster enhances RAS-GTP loading and downstream pathway activation, including MAPK, PI3K and JNK signaling, highlighting miR-143/145 as a central node in

Table I. Differentially expressed miRNAs and their target proteins in pancreatic cancer.

First author/s, year	miRNAs	Roles in pancreatic cancer	Role/expression	Context-dependency	Targets	(Refs.)
A, miRNAs directly regulating KRAS						
Dai *et al*, 2015	Let-7	Drug resistance, proliferation	Tumor suppressor/ down regulated	Depends on KRAS mutation burden and LIN28 expression; loss is particularly oncogenic in KRAS-driven PDAC	KRAS, MAPK, IGF family, c- Myc, STAT3, HMGA1, IGF2BP1/3, RRM2, N-cadherin/ ZEB1, NF2, LIN28	(151)
Lavacchi *et al*, 2023	miR-143	Proliferation, invasion, metastasis	Tumor suppressor/ down regulated	Context-dependent via stromal-epithelial interactions and KRAS signaling activity	KRAS, COX2, GET1, GET2, TAK1, RREB1	(215)
Jin *et al*, 2015; Khalilian *et al*, 2026	miR-193b	Inhibit cell growth and malignant transformation	Tumor suppressor/ down regulated	Suppressive effects depend on KRAS dependency and early tumorigenic stage	KRAS	(161,216)
Hara *et al*, 2014	miR-126	Proliferation	Tumor suppressor/ down regulated	Function varies with angiogenic signaling and growth-factor-rich microenvironment	KRAS, c-Myc, MAPK, E2F2, STAT3, ADAM9	(217)
Liu *et al*, 2021	miR-96	Tumor growth, invasion	Tumor suppressor/ down regulated	Highly context-dependent; tumor-suppressive in pancreatic cancer but oncogenic in other tissues	KRAS, AKT	(218)
Singh *et al*, 2021	miR-206	Inhibits angiogenesis, inflammation	Tumor suppressor/ down regulated	Depends on inflammatory signaling and NF-κB activation status	KRAS, KRAS-induced NF-κB	(219)
Zhao *et al*, 2010	miR-217	Decreases proliferation and survival	Tumor suppressor/ down regulated	Context-dependent on KRAS addiction and metabolic rewiring	KRAS, AKT, ATAD2	(164)
Li *et al*, 2016	miR-3923	Emerging regulator	Tumor suppressor	Function influenced by lncRNA-miRNA-mRNA networks and ceRNA competition	KRAS via lncRNA/ miRNA network	(165)
B, miRNAs regulating downstream or parallel components of the KRAS signaling pathway						
Hu *et al*, 2025	miR-203	EMT, cell cycle, apoptosis	Tumor suppressor/ down regulated	Depends on EMT status and epigenetic silencing in advanced tumors	Bmi-1, CAV1, CKAP2, WASF1, ASAP1, SNAI1/2, RUNX2, LASP1, ZEB1/2, AKT2	(220)
Guo *et al*, 2020	miR-34a/b	DNA repair, angiogenesis, apoptosis	Tumor suppressor/ down regulated	Strongly dependent on TP53 mutational status	TP53, c-Myc, Notch1/ 2/3, Snail1, E2F1/3, Bcl-2, CDK6, SIRT1, SMAD3, CCND1	(221)
Jin *et al*, 2023	miR-124	Proliferation, invasion, metastasis	Tumor suppressor/ down regulated	Context-dependent via epigenetic regulation and invasive tumor phenotype	RAC1	(222)

Table I. Continued.

First author/s, year	miRNAs	Roles in pancreatic cancer	Role/expression	Context-dependency	Targets	(Refs.)
B, miRNAs regulating downstream or parallel components of the KRAS signaling pathway						
Zhang *et al*, 2021	miR-146a	Invasion	Tumor suppressor/down regulated	Function varies with EGFR and inflammatory pathway activation	EGFR, IRAK1	(223)
Diaz-Riascos *et al*, 2019	miR-200a	EMT	Tumor suppressor/down regulated	Dependent on epithelial-mesenchymal plasticity and tumor stage	ZEB1/2, Vimentin, PTEN, MMPs, SOX2, E-cadherin	(224)
Chen *et al*, 2024	miR-21	Cell division, proliferation	Oncogene/ upregulated	Oncogenic role amplified by TGF-β signaling and fibrotic tumor microenvironment	PTEN, EGFR, CDK6, PDCD4, BCL2, TIMP2/3, SOCS5, FAS	(117)
Wang *et al*, 2015	miR-155	Apoptosis	Oncogene/ upregulated	Context-dependent via immune-cell infiltration and inflammatory cytokines	SOCS1, SOCS3, TP53INP1	(225)
Ghafouri-Fard *et al*, 2023	miR-424	Migration, proliferation	Oncogene/ upregulated	Depends on cell-cycle dependency and SOCS6 repression	SOCS6	(226)
Yang *et al*, 2025	miR-192	Cell cycle, proliferation	Oncogene/ upregulated	Context-dependent via p53 signaling and DNA damage response	Cell cycle regulators, SIP1	(227)
Ouyang *et al*, 2017	miR-10	Invasion, metastasis	Oncogene/ upregulated	Dependent on HOX gene dysregulation and metastatic potential	HOXB8, TFAP2C, HOXA1, HOXA3	(228)
Ji *et al*, 2025	miR-208a	EMT	Oncogene/ upregulated	Context-dependent through EMT signaling activation in late-stage tumors	CDH1	(229)
Yang *et al*, 2016	miR-375	Apoptosis, proliferation	Oncogene/ upregulated	Dual behavior depending on metabolic state and cancer subtype	14-3-3ζ, PDK1	(230)
Ding *et al*, 2020	miR-16-1/2	Angiogenesis, apoptosis	Oncogene/ upregulated	Oncogenic in PDAC despite suppressive roles in other cancers	BCL2L1, MYBL2, FGFR2, NAIP5	(231)
Kanno *et al*, 2017	miR-196a-2/miR-196	-	Oncogene/ upregulated	Depends on HOX gene regulation and gastrointestinal lineage	HOXB8, HMGA2, ANXA1	(232)
Shopit *et al*, 2020	miR-421	Colony formation, proliferation	Oncogene/ upregulated	Oncogenic effects enhanced in SMAD4-deficient tumors	SMAD4	(233)
Di Martino *et al*, 2022	miR-221/222	Cell cycle progression	Oncogene/ upregulated	Context-dependent via PTEN loss and checkpoint dysregulation	PTEN, MMP-2/9, CDKN1B, PUMA, BIM	(234)

Table I. Continued.

First author/s, year	miRNAs	Roles in pancreatic cancer	Role/expression	Context-dependency	Targets	(Refs.)
B, miRNAs regulating downstream or parallel components of the KRAS signaling pathway						
Pancratov *et al*, 2013	miR-310a	Proliferation, metastasis	Oncogene/ upregulated	Depends on apoptotic threshold and BIM repression	NKRF, BIM	(235)
Ghafouri-Fard *et al*, 2022	miR-15a/b	Angiogenesis, apoptosis	Oncogene/ upregulated	Oncogenic in pancreatic cancer despite tumor-suppressive roles elsewhere	BCL2L1, MYBL2, FGFR2, WNT3A, BMI-1	(236)
Liu *et al*, 2020	miR-210	Tumor-stroma interaction	Oncogene/ upregulated	Strongly dependent on hypoxia and stromal remodeling	HOXA9, RAD52, E2F3, ACVR1B	(237)

ACVR1B, Activin A receptor type 1B; ADAM9, A disintegrin and metalloproteinase 9; AKT, Protein kinase B; AKT2, AKT serine/threonine kinase 2; ANXA1, Annexin A1; ASAP1, ArfGAP with SH3 domain, Ankyrin repeat and PH domain 1; ATAD2, ATPase family AAA domain-containing protein 2; Bcl-2, B-cell lymphoma 2; BCL2L1, B cell lymphoma 2 like 1; BIM, BCL2 interacting mediator of cell death; SMAD4, SMAD family member 4; BMI-1, B-cell specific Moloney murine leukemia virus integration site 1; CAV1, Caveolin 1; CCND1, Cyclin D1; CDK6, cyclin-dependent kinase 6; CDKN1B, Cyclin dependent kinase inhibitor 1B; CKAP2, Cytoskeleton associated protein 2; CDH1, Cadherin 1; c-Myc, Cellular myelocytomatosis oncogene; COX2, Cyclooxygenase 2; E2F1/3, E2F transcription factor 1/3; E2F2, E2F transcription factor 2; EGFR, Epidermal growth factor receptor; FAS, Fas cell surface death receptor; FGFR2, Fibroblast growth factor receptor 2; GET1, Guided entry of tail-anchored protein 1; GET2, Guided entry of tail-anchored protein 2; HMGA2, High mobility group AT-hook 2; HOXA1, Homeobox A1, HOXA3, Homeobox A3; HOXB8, Homeobox B8; HOXA9, Homeobox A9; IGF, Insulin-like growth factor; IGF2BP1/3, Insulin-like growth factor 2 mRNA-binding protein 1/3; IRAK1, Interleukin-1 receptor associated kinase 1; KRAS, Kirsten rat sarcoma viral oncogene homolog; LASP1, LIM and SH3 protein 1; LIN28, Lineage abnormal 28; lncRNA, long noncoding RNA; MAPK, mitogen-activated protein kinase; miRNAs, microRNAs; MMPs, Matrix metalloproteinases; MMP-2/9, Matrix metalloproteinase-2/9; MYBL2, MYB proto-oncogene like 2; NAIP5, NLR family apoptosis inhibitory protein 5; N-cadherin/ZEB1, Neural cadherin/Zinc finger E-box-binding homeobox 1; NF-κB, Nuclear factor-kappa-light-chain enhancer of activated B cells; NF2, Neurofibromin 2; NKRF, NF-κB repressing factor; Notch1/2/3, Neurogenic locus notch homolog 1/2/3; PDAC, Pancreatic ductal adenocarcinoma; PDCD4, Programmed cell death protein 4; PDK1, Phosphoinositide-dependent kinase 1; PTEN, Phosphatase and tensin homolog; PUMA, p53 upregulated modulator of apoptosis; RAC1, Ras-related C3 botulinum toxin substrate 1; RAD52, RAD52 homolog DNA repair protein; RREB1, Ras responsive element binding protein 1; RRM2, Ribonucleotide reductase M2 subunit; RUNX2, Runt-related transcription factor 2; SIRT1, Sirtuin 1; SIP1, SMAD interacting protein 1; SMAD3, SMAD family member 3; SNAI1/2, Snail family transcription repressor 1/2; SOCS1, Suppressor of cytokine signaling 1; SOCS3, Suppressor of cytokine signaling 3; SOCS5, Suppressor of cytokine signaling 5; SOCS6, Suppressor of cytokine signaling 6; SOX2, SRY-box transcription factor 2; STAT3, Signal transducer and activator of transcription 3; TAK1, Transforming growth factor-β activated kinase 1; TFAP2C, Transcription factor activating enhancer binding protein 2 gamma; TP53, Tumor protein 53; TIMP2/3, Tissue inhibitor of metalloproteinases 2/3; TP53INP1, Tumor protein p53 inducible nuclear protein 1; WASF1, WAS protein family member 1; WNT3A, Wnt family member 3A; ZEB1/2, Zinc-finger E-box binding homeobox 1/2.

KRAS-driven regulatory circuitry rather than a simple unidirectional regulator (47,160).

miR-193b. miR-193b is frequently downregulated in multiple types of cancer and functions as a tumor-suppressive miRNA in PDAC. Evidence indicates a unidirectional regulatory relationship, where miR-193b directly targets the KRAS 3'-UTR, resulting in reduced KRAS expression and suppression of both AKT and ERK signaling pathways (161). Functional restoration of miR-193b inhibits PDAC cell proliferation and invasion (161). Although KRAS-dependent transcriptional repression of miR-193b has been suggested in other tumor contexts, direct confirmation of a feedback loop in pancreatic cancer remains lacking. Current data support miR-193b primarily as an upstream regulator of KRAS rather than a reciprocal component of a feedback loop.

miR-206. miR-206 is markedly downregulated in PDAC, as demonstrated by gene expression omnibus-based expression profiling and validation studies (162). miR-206 directly targets KRAS mRNA, leading to inhibition of the KRAS-NF-κB signaling axis. This interaction has been validated across multiple *in vitro* and *in vivo* PDAC models (162). Reduced KRAS-NF-κB activity subsequently diminishes inflammatory and pro-angiogenic gene expression, including IL-8, CXCL1, CXCL2, CCL2, GM-CSF and VEGF-C (162). While KRAS-driven inflammatory signaling may indirectly influence miR-206 expression, a defined reciprocal feedback loop has not yet been conclusively demonstrated in PDAC.

miR-216/217. The miR-216/217 cluster is highly expressed in normal pancreatic tissue and markedly reduced in PDAC (163). This cluster exhibits features of a bidirectional regulatory

relationship. miR-217 directly targets KRAS, suppressing tumor growth in PDAC models (164). Conversely, KRAS activation suppresses miR-216/217 expression, as demonstrated in KRAS-mutant mouse models, suggesting a feed-forward oncogenic loop in which KRAS signaling reinforces its own expression by repressing inhibitory miRNAs (163). This reciprocal regulation positions the miR-216/217 cluster as an important brake on KRAS signaling that is actively dismantled during pancreatic tumorigenesis.

miR-3923. miR-3923 has been implicated in PDAC with context-dependent roles. Although some data indicate that miR-3923 can target the 3'-UTR of KRAS mRNA, potentially reducing KRAS expression, the predominant behavior of miR-3923 in PDAC appears oncogenic. Li *et al* (165) demonstrated that hypoxia-induced lncRNA NUTF2P3-001 acts as a competitive endogenous RNA, derepressing KRAS by sponging miR-3923, which suggested that miR-3923 can directly bind KRAS 3'-UTR but fails to suppress its expression when sequestered.

Studies have consistently reported aberrant overexpression of miR-3923 in PDAC tissues and patient serum, associating elevated levels with increased tumor cell proliferation, invasion and migration. These oncogenic effects are considered to result from suppression of tumor suppressor genes and activation of pathways related to EMT and metastasis (165,166).

Consequently, miR-3923 is emerging as a potential diagnostic biomarker and prognostic indicator in PDAC (165). The regulation is unidirectional as miR-3923 acts upstream, capable of targeting KRAS mRNA but unable to initiate any feedback control over its own expression via KRAS signaling. However, Further research is necessary to delineate its full molecular targets and determine whether a dual regulatory potential exists under differing cellular contexts.

12. miRNAs for pancreatic cancer therapy

miRNAs represent a promising class of therapeutic agents in pancreatic cancer, owing to their capacity to simultaneously modulate several tumor-suppressive and oncogenic pathways. Therapeutic strategies focus on either restoring the expression of tumor-suppressive miRNAs or inhibiting oncogenic miRNAs, using synthetic mimics or antagomirs, respectively. These interventions target critical molecular regulators such as KRAS, TP53 and signaling pathways that govern cell proliferation, apoptosis and metastasis. Although some challenges exist regarding efficient stability, delivery and off-target effects, miRNA-based therapies are being actively investigated in preclinical models and early-phase clinical trials, offering a novel, personalized approach to improving outcomes in pancreatic cancer treatment.

miRNAs as therapeutic targets for PDAC. RAS proteins are central drivers of multiple oncogenic signaling pathways across various cancers, making them prime targets for therapeutic intervention (167,168). Emerging evidence indicates that modulating KRAS-directing miRNAs can effectively suppress cancer growth (147). For example, miR-34 expression inhibits migration and cell proliferation in lung cancer and markedly reduces cancer growth by targeting KRAS (169). Similarly, downregulation of miR-31, which directly affects RASA1, a RAS-MAPK pathway regulator, decreases cell proliferation and tumor size in colorectal cancer models (170). In squamous cell cancer, miR-181a has been shown to directly target KRAS and suppress its proliferation (171), while miR-451 overexpression suppresses tumor growth in NSCLC by targeting RAB14 (172).

Considering the significant role of KRAS signaling in PDAC, miRNA-based strategies targeting KRAS represent an underexplored therapeutic opportunity. Although limited, studies in PDAC have demonstrated promising results. For instance, nanoparticle-mediated delivery of miR-34a, miR-143 and miR-145 in animal models potentially inhibited the cancerous growth (173). Antisense oligonucleotides targeting overexpressed oncogenic miRNAs such as miR-21, miR-221, miR-132 and miR-212 enhanced gemcitabine efficacy and inhibited tumor growth by modulating tumor suppressors like Rb1 (174,175). Suppression of miR-10a reduces pancreatic tumor growth and metastasis.

Alternative delivery strategies, including viral vectors and adenovirus-mediated expression, have been employed to deliver miR-143, miR-145 and miR-150, effectively suppressing pancreatic tumor development and metastasis (47). However, restoration of Let-7, a well-characterized anticancer miRNA, reduces proliferation in PDAC cells by downregulating KRAS and inhibiting MAPK signaling (153).

P21-activated kinase 4 inhibition, together with Nicotinamide phosphoribosyl transferase modulators, suppresses proliferation in pancreatic cancer cells. This effect is mediated by reduced phosphorylation and enhanced expression of tumor-suppressive miRNAs including Let-7c/d, miR-145, miR-34c, miR-320 and miR-100 (176). These findings suggest that therapeutic strategies aimed at enhancing cancer-suppressive miRNAs targeting the KRAS cascade could offer an encouraging approach to overcome treatment-resistant pancreatic cancer.

Strategies to target miRNAs in PDAC. Despite extensive efforts, direct targeting of KRAS protein or its signaling pathway in pancreatic cancer has achieved limited success. However, modulating miRNAs that regulate RAS and other oncogenic pathways offers a promising alternative. Although no clinical trials currently focus on KRAS-targeting miRNAs, the rapidly expanding field of miRNA research suggests that innovative therapeutic applications are likely to emerge in future. The identification of dysregulated miRNAs as novel contributors in PDAC highlights the requirement for effective tools to manipulate these molecules.

One prominent strategy involves the use of AMOs to inhibit oncogenic miRNAs. These molecules bind specifically to target miRNAs, inducing miRNA silencing (177). For instance, anti-miRNA strategy has demonstrated the ability to specifically block mutant $KRAS^{G12D}$, while sparing wild-type KRAS, thereby selectively downregulating oncogenic signaling (178).

Another approach, miRNA replacement therapy, restores the expression of anticancer miRNAs that are downregulated in PDAC. Synthetic miRNA mimics supplement endogenous miRNA levels and are effective because of their smaller size,

high target affinity and minimal immunogenicity (179). For example, miR-489, an anticancer nucleic acid, is downregulated by KRAS signaling in pancreatic cancer, which can be restored using miRNA mimetics to potentially inhibit metastasis (180).

Despite their therapeutic potential, miRNA-based treatments face several challenges, including limited cell specificity, minimal *in vivo* stability, uneven biodistribution, interference with endogenous RNA system and substantial off-target effects. All these parameters complicate the efficient delivery and function of miRNA-based approaches (181). To overcome these limitations, chemical modifications of oligonucleotides are engineered to enhance their stability and binding affinity. One successful example is Locked Nucleic Acid (LNA) technology, in which nucleic acid analogs contain LNA nucleotide monomers possessing a furanose unit fastened in an RNA-like conformation. This configurational constraint enhances hybridization to complementary RNA targets and has demonstrated higher efficacy (181).

13. miRNAs as PDAC biomarkers

Early detection of PDAC is critical, as surgical intervention remains the only option for cure, yet is practicable in only 15-20% of patients diagnosed at early stages (182,183). In addition, postoperative complications are common and conditions such as pancreatic tuberculosis or chronic pancreatitis are often difficult to distinguish from malignancy (184). Currently, only carbohydrate antigen 19-9 (CA 19-9) is FDA-approved biomarker for monitoring treatment response in PDAC (185), but it suffers from low sensitivity and specificity. Other markers, including CEA and CA125, have limited utility for early detection but may still aid in monitoring therapy (186).

In this situation, miRNAs have played a novel role as biomarkers for early PDAC detection due to their stability in serum, non-invasive accessibility and ease of measurement (187). For example, Lee *et al* (188) profiled over 200 miRNA precursors across normal pancreas, pancreatic cancer tissues, paired benign tissues, pancreatitis tissues and related cell lines, enabling detection of premalignant changes during the transition from benign to malignant states. Key upregulated cancer-related miRNAs included miR-100, miR-424, miR-212, miR-301 and miR-125b-1, while miR-142-P, miR-345 and miR-139 were downregulated as compared to normal pancreas (189).

Several miRNAs are also associated with precursor lesions and histological progression. Notably, miR-21 and miR-155 are expressed more in pancreatic PanIN and show specificity in pancreatic juice samples (190). Other studies recognized miR-21, miR-196a, miR-27a, miR-146a and miR-200a as most upregulated miRNAs via FNA, while miR-96, miR-217, miR-141, miR-20a and miR-29c were among the most downregulated (184). Additional upregulated candidates confirmed by reverse transcription-quantitative PCR include miR-15b, miR-186, miR-190, miR-196a, miR-200b, miR-221, miR-222 and miR-95 (191), as well as miR-21, miR-26b, miR-194, miR-200b/c, miR-320, miR-374 and miR-429 in pancreatic cancer cell lines compared to normal pancreatic cells (Table I).

Early KRAS mutations, frequently identified in PanIN lesions, can alter miRNA expression (192). Using a $KRAS^{G12D}$ mouse model, upregulation of miR-21, miR-205 and miR-200, was identified in early adenocarcinoma lesions and miR-21 levels associated with the level of morphological changes in PanIN samples (193). These findings indicate that miRNA profiling may have strong potential for early diagnosis, risk stratification and monitoring disease progression in pancreatic cancer.

14. miRNAs as PDAC prognostic factors

Beyond their roles in diagnosis and therapy, miRNAs have emerged as important prognostic indicators in PDAC. Dysregulated expression of specific miRNAs correlates with tumor aggressiveness, metastatic potential and overall patient survival. For example, enhanced levels of miR-155, miR-21 and miR-196a are consistently designated with low prognosis, reflecting their involvement in promoting proliferation, invasion and resistance to apoptosis (194). Conversely, minimal expression of tumor-suppressive miRNAs such as Let-7, miR-34a, miR-217 and miR-96 often predicts more aggressive disease and worse clinical outcomes, likely due to their role in restraining oncogenic pathways such as KRAS and RAS-MAPK signaling (195).

In addition to single miRNAs, miRNA expression signatures or panels are proposed as more robust prognostic tools. These signatures integrate multiple upregulated oncogenic miRNAs and downregulated tumor suppressors for improved stratification of patients according to risk and likely response to therapy. The prognostic relevance of miRNAs is further supported by their detectability in serum, plasma, or pancreatic juice, enabling non-invasive monitoring of disease progression and response to treatment. Overall, miRNAs serve as both molecular readouts of tumor biology and predictive biomarkers, providing valuable insight into patient outcomes and helping guide personalized therapeutic strategies in PDAC (196,197).

miRNAs may also serve as valuable predictors of chemoresistance and therapeutic responsiveness in pancreatic cancer. For instance, miR-320c has been identified as a prognostic marker for predicting clinical response to gemcitabine (198). Similarly, patients exhibiting higher post-surgical levels of miR-200c demonstrated improved survival compared to those with lower expression. This clinical observation aligns with *in vitro* findings, where upregulation of miR-200c reduced cellular invasiveness, suggesting a functional role in modulating tumor aggressiveness (199).

15. Clinical trials involving KRAS and miRNAs in pancreatic cancer

Multiple preclinical studies have demonstrated that specific miRNAs can directly suppress KRAS expression or modulate its downstream signaling pathways, resulting in reduced pancreatic cancer cell proliferation, invasion and therapeutic resistance (200). Conversely, oncogenic KRAS signaling has been shown to reprogram the miRNA regulatory landscape by altering miRNA transcription, processing and maturation, such as through DROSHA, DICER and AGO2 modulation,

thereby reinforcing tumor-promoting networks in PDAC (46). These findings establish a strong biological basis for targeting the KRAS-miRNA axis in pancreatic cancer.

Despite this compelling preclinical rationale, translation of miRNA-based modulation of KRAS signaling into clinical practice remains limited and no registered clinical trial has yet combined KRAS-targeted agents with miRNA-based therapeutics in PDAC as of 2025. Current clinical efforts primarily focus on either KRAS inhibition or RNA interference strategies. For example, a phase I clinical trial (NCT03608631; iExoKrasG12D) is evaluating mesenchymal stromal cell-derived exosomes loaded with $KRAS^{G12D}$ siRNA in patients with metastatic $KRAS^{G12D}$-mutant pancreatic cancer (201). Recent reports indicate that this approach is well tolerated, with no dose-limiting toxicities observed, alongside evidence of $KRAS^{G12D}$ DNA downregulation, reduced phospho-ERK signaling and increased intratumoral $CD8^+$ T-cell infiltration in a subset of patients (201,202).

In parallel, small-molecule KRAS inhibitors have entered early-phase clinical testing. A phase I/Ib study of the $KRAS^{G12D}$-selective inhibitor zoldonrasib (RMC-9805; NCT06040541) is currently recruiting patients with advanced solid tumors, including PDAC (203). Initial clinical data reported in 2025 demonstrate promising antitumor activity, including reductions in circulating $KRAS^{G12D}$ mutant ctDNA in treated PDAC patients (204).

In preclinical models, MRTX1133 has shown potent inhibition of KRAS signaling, reduced cell viability and caused tumor regressions in xenograft and immunocompetent tumor models, especially in pancreatic ductal adenocarcinoma (205). Additionally, the pan-RAS inhibitor daraxonrasib (RMC-6236; NCT05379985) is undergoing phase I/II evaluation in pancreatic and other gastrointestinal cancers, with phase III studies active in previously treated metastatic PDAC (206).

ASP3082 is a KRAS G12D-selective degrader, proteolysis targeting chimera (PROTAC), designed to induce targeted degradation of the oncogenic KRAS G12D protein rather than just inhibiting it. It has entered Phase I clinical trials for advanced solid tumors harboring the KRAS G12D mutation, including studies both as monotherapy and in combination regimens (207). BI-1823911 is a small-molecule KRAS inhibitor developed by Boehringer Ingelheim that has also entered a Phase I clinical trial (NCT04973163) to assess safety, dosing and preliminary efficacy in patients with advanced cancers that harbor KRAS mutations. While BI-1823911 was initially characterized as targeting KRAS G12C, its clinical study enrollment includes patients with diverse KRAS mutations and it is being evaluated both alone and in combination with other agents.

Notably, none of these clinical strategies integrate miRNA-based therapeutics with KRAS-targeted agents, despite strong preclinical evidence suggesting potential synergy. Several miRNAs, such as miR-34a, miR-143/145, Let-7 family members and miR-217 have been shown to concurrently suppress KRAS expression, attenuate MAPK and PI3K signaling and overcome adaptive resistance mechanisms induced by KRAS inhibition (42,200). From a mechanistic standpoint, combining KRAS inhibitors with tumor-suppressive miRNAs could i) enhance pathway suppression at multiple regulatory levels, ii) prevent or delay compensatory feedback activation and iii) target parallel oncogenic programs driven by KRAS, including metabolic reprogramming and immune evasion (46,200).

However, several scientific and clinical challenges likely explain the current absence of such combination trials. miRNAs exhibit pleiotropic effects and regulate hundreds of targets, raising concerns regarding off-target toxicity and unpredictable pharmacodynamic interactions when combined with KRAS inhibitors (208). Furthermore, KRAS-mutant PDAC is known to disrupt miRNA biogenesis machinery, including DROSHA, DICER and AGO2, which may compromise the efficacy of exogenously delivered miRNAs (46). From a clinical perspective, efficient and tumor-selective delivery of miRNA therapeutics to the dense and desmoplastic PDAC microenvironment remains a major barrier, particularly when combined with systemic targeted agents (208,209).

In summary, while early-phase clinical trials targeting KRAS through siRNA or small-molecule inhibitors represent significant progress, the lack of clinical studies combining KRAS-directed therapies with miRNA-based approaches reflects unresolved biological, pharmacological and delivery-related challenges rather than a lack of scientific rationale. Future advances in RNA delivery platforms, improved miRNA target specificity and rational biomarker-driven patient selection may enable the successful clinical translation of KRAS-miRNA combination strategies in pancreatic cancer.

16. Future perspectives

Although compelling evidence supports miRNA-mediated regulation of KRAS signaling in pancreatic cancer, the translation of these findings into effective therapies has been markedly limited, underscoring several unresolved biological and technical challenges. While numerous miRNAs, including Let-7, miR-143/145 and miR-217, exhibit tumor-suppressive activity through direct or indirect targeting of KRAS, the complexity of KRAS-driven regulatory networks and the pancreatic tumor microenvironment have hindered therapeutic progress.

One major challenge lies in the delivery efficiency of miRNA-based therapeutics. PDAC is characterized by an extensive desmoplastic stroma, hypovascularity and elevated interstitial pressure, all of which markedly impair the penetration and distribution of nucleic acid-based drugs. Even advanced delivery platforms, including lipid nanoparticles, polymeric carriers and viral vectors, show limited intratumoral accumulation in PDAC models. Studies emphasize that stromal targeting or co-delivery strategies may be required to overcome these physical barriers, yet such approaches increase formulation complexity and regulatory burden (210,211).

Another critical limitation is the pleiotropic nature of miRNAs. Unlike small-molecule inhibitors or allele-specific KRAS inhibitors, individual miRNAs can regulate dozens to hundreds of targets. While this multi-target capacity may be advantageous for suppressing oncogenic networks, it also raises concerns regarding off-target effects, unintended pathway activation and systemic toxicity. The termination of the MRX34 clinical trial, despite its success in preclinical models, highlighted immune-related adverse events as a significant obstacle for systemic miRNA delivery (212). These findings underscore the need for more precise miRNA engineering, tissue-specific delivery and improved immunocompatibility.

Importantly, context-dependent and occasionally contradictory roles of miRNAs further complicate therapeutic development. Several miRNAs reported as tumor suppressors in PDAC may exhibit oncogenic or neutral effects in other cellular contexts or disease stages. Additionally, KRAS-driven feedback mechanisms, such as repression of miR-143/145 suggest that restoring a single miRNA may be insufficient to durably suppress KRAS signaling due to compensatory network rewiring (47). Recent systems-level analyses indicate that combinatorial miRNA strategies or integration with KRAS pathway inhibitors may be required to achieve sustained therapeutic benefit (110).

Despite these challenges, emerging evidence suggests potential avenues for progress. For example, overexpression of KRAS-targeting miRNAs such as Let-7 has been shown to enhance radiosensitivity and chemosensitivity in PDAC models, supporting the concept of miRNA-based adjuvant therapies rather than standalone treatments (213). Advances in RNA chemistry, including backbone modifications and ligand-directed nanoparticles, have improved miRNA stability and tumor targeting in preclinical studies (214). Furthermore, the growing clinical success of RNA-based therapeutics, such as patisiran (Onpattro™), demonstrates the feasibility of overcoming delivery and safety barriers when appropriate platforms are employed.

In the future, large-scale clinical validation, standardized miRNA detection methodologies (including liquid biopsy approaches) and rigorous patient stratification will be essential for successful translation. Given the pronounced heterogeneity of pancreatic cancer, miRNA expression profiling may enable personalized therapeutic strategies, identifying patients most likely to benefit from miRNA modulation in combination with chemotherapy, radiotherapy, or emerging KRAS inhibitors. Ultimately, integrating miRNA-based approaches into multimodal treatment frameworks, while acknowledging and addressing their inherent limitations, will be critical for realizing their potential in pancreatic cancer management.

17. Conclusion

KRAS mutation remains a central oncogenic driver in pancreatic cancer, orchestrating tumor initiation, progression and therapeutic resistance. The present review underscored a critical insight: The miRNA-KRAS negative feedback loop is a defining feature of PDAC biology. Under normal conditions, KRAS and its regulatory miRNAs maintain a tightly controlled equilibrium; however, in the cancerous state, activated KRAS disrupts this balance by downregulating tumor-suppressive miRNAs such as miR-126, miR-96, miR-145, miR-143, miR-193b, miR-206, miR-217 and the Let-7 family, thereby fueling uncontrolled signaling and disease progression. Recognizing this feedback loop not only deepens our mechanistic understanding of PDAC but also opens new avenues for precision medicine. Therapeutic strategies aimed at restoring miRNA expression or targeting KRAS-driven pathways could overcome resistance and improve patient outcomes. Furthermore, integrating miRNA profiling into clinical workflows, alongside imaging and liquid biopsy, may enable early detection, dynamic monitoring and personalized treatment planning. Future research should prioritize unraveling the context-specific regulation of this axis, optimizing miRNA delivery systems and validating these approaches in large-scale clinical trials to translate these insights into tangible benefits for PDAC patients.

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Authors' contributions

AAA and AAK conceived the study. AAA, AMA and AAK wrote the original draft. AAA, AMA, MA, AHR and AAK reviewed and edited the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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