Chinese Medical Journal®

Role of noncoding RNA and protein interaction in pancreatic cancer

Zhang Li, Tingting Zhang, Xiaojuan Yang, Yong Peng

Center for Molecular Oncology, Frontiers Science Center for Disease-Related Molecular Network, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China.

Abstract

Noncoding RNAs (ncRNAs) are a class of RNA molecules with little or no protein-coding potential. Emerging evidence indicates that ncRNAs are frequently dysregulated and play pivotal roles in the pathogenesis of pancreatic cancer. Their aberrant expression can arise from chromosomal abnormalities, dysregulated transcriptional control, and epigenetic modifications. ncRNAs function as protein scaffolds or molecular decoys to modulate interactions between proteins and other biomolecules, thereby regulating gene expression and contributing to pancreatic cancer progression. In this review, we summarize the mechanisms underlying ncRNA dysregulation in pancreatic cancer, emphasize the biological significance of ncRNA–protein interactions, and highlight their clinical relevance. A deeper understanding of ncRNA–protein interactions is essential to elucidate molecular mechanisms and advance translational research in pancreatic cancer.

Keywords: Noncoding RNAs; Protein; Pancreatic cancer; Circular RNAs; Long non-coding RNAs

Introduction

Pancreatic cancer is a highly aggressive malignancy with a 5-year survival rate of only 10% and a median survival time of 5–8 months.[1] According to global cancer statistics, 495,773 new cases of pancreatic cancer were diagnosed in 2020, with a nearly equivalent number of deaths worldwide.[2] The most common histological subtype is pancreatic ductal adenocarcinoma (PDAC), which accounts for 85% of all cases of pancreatic cancer. Due to the pancreas's deep anatomical location, pancreatic cancer is often diagnosed at advanced stages when clinical symptoms become apparent. At the time of diagnosis, only 10–15% of patients are eligible for surgical resection, while the majority present with either locally advanced unresectable disease (about 40%) or metastatic diseases (about 45%).[3] Even after surgical resection, the 5-year survival rate remains low (15–20%) because of high rates of local recurrence and distal metastasis.[4] Current first-line therapies, such as FOLFIRINOX or gemcitabine combined with nab-paclitaxel, have limited efficacy because of intrinsic or acquired resistance.[5] Although pancreatic cancer is a highly heterogeneous disease, mutations in the key driver genes, including *KRAS*, *TP53*, *CDKN2A*, and *SMAD4*, play a critical role in its malignant transformation.[6] Further investigation into the cellular and molecular mechanisms underlying pancreatic cancer progression is urgently needed to identify novel therapeutic targets and develop treatment strategies.

Over the past two decades, a growing body of research has highlighted the importance of noncoding RNAs (ncRNAs) in the development of pancreatic cancer.[7,8] NcRNAs, which are RNA molecules with little or no protein-coding potential, have been recognized as functional regulators rather than transcriptional junk.[9] These ncRNAs include long ncRNAs (lncRNAs), circular RNAs (circRNAs), microRNAs (miRNAs), transfer RNAs (tRNA)-derived small RNAs (tsRNAs), P-element-induced wimpy testis-interacting RNAs (piRNAs), and small nucleolar RNAs (snoRNAs). Genomic and transcriptomic analyses of pancreatic cancer have identified profound alternations in ncRNAs,[10] underscoring their roles in pancreatic cancer progression. For instance, the hypoxia-inducible miR-210 regulates normoxic gene expression pathways involved in tumor initiation.[11] Similarly, the lncRNA GLS-AS is transcriptionally downregulated by nutrient stress-induced c-Myc, and its depletion promotes pancreatic cancer progression.[12]

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000003587

Zhang Li and Tingting Zhang contributed equally to this work.

Correspondence to: Xiaojuan Yang, Center for Molecular Oncology, Frontiers Science Center for Disease-Related Molecular Network, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China
E-Mail: yangxiaojuan@wchscu.edu.cn;
Yong Peng, Center for Molecular Oncology, Frontiers Science Center for Disease-Related Molecular Network, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China
E-Mail: yongpeng@scu.edu.cn

Chinese Medical Journal 2025;138(9)

Received: 01-01-2025; **Online:** 10-04-2025 **Edited by:** Sihan Zhou and Xiuyuan Hao

NcRNAs function in the regulatory networks of pancreatic cancer through diverse mechanisms, including interactions with other biomolecules and, in some cases, translation into functional peptides. Among these mechanisms, protein coupling is a major mode of action, where ncRNAs act as protein scaffolds or decoys, sequestering or tethering proteins to modulate their interactions with other molecules. For example, the exosomal circRNA circPLEKHM1 facilitates the interaction between poly(A)-binding protein cytoplasmic 1 (PABPC1) and eukaryotic translation initiation factor 4G (eIF4G), promoting the translation of oncostatin M receptor (OSMR), thereby driving macrophage polarization and cancer metastasis.[13] Similarly, the overexpressed lncRNA LINC00842 induces metabolic remodeling in PDAC cells by blocking the interaction between the transcriptional coactivator PGC-1α and the deacetylase enzyme SIRT1, thus preventing the deacetylation of acetylated PGC-1α by SIRT1, contributing to tumor progression.[14] These examples underscore the important roles of ncRNA–protein interactions in regulating key cellular processes in pancreatic cancer.

Although the functions of ncRNAs, particularly miRNAs, in pancreatic cancer progression have been extensively reviewed,[8,15–20], the interactions between ncRNAs and proteins and their contributions to pancreatic cancer development remain poorly summarized. In the review, we provide a concise overview of different classes of ncRNAs, summarize the mechanism underlying their dysregulation in pancreatic cancer, emphasize the biological significance of ncRNA–protein interactions, and highlight their clinical relevance in pancreatic cancer.

Overview of Different NcRNAs

Based on their shape, ncRNAs are classified into circRNAs and linear ncRNAs. Linear ncRNAs are further categorized by length into lncRNAs and small ncRNAs that include miRNAs, tsRNAs, piRNAs, and snoRNAs.

CircRNAs

CircRNAs are a class of covalently closed, single-stranded RNA molecules generated through a noncanonical splicing event called back-splicing, where a downstream 5′ splice site is joined with an upstream 3′ splice site. CircRNAs can originate from exons, introns, or a combination of them, and the majority of circRNAs are derived from a single exon or multiple exons of protein-coding genes.[21] The covalently closed structure confers circRNAs more stable because of resistance to exonuclease-mediated degradation, implying the potential of circRNAs as biomarkers.[22] CircRNAs exhibit distinct cell- and tissue-specific expression patterns, indicating their important functions among different cells. For example, the circRNA ci-Ins2 is specifically expressed in β-cells of pancreatic islet, where it modulates insulin secretion and calcium signaling pathway. This regulatory function is mediated through its interaction with the RNA-binding protein TAR DNA-binding protein 43, which subsequently influences gene expression in pancreatic islets.[23] Similarly, circNfix is predominately enriched in adult cardiac tissue, and depletion of circNfix promotes cardiomyocyte proliferation and angiogenesis while suppressing apoptosis after myocardial infarction.[24]

Increasing evidence proves that circRNAs act as miRNA sponges to regulate gene expression. A well-characterized example is the circRNA CDR1as (also known as ciRS-7), which contains 63 conserved binding sites for miR-7. Overexpression of CDR1as has been shown to recapture the effects of miR-7 knockdown in model organisms such as zebrafish and mice, underscoring its role as a competitive endogenous RNA (ceRNA).[25–27] Beyond their role as miRNA sponges, circRNAs can also serve as molecular scaffolds to modulate protein interactions and functions. For instance, circCGNL1 interacts with the phosphorylase nudix hydrolase 4 (NUDT4) to promote the dephosphorylation and subsequent nuclear translocation of HDAC4, thereby activating the proapoptosis RUNX2–GAMT axis.[28] In addition, a small subset of circRNAs can be translated into small functional peptides or proteins in a cap-independent manner. One such sample is circ-E-cad, which encodes a secretory E-cadherin variant to activate epidermal growth factor receptor (EGFR)-signal transducer and activator of transcription 3 (STAT3) signaling.[29]

LncRNAs

LncRNAs are a class of ncRNA molecules longer than 200 nucleotides, which are transcribed by RNA polymerase II. Although lncRNAs are generally expressed at lower levels compared with mRNAs, they share similar structural features, including a 5′ cap and a 3′ poly(A) tail.[30] A single lncRNA gene can produce multiple transcript isoforms through alternative splicing, contributing to the vast complexity of the transcriptome. To date, over 100,000 lncRNAs have been identified. Unlike protein-coding genes, lncRNAs exhibit lower evolutionary conservation at the sequence level, implying that their functional conservation may rely more on their structures rather other primary nucleotide sequences.[31]

LncRNAs exhibit cell-specific expression pattern and exert important functions under physiological condition. Moreover, lncRNA dysregulation has been implicated in the pathogenesis of various diseases.[32] For example, the lncRNA βFaar is dramatically downregulated in pancreas islet of obese mice, and its reduced expression contributes to β-cell dysfunction and apoptosis.[33] Conversely, the lncRNA HIF1A-AS1 is markedly upregulated in gemcitabine-resistant pancreatic cancer cells, where its overexpression promotes gemcitabine resistance by enhancing glycolysis metabolism.[34]

LncRNAs exert their regulatory functions by interacting with other biomolecules, such as RNAs, DNAs, or proteins, to modulate gene expression.[35] For instance, H19 acts as a ceRNA by sequestering members of the let-7 family to regulate muscle differentiation.[36] Similarly, the lncRNA MEG3 contains GA-rich sequences, which enable it to form RNA-DNA triplex structures, facilitating its binding to chromatin and subsequently regulation of transforming growth factor (TGF)-β signaling.[37]

MiRNAs

MiRNAs are a group of highly conserved ncRNAs, typically approximately 22 nucleotides in length. MiRNA genes are transcribed by RNA polymerase II into long primary transcripts (pri-miRNAs) with a 5′ cap and a 3′ poly(A) tail, which are subsequently processed in the nucleus by the microprocessor complex, comprising the RNase III enzyme Drosha and the RNA-binding protein DGCR8, to generate precursor miRNAs (pre-miRNAs) with a stem-loop structure. After exporting from the nucleus to the cytoplasm via RAN/GTP/Exportin-5 complex, pre-miRNAs undergo further cleavage by another RNase III enzyme called Dicer to produce mature miRNAs.[38]

Mature miRNAs are incorporated into Argonaute proteins to form the RNA-induced silencing complex (RISC) and guide RISC to target mRNAs through complementary base pairing, primarily mediated by the 5′ seed sequence of miRNAs. In general, miRNAs bind to the 3′ untranslated regions (3′ UTR) of target mRNAs to repress protein translation or induce mRNA degradation, thus downregulating gene expression. Compelling evidence indicates that miRNAs are frequently dysregulated in pancreatic cancer, where they can play oncogenic or tumor suppressive roles during tumor development.[39] For example, miR-25 has been shown to promote pancreatic cancer progression by inhibiting the expression of AKT phosphatase PHLPP2 to activate AKT-p70S6K signaling pathway.[40] Given that the functional roles and clinical implications of miRNAs in pancreatic cancer have been extensively reviewed,[41–45] such contents will not be discussed in detail in this review.

TsRNAs

TsRNAs, also referred to as tRNA-derived fragments (tRFs), represent a novel class of small ncRNAs produced by specific cleavage of precursor or mature tRNAs. Based on their cleaving sites, tsRNAs are classified into three main groups: (1) 3′U tRFs, which are 20–40 nucleotides in length and originate from the 3′ end of precursor tRNAs; (2) tRNA halves (also named tRHs or tiRNAs), which are 30–40 nucleotides in length and are produced by cleavage within the anticodon-loop of mature tRNAs; (3) tRFs, including 5′-tRFs, 3′-tRFs, and inter tRF (i-tRF), which are 14–30 nucleotides in length.[46] Notably, tsRNAs are predominately derived from a limited set of tRNAs, and fragments from different regions of same tRNA exhibit different abundance. Although the precise mechanisms underlying tsRNA biogenesis remain incompletely understood, posttranscriptional modifications of tsRNAs, such as 5-methylcytosine (m^5C) and N7-methylguanosine (m^7G), have been implicated in regulating tRNA cleavage and the generation of tsRNAs.[47]

Similar to miRNAs, tsRNAs can be incorporated into Argonaute proteins to induce cleavage of target RNAs. For example, tRF-33 is significantly downregulated in gastric cancer and inhibits tumor growth and metastasis by silencing STAT3 expression in an AGO2-dependent manner.[48] Besides, tsRNAs can also interact with RNA-binding proteins to regulate gene expression. A notable example is tiRNA-Val-CAC-2, which potently promotes the metastatic potential of pancreatic cancer cells.[49] Mechanistically, tiRNA-Val-CAC-2 binds to the RNA-binding protein far upstream element binding protein 1 (FUBP1) to stabilize it, leading to more enrichment of FUBP1 in the promoter region of *c-MYC* gene and activating *c-MYC* transcription.

Notably, tsRNAs are abundantly presented in various body fluids, making them promising candidates for diagnostic and prognostic biomarkers in liquid biopsy applications.[50] For instance, Jin *et al*[51] identified serum tRF-Pro-AGG-004 and tRF-Leu-CAG-002 as potential biomarkers for the diagnosis of pancreatic cancer, even in the early stage. Moreover, the expression levels of these two tsRNAs in tumor tissues are found to correlate with patient outcomes, indicating their potential as prognostic biomarkers for predicting survival time in pancreatic cancer patients following surgery intervention. Besides, Xue *et al*[52] found that 45 tsRNAs are significantly upregulated in the serum of patients with PDAC compared with healthy controls. Among these, the combination of serum tsRNA-MetCAT-37 or tsRNA-ValTAC-41 with CA19-9, a current biomarker for pancreatic cancer, significantly increases the area under the curve (AUC) of the receiver operating characteristic (ROC) curve, thereby improving the diagnostic accuracy for PDAC.

PiRNAs

PiRNAs represent a distinct class of small ncRNAs, typically ranging from 18 to 35 nucleotides in length, which are characterized by their specific association with the PIWI subfamily of Argonaute proteins and the presence of 2′-O-methyl modification at their 3′ terminus. Unlike miRNAs, piRNAs are transcribed from specific genomic loci and processed by various enzymes in a Dicer-independent manner. Over 90% of piRNAs originate from piRNA clusters, where piRNAs line up end-to-end or overlap slightly.[53,54] Upon generation, piRNAs form functional complexes with PIWI proteins, enabling them to recognize and bind to target transcripts via base pairing. Currently, it is estimated that the human genome encodes approximately 23,000 piRNAs.[55]

Emerging evidence indicates that piRNAs are differentially expressed between pancreatic cancer tissues and normal tissues, implicating their roles in cancer progression. For instance, piR-017061 is significantly downregulated in pancreatic cancer and has been demonstrated to inhibit tumor cell proliferation through its binding with PIWIL1, leading to the degradation of oncogenic *EFNA5* mRNA.[56] Furthermore, Saha *et al*[57] identified dysregulation of 36 piRNAs in pancreatic cancer tissues, with 11 of these piRNAs also showing altered expression in the plasma of pancreatic cancer patients. These observations suggest their roles in intercellular communication and highlight their potential as noninvasive biomarkers. In addition, Zhong *et al*[58] reported that small extracellular vesicle piR-hsa-30937, originating from pancreatic neuroendocrine, neoplasms, targets PTEN to activate the AKT pathway and upregulates the expression of the

immune checkpoint molecule CD276 in tumor-associated macrophages (TAMs), thereby contributing to the suppression of antitumor T-cell immunity.

SnoRNAs

SnoRNAs are a class of ncRNAs typically ranging from 60 to 300 nucleotides in length, predominantly localized within the nucleolus.[59] These RNAs have specific secondary structures and are classified into three major categories: (1) C/D box snoRNAs (SNORDs), which contain C/D box motifs; (2) H/ACA box snoRNAs (SNORAs), which feature H/ACA box motifs; and (3) small Cajal body-specific RNAs (SCARNAs), which include both C/D and H/ACA motifs.[60,61] SnoRNAs are primarily generated from the intronic regions of genes encoding proteins involved in ribosome biogenesis and function. This genomic arrangement may facilitate the maintenance of an appropriate balance between ribosomes and associated snoRNAs.[62,63] Functionally, snoRNAs play an important role in the posttranscriptional modifications (e.g., 2′-O-ribose methylation and psuedouridylation) of ribosomal RNAs (rRNAs) and small nuclear RNAs (snRNAs).[64]

Accumulating evidence indicates that snoRNAs are implicated in the pathogenesis of human diseases, including pancreatic cancer.[59,65] For example, SNORA23 is upregulated in PDAC and promotes growth and metastasis of PDAC cells *in vitro* and *in vivo* through increasing the expression of spectrin repeat-containing nuclear envelope 2 (SYNE2).[65] Given their dysregulation in disease states, snoRNAs have emerged as potential diagnostic biomarkers for pancreatic cancer. Notably, Kitagawa *et al*[66] identified that serum SNORA74A and SNORA25, when combined with the mRNA expression profiles of *WASF2* and *ARF6*, exhibit strong diagnostic performance for the early detection of pancreatic cancer, achieving an AUC value exceeding 0.9.

NcRNA Dysregulation in Pancreatic Cancer

Extensive research documents that the expression of ncRNAs is dysregulated in pancreatic cancer.[7,8,16] Their dysregulation can be attributed to a variety of underlying mechanisms, including chromosomal abnormalities, alterations in transcriptional control, epigenetic regulation, RNA modifications, and disruptions in the machinery responsible for ncRNAs biogenesis.

Chromosomal abnormalities

Chromosomal abnormalities, such as amplifications, deletions, and mutations in protein-coding genes, can change protein expression. Similar mechanisms are observed in the dysregulation of ncRNAs. Whole-genome analyses have revealed extensive chromatin abnormalities in noncoding regions across various cancers, including pancreatic cancer.[67] These findings suggest that the dysregulation of ncRNAs may arise from genetic alternation in ncRNA-coding genes. Notably, recurrent mutations have been identified in noncoding regions of pancreatic cancer genomes, particularly in loci associated with lncRNAs, pseudogenes, miRNAs, and snRNAs.[10] A compelling example is the single nucleotide polymorphism (SNP) rs11655237 located in exon 4 of LINC00673, which is identified as a risk variant for pancreatic cancer in the Chinese Han population.[68] This SNP creates a binding site for miR-1231, leading to the suppression of LINC00673 in pancreatic cancer cells [Figure 1A]. Another case involves p53-transactivated miR-34a broadly influences gene expression and promotes apoptosis.[69] Given that the miR-34a gene locus is frequently deleted in pancreatic cancer, the p53-mediated regulatory network is likely disrupted, contributing to tumorigenesis [Figure 1B].

Alterations in transcriptional control

The expression of ncRNAs is tightly regulated by a variety of transcription factors, and dysregulation of these factors can lead to aberrant ncRNA expression. Specifically, transcription factors such as c-Myc and E2F1, which play critical roles in cell cycle progression, are frequently dysregulated in pancreatic cancer. For example, under acidic conditionS, c-Myc is significantly upregulated in pancreatic cancer cells, leading to the transcriptional repression of the lncRNA MTSS1-AS.[70] In addition, the promoter region of the lncRNA PLACT1 contains two binding sites for E2F1, and upregulation of E2F1 enhances the transcription of *PLACT1* in pancreatic cancer [Figure 1C].[71] The tumor microenvironment in pancreatic cancer is often characterized by severe hypoxia, which induces the expression of the transcript factor HIF1α. It has been reported that HIF1α promotes the transcription of several lncRNAs, including HIF1A-AS1[34] and PVT1,[72] in pancreatic cancer cells.

Epigenetic regulation

Aberrant DNA methylation and histone modifications are well-established epigenetic events to regulate gene expression in pancreatic cancer.[73] DNA methylation typically suppresses gene expression by recruiting proteins involved in gene repression or by hindering the binding of transcription factors to their target regions. For example, LINC00261 is dramatically downregulated in pancreatic cancer due to hypermethylation of its promoter region. However, treatment with demethylation agents such as azacitidine or decitabine has been shown to markedly restore LINC00261 expression in pancreatic cancer cells [Figure 1D].[74] Similarly, histone modifications (e.g., methylation and acetylation) play critical roles in regulating the transcriptional activity of ncRNAs in pancreatic cancer. For instance, menin is a component of the multiprotein MLL complex that promotes H3K4 trimethylation of chromatin. In pancreatic neuroendocrine tumors, the loss or inactivation of menin leads to the downregulation of the lncRNA MEG3, mediated by reduced H3K4 trimethylation and concurrent CpG hypermethylation within MEG3 promoter.[75] In addition, the lncRNA PACERR is highly expressed in pancreatic cancer. PACERR interacts with the transcription factor KLF12 to recruit the histone acetyltransferase EP300 to its promoter region, thereby enhancing H3K27 acetylation and promoting PACERR transcription [Figure 1E].[76]

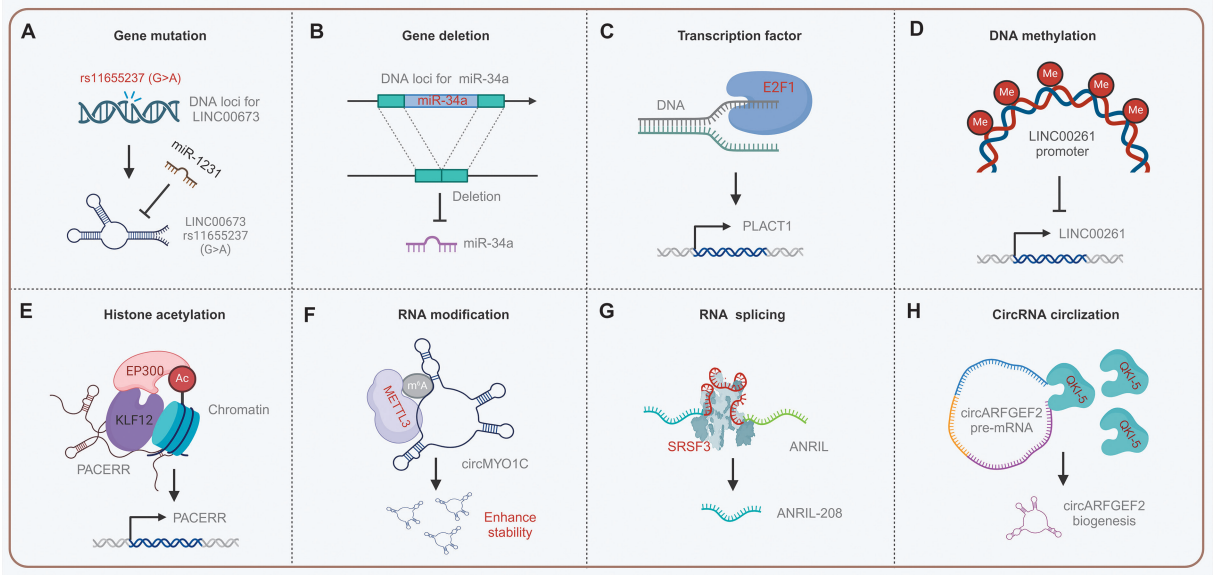

Figure 1: Mechanisms underlying the dysregulation of ncRNAs in pancreatic cancer. (A and B) Effects of chromosomal abnormalities on ncRNA expression. (A) The SNP rs11655237 in LINC00673 creates a binding site for miR-1231, leading to the suppression of LINC00673 expression. (B) The miR-34a gene locus is frequently deleted in pancreatic cancer, resulting in the depletion of its expression. (C) The upregulation of PLACT1 is mediated by the enhanced expression and binding of the transcription factor E2F1 to its promoter region. (D and E) Effects of epigenetic modifications on ncRNA expression. (D) Hypermethylation of the promoter region of LINC00261 leads to its downregulation. (E) PACERR interacts with the transcription factor KLF12 and recruits the histone acetyltransferase EP300 to its promoter region, increasing H3K27 acetylation and promoting PACERR transcription. (F) The upregulation of METTL3 promotes the cyclization and expression of circMYO1C by inducing m6A modification at its flanking introns. (G and H) Dysregulation of ncRNAs biogenesis machinery contributes to aberrant ncRNA expression. (G) SRSF3 overexpression promotes the alternative splicing of ANRIL, leading to the production of ANRIL-208 splic variant. (H) The upregulation of QKI-5 binds to the flanking introns of circARFGEF2, facilitating its biogenesis. Ac: Acetylated modification; ANRIL: antisense noncoding RNA in the INK4 locus; E2F1: E2F transcription factor 1; EP300: E1A binding protein P300; KLF12: KLF transcription factor 12; m6A: N6-methyladenosine; Me: Methylated modification; METTL3: Methyltransferase 3; ncRNA: noncoding RNA; PACERR: PTGS2 antisense NFKB1 complex-mediated expression regulator RNA; PLACT1: pancreatic cancer associated transcript 1; QKI-5: Quaking 5; SNP: Single nucleotide polymorphism; SRSF3: Serine/arginine-rich splicing factor 3.

RNA modifications

RNA modifications, such as N6-methyladenosine (m^6A) and m^5C, serve as critical regulators of RNA splicing and stability. These modifications are reversible and subject to dynamic regulation by different factors. Consequently, dysregulation of RNA-modified enzymes contributes to aberrant expression of ncRNAs in pancreatic cancer. The m^6A modification is catalyzed by a methyltransferase complex, with METTL3 acting as the principal catalytic subunit. In pancreatic cancer, overexpression of METTL3 has been shown to promote the cyclization and expression of circMYO1C by inducing m^6A modifications at its flanking introns [Figure 1F].[77] In addition, IGF2BP2 is a m^6A reader that recognizes and binds to m6A-modified transcripts, playing a pivotal role in the posttranscriptional regulation of RNA molecules. In pancreatic cancer, IGF2BP2 is upregulated and stabilizes the lncRNA DANCR through its interaction with the m^6A modification site at adenosine 664.[78] Furthermore, Yuan *et al*[79] identified a panel of m^5C-associated lncRNAs that exhibit dysregulation in pancreatic cancer and hold significant prognostic potential.

Disruption in ncRNA biogenesis machinery

The biogenesis of ncRNAs is tightly controlled by splicing factors and dysregulation of these factors can lead to aberrant ncRNA expression in pancreatic cancer. For example, serine/arginine-rich splicing factor 3 (SRSF3) has been shown to promote gemcitabine resistance in PDAC cells by modulating the splicing and m^6A methylation of the lncRNA ANRIL [Figure 1G].[80] In addition, the RNA-binding protein Quaking (QKI) is well-known for its regulatory function on circRNA biogenesis through its binding to the flanking introns of circRNAs. In $Kras^{G12D}$ PDAC cells, the isoform QKI-5 is significantly overexpressed and facilitates the biogenesis of circARFGEF2 by binding to its flanking introns [Figure 1H].[81] Furthermore, the upregulation of hsa_circ_0007919 in gemcitabine-resistant PDAC cells is attributed to the increased binding of QKI to the flanking introns of hsa_circ_0007919 pre-RNAs after gemcitabine treatment.[82]

NcRNA–protein Interactions in Pancreatic Cancer

The interactions between ncRNAs and proteins in pancreatic cancer can be classified into distinct mechanistic modes: (1) ncRNAs function as protein scaffolds, facilitating and stabilizing interactions between protein–protein, protein–mRNA, or protein–DNA/chromatin complexes; (2) ncRNAs act as protein sponges or decoys, sequestering or tethering proteins to inhibit interactions between protein–protein, protein–mRNA, or protein–DNA/chromatin complexes; (3) ncRNAs mediate the translocation or redistribution of proteins to specific subcellular compartments. A comprehensive summary of studies about ncRNA–protein interactions in pancreatic cancer is provided in Supplementary Tables 1 and 2, http://links.lww.com/CM9/C408.

NcRNAs act as protein scaffold to enhance protein interaction with other molecules

NcRNAs may form multidomain structures capable of simultaneously binding to proteins and other effector molecules, thereby serving as central platforms that facilitate the assembly of protein complexes.[83] A well-documented example is the lncRNA HOTAIR, which functions as a protein scaffold by bridging two distinct histone modification complexes, PRC2 and LSD1, and directing them to chromatin to coordinately regulate H3K27 methylation and H3K4 demethylation.[84] Similarly, circ-Foxo3 acts as a scaffold to promote the association between cell cycle regulators CDK2 and p21, leading to the formation of circ-Foxo3-p21-CDK2 ternary complex that inhibits cell cycle progression in pancreatic cancer cells.[85]

Enhancing protein interaction with other proteins

NcRNAs have the capacity to interact with one or more protein molecules, thereby facilitating and stabilizing their molecular interactions. In such scenarios, protein A may undergo specific posttranslational modifications (PTMs) (e.g., ubiquitination, acetylation, or phosphorylation) mediated by the catalytic activity of protein B. Alternatively, protein A may be transactivated by the regulatory function of protein B.

In pancreatic cancer cells, the lncRNA MTSS1-AS binds to the transcription factor MZF1 through its nucleotide spanning positions 700–1018 and enhances the interaction between MZF1 and the E3 ubiquitin ligase STUB1, resulting in the polyubiquitination and subsequent proteasomal degradation of MZF1.[70] The downregulation of MZF1, in turn, upregulates the expression of the tumor suppressor gene *MTSS1*, thereby inhibiting acidity-induced metastasis in pancreatic cancer. Besides, the lncRNA FGD5-AS1 is upregulated by interleukin-6 (IL-6)/STAT3 signaling in pancreatic cancer cells and promotes tumor growth and metastasis by inducing M2 macrophage polarization.[86] Mechanistically, FGD5-AS1 strengthens the interaction between the histone acetyltransferase p300 and the transcription factor STAT3 by binding to p300 at its 5′ end and STAT3 at its 3′ end. This interaction leads to the acetylation of STAT3 at lysine 685 (K685), activating the STAT3/NF-κB signaling cascade in macrophages.

Tumor-associated nonmyelinating Schwann cells (TASc) have been implicated in poor prognosis and the establishment of immunosuppressive microenvironment in patients with PDAC, primarily through excessive production of kynurenine. Depletion of TASc has been shown to repress PDAC tumor formation. Among the lncRNAs upregulated in TASc, PVT1 is the most prominently expressed. Nucleotides 1200 to 1260 of PVT1 interact with the protein TDO2, an enzyme that converts l-tryptophan to N-formyl-l-kynurenine, and nucleotides 480-540 of PVT1 associate with the serine/threonine protein kinase RAF1. These interactions enhance RAF1-medicated phosphorylation and activation of TDO2 [Figure 2A], ultimately leading to the accumulation of kynurenine in PDAC microenvironment and contributing to tumor immune exclusion.[87]

Enhancing protein interaction with RNAs

NcRNAs can serve as molecular scaffolds to strengthen interactions between proteins and RNA molecules. These proteins are typically RNA-binding proteins (RBPs), which play an important role in posttranscriptional regulatory processes by binding to RNA transcripts.[88] In pancreatic cancer, interactions between ncRNAs and RBPs may enhance the association between RBPs and their target RNAs, thereby modulating RNA stability and translation.

CircMYO1C is significantly upregulated in PDAC tissues and participates in tumor immune surveillance to promote tumor growth.[77] Mechanistically, circMYO1C interacts with KH3/KH4 domains of the RNA-binding protein IGF2BP2 through its m^{6}A modification sites and then enhances the interaction between IGF2BP2 and *PD-L1* mRNA, which stabilizes *PD-L1* mRNAs in PDAC cells [Figure 2B]. Similarly, the 5′ end region (nucleotides 1–293) of PACERR binds to KH1/KH2 domains of IGF2BP2 to strengthen the association of IGF2BP2 to *KLF12* and *c-Myc* mRNAs, thus enhancing their stability.[76] Consequently, the upregulation of PACERR promotes the proliferation and metastasis of PDAC cells. In addition, the pseudogene WTAPP1 is dramatically upregulated in PDAC tumors and correlates with poor patient prognosis.[89] The exon 1-2 region of *WTAPP1* RNA interacts with the mRNA of its protein-coding counterpart WTAP to strengthen the association of *WTAP* mRNAs with translation initiation factors, such as components of the EIF3 complex, thus promoting *WTAP* translation. Then, the elevated WTAP expression activates Wnt signaling and drives pancreatic cancer progression. Besides, extracellular vesicles (EV)-encapsulated lncRNA RP11-161H23.5 from cancer-associated fibroblasts (CAFs) contributes to PDAC immune evasion by downregulating expression of human leukocyte antigen HLA-A, a critical mediator of antigen presentation.[90] This effect is mediated by the interaction of RP11-161H23.5 with the RRM domain of CNOT4, a subunit of the CCR4-NOT mRNA deadenylase complex, which results in the shortening of *HLA-A* mRNA poly(A) tail and accelerates its degradation.

Enhancing protein interaction with DNA or chromatin

In addition to mediating protein–protein and protein–RNA interactions, ncRNAs are also reported to enhance protein interaction with DNA or chromatin. For example, hsa_circ_0007919 has been implicated in enhancing the DNA damage response and promoting gemcitabine resistance in pancreatic cancer cells by upregulating the expression of LIG1, a key DNA ligase involved in DNA recombination and repair. Mechanistically, hsa_circ_0007919 binds to and recruits the transcriptional activator FOXA1 and the DNA methylhydroxylase TET1 to the promoter region of *LIG1* gene, thus decreasing the methylation of *LIG1* promoter and enhancing its transcription [Figure 2C].[82]

In eukaryotic cells, genetic information is organized into chromatin, a dynamic structure regulated by post-translational histone modifications, such as methylation and acetylation. These modifications are regulated by specific enzymes and involved in gene expression, DNA

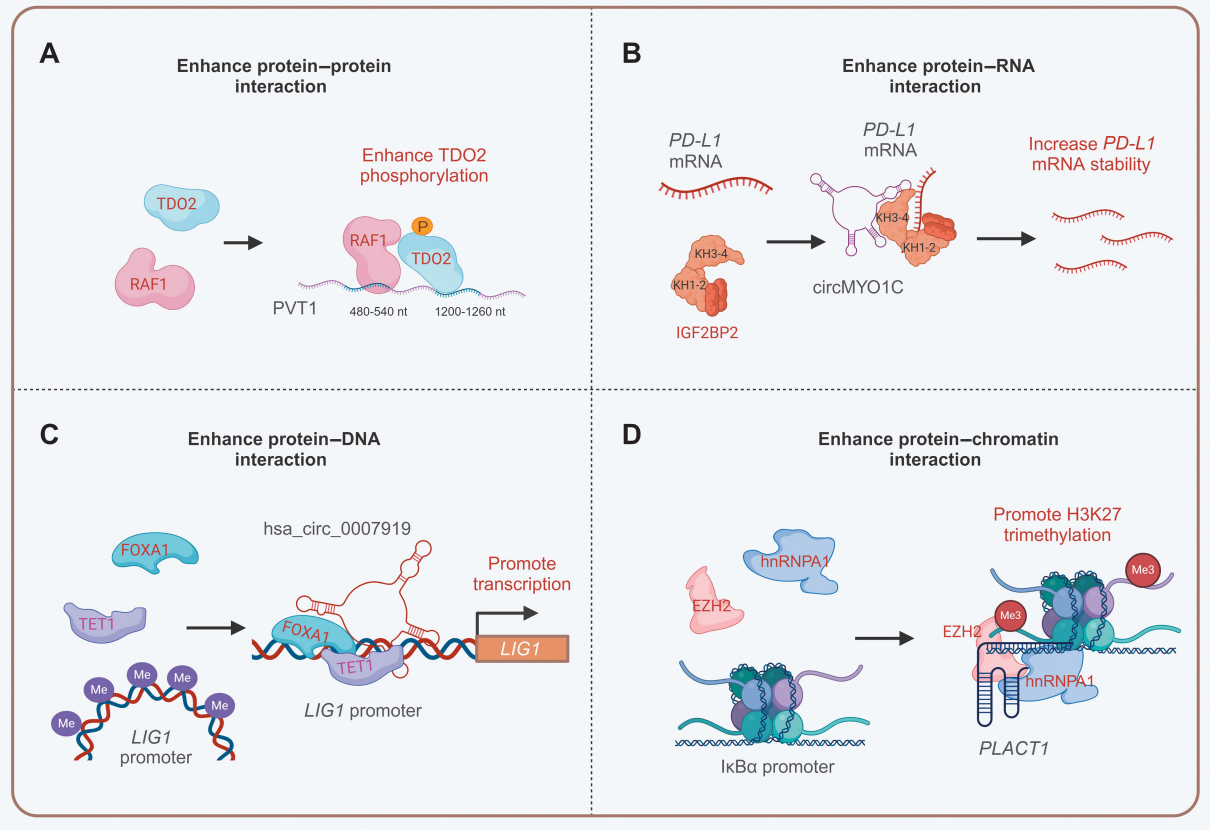

Figure 2: NcRNAs function as protein scaffolds to enhance protein interaction with other molecules. (A) PVT1 interacts with TDO2 at nucleotides 1200–1260 and RAF1 at nucleotides 480–540, enhancing RAF1-medicated phosphorylation of TDO2. (B) circMYO1C binds to the KH3 and KH4 domains of IGF2BP2 and promotes its association with *PD-L1* mRNA, increasing the stability of *PD-L1* mRNA. (C) hsa_circ_0007919 interacts with and recruits the transcriptional activator FOXA1 and the DNA methylhydroxylase TET1 to the promoter region of *LIG1*, promoting promoter demethylation and enhancing the transcription of *LIG1*. (D) PLCAT1 forms a DNA–RNA–protein triplex in the *IκBα* promoter and promotes H3K27 trimethylation at the *IκBα* promoter through its interaction with hnRNPA1 and EZH2. EZH2: Enhancer of zeste homolog 2; FOXA1: Forkhead box A1; hnRNPA1: Heterogeneous nuclear ribonucleoprotein A1; LIG1: DNA ligase I; Me, methylated modification; Me3: H3K27 trimethylation; ncRNA: Noncoding RNA; P: phosphorylated modification; PLACT1: pancreatic cancer associated transcript 1; PD-L1: Programmed cell death 1 ligand 1; PVT1: Plasmacytoma variant translocation 1; RAF1: Raf-1 proto-oncogene, serine/threonine kinase; TDO2: Tryptophan 2,3-dioxygenase; TET1: Tet methylcytosine dioxygenase 1.

replication, and DNA damage repair.[91] NcRNAs can interact with histone-modifying enzymes and enhance their binding with chromatin. For example, the lncRNA PLACT1 is highly overexpressed in PDAC tumors and promotes the proliferation and metastasis of PDAC cells *in vitro* and *in vivo*[71]. Mechanistically, PLACT1 interacts with the RNA-binding protein hnRNPA1 and also recruits the histone methyltransferase EZH2 to the promoter of *IκBα* gene, forming a DNA–RNA–protein triplex to promote H3K27 trimethylation at the IκBα promoter and activation of the NF-κB signaling pathway [Figure 2D]. Similarly, circ_0005397 is abundantly expressed in pancreatic cancer and inhibits ferroptosis by upregulating the expression of the RNA-binding protein PCBP2, which is important for iron transport.[92] The underlying mechanism is that circ_0005397 binds to the histone acetyltransferase KAT6A and directs it to the promoter region of the *PCBP2* gene, thus increasing H3K9 acetylation at the *PCBP2* promoter to promote PCBP2 expression.[93]

NcRNAs tether or sequester protein to block interaction with other molecules

NcRNAs can participate in the gene regulatory networks by acting as molecular sponges or decoys, sequestering target molecules and preventing their interactions with other binding partners. A well-characterized example is the lncRNA NORAD, which regulates genomic stability by sequestering PUMILIO proteins.[94,95] Similarly, the mitochondria-localized circRNA SCAR has been implicated in the pathogenesis of nonalcoholic steatohepatitis (NASH). SCAR interacts to ATP5B and shuts down mPTP by blocking CypD-mPTP interaction, thus reducing mROS output.[96]

Blocking protein interaction with other proteins

The interaction between ncRNA and protein A may competitively inhibit the binding of protein A to protein B, thereby disrupting the posttranslational modifications (PTMs) of protein A that are typically catalyzed by protein B. In addition, such ncRNA-mediated interference can impede the transactivation of protein A by protein B.

In pancreatic cancer, circRTN4 interacts with the epithelial-to-mesenchymal transition (EMT)- driver RAB11FIP1 to block its ubiquitination site at Lys578, thus preventing the polyubiquitination and subsequent proteasomal degradation of RAB11FIP1 in PDAC cells.[97] The lncRNA LINC00842 is induced by high concentration of glucose

in PDAC cells, and its overexpression confers metabolic remodeling of PDAC cells by regulating the transcriptional co-regulator PGC-1α.[14] Mechanistically, the 5′-end region (nucleotides 1-690) of LINC00842 binds to the repression domain (amino acids 181-460) of PGC-1α, and such interactions hinder the access of the deacetylase enzyme SIRT1 to acetylated PGC-1α, thus preventing the inactivated PGC-1α from deacetylation and activation by SIRT1 [Figure 3A]. In addition, the lncRNA DDIT4-AS1 is upregulated in PDAC tumors and promotes stemness properties and gemcitabine sensitivity of pancreatic cancer cells by downregulating DDIT4, a negative regulator of mTOR signaling.[98] Binding of DDIT4-AS1 to UPF1, a well-known RNA helicase involved in nonsense-mediated mRNA decay, blocks the association of UPF1 with the protein phosphatase PP2A, thus increasing UPF1 phosphorylation and *DDIT4* mRNA degradation and eventually activating mTOR pathway to promote stemness.

Blocking protein interaction with RNAs

As previously discussed, ncRNA-protein interactions may also disrupt the binding of RBPs with target RNAs, thus influencing RNA stability and degradation. In pancreatic cancer, the lncRNA MALAT1 is highly expressed to promote the proliferation and metastasis of PDAC cells via stimulating TIA-1-mediated autophagy.[99] MALAT1 binds to the RNA-binding protein HuR and prevents the binding of HuR to the 3′UTR of *TIA-1* mRNAs, thus increasing the autophagic flux by post-transcriptional downregulation of *TIA-1* mRNAs in PDAC cells [Figure 3B]. Besides, hsa_circ_0007590 is upregulated in PDAC tumors and promotes proliferation, migration, and invasion of PDAC cells by downregulating PTEN expression and subsequently activating PI3K/Akt/mTOR signaling.[100] Mechanistically, hsa_circ_0007590 binds to the RNA-binding protein PTBP1 and reduces the mRNA stability of *PTEN* in a m^{6}A-dependent manner.

Blocking protein interaction with DNAs or chromatin

NcRNA-protein interactions may tether or sequester proteins to block the binding of protein with DNA or chromatin. In pancreatic cancer, the lncRNA ZNFTR is significantly downregulated, and its enforced expression suppresses proliferation, metastasis, and proangiogenic abilities of pancreatic cancer cells through ZNF24-dependent downregulation of VEGFA. Mechanistically, the 194-493 nucleotide segment of ZNFTR interacts with the transcription factor ATF3 and sequesters ATF3 away from the *ZNF24* promoter, which consequently enhances ZNF24 expression [Figure 3C].[101] The upregulation of ZNF24, in turn, represses *VEGFA* transcription in pancreatic cancer cells. In addition, LINC00261 is

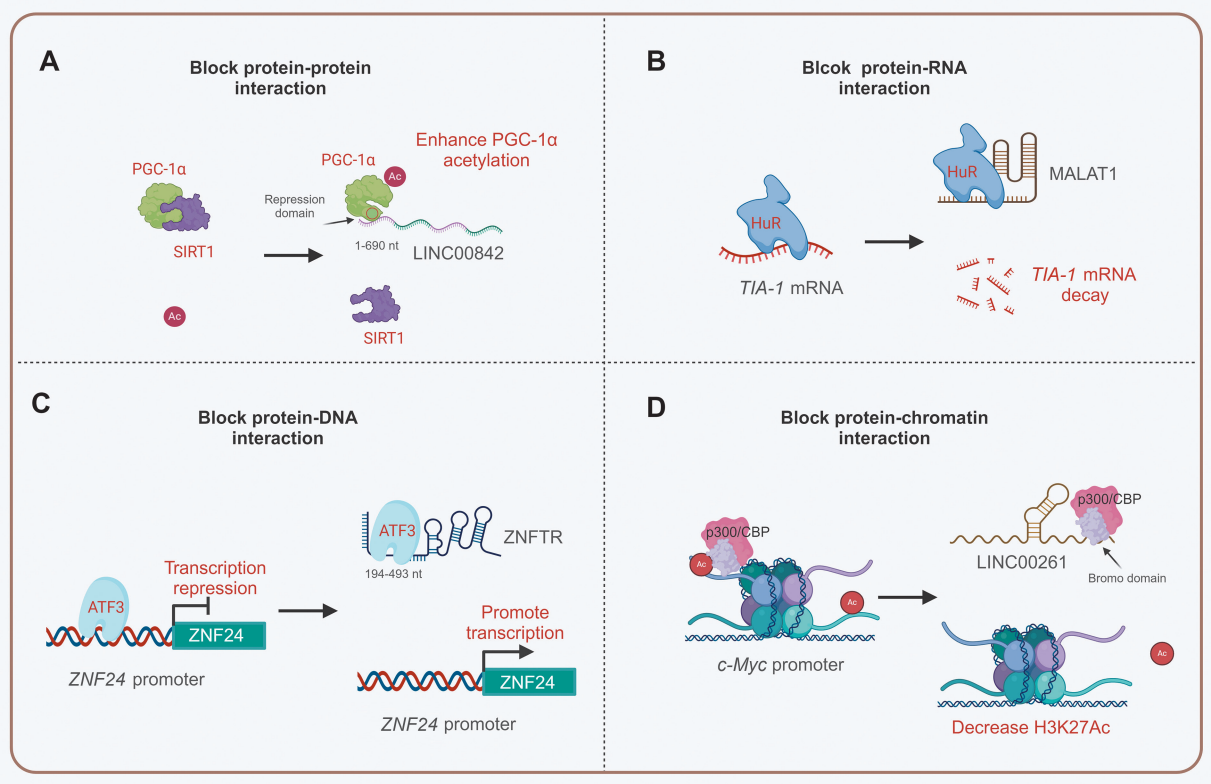

Figure 3: NcRNAs sequester or tether proteins to inhibit interactions with other molecules. (A) The 5′ end region of LINC00842 binds to the repression domain of PGC-1α, blocking the access of the deacetylase enzyme SIRT1 to acetylated PGC-1α, preventing the deacetylation and subsequent activation of PGC-1α by SIRT1. (B) MALAT1 binds to HuR and prevents its binding to the 3′UTR of TIA-1 mRNA, decreasing the stability of TIA-1 mRNA. (C) The 194-493 nucleotide segment of ZNFTR interacts with ATF3, sequestering it and preventing its binding to the promoter region of *ZNF24*. Consequently, this sequestration enhances ZNF24 transcription. (D) LINC00261 binds to the Bromo domain of p300/CBP and prevents its binding to c-Myc promoter, downregulating H3K27 acetylation and c-Myc expression. Ac: Acetylated modification; ATF3: Activating transcription factor 3; CBP: CREB binding protein; HuR: Human antigen R; MALAT1: Metastasis associated lung adenocarcinoma transcript 1; ncRNA: Noncoding RNA; p300: E1A binding protein p300; PGC-1α: PPARG coactivator 1 alpha; SIRT1: Sirtuin 1; TIA-1: T-cell-restricted intracellular antigen-1; ZNF24: Zinc finger protein 24; ZNFTR: ZNF24 transcription regulator.

dramatically downregulated in pancreatic cancer tissues and its expression is positively associated with the prognosis of pancreatic cancer patients.[74] LINC00261 physically interacts and binds with the Bromo domain of p300/CBP, thus preventing the recruitment of p300/CBP to the promoter region of c-Myc, decreasing the H3K27Ac level and eventually repressing c-Myc transcription in pancreatic cancer cells [Figure 3D]. Therefore, LINC00261 overexpression inhibits the proliferation and metastasis of pancreatic cancer cells

NcRNAs translocate or redistribute proteins to specific subcellular compartments

NcRNAs can bind with proteins to translocate or redistribute them to specific subcellular compartments. For example, P53RRA is a cytosolic lncRNA, and the interaction between P53RRA and G3BP1 protein in the cytoplasm disrupts the G3BP1-p53 complex, promoting nuclear retention of p53.[102] Circ-Foxo3 is primarily localized in the cytoplasm, where it interacts with nuclear transcription factors E2F1 and HIF1α, thus sequestering them in the cytoplasm.[103] Besides, circSKA3 has been reported to recruit Tks5 to the cell membrane and induce the formation of invadopodia.[104]

In pancreatic cancer, circRNAs have been shown to translocate or redistribute proteins to specific subcellular compartments. For example, circCGNL1 is predominantly distributed in the cytoplasm of pancreatic cancer cells, where it enhances the interaction between the phosphorylase NUDT4 and HDAC4 to promote NUDT4-dependent dephosphorylation of HDAC4, leading to its nuclear translocation [Figure 4A].[28] Another example is circBIRC6, which contributes to oxaliplatin resistance in pancreatic cancer cells and organoids by regulating the nonhomologous end joining (NHEJ) dependent DNA repair. Mechanistically, circBIRC6 directly binds with XRCC4, an important DNA repair protein, and strengthens the interaction of XRCC4 with the E1 SUMO-activating enzyme SAE1, thus promoting XRCC4 SUMOylation at lysine 155 (K155) and subsequent chromatin localization of XRCC4 in pancreatic cancer cells [Figure 4B].[105] In addition, the cytoplasmic circEIF3I facilitates the recruitment of SMAD3 to early endosomes to promote TGF-β signaling pathway in PDAC. In detail, circEIF3I directly binds to the transcription factor SMAD3 and increases SMAD3 phosphorylation by strengthening the interactions between SMAD3 and TGFβRI on early endosomes. Furthermore, AP2A1, a protein plays crucial role in Clathrin-mediated endocytosis, directly binds to circEIF3I and promotes circEIF3I-bound SMAD3 recruitment to TGFβRI on early endosomes [Figure 4C].[106] These events eventually lead to the nuclear translocation of phosphorylated SMAD3 to regulate gene expression in PDAC cells.

Roles of NcRNA–protein Interaction in the Progression of Pancreatic Cancer

Compelling evidence indicates that ncRNAs are dysregulated and participate in pancreatic cancer progression

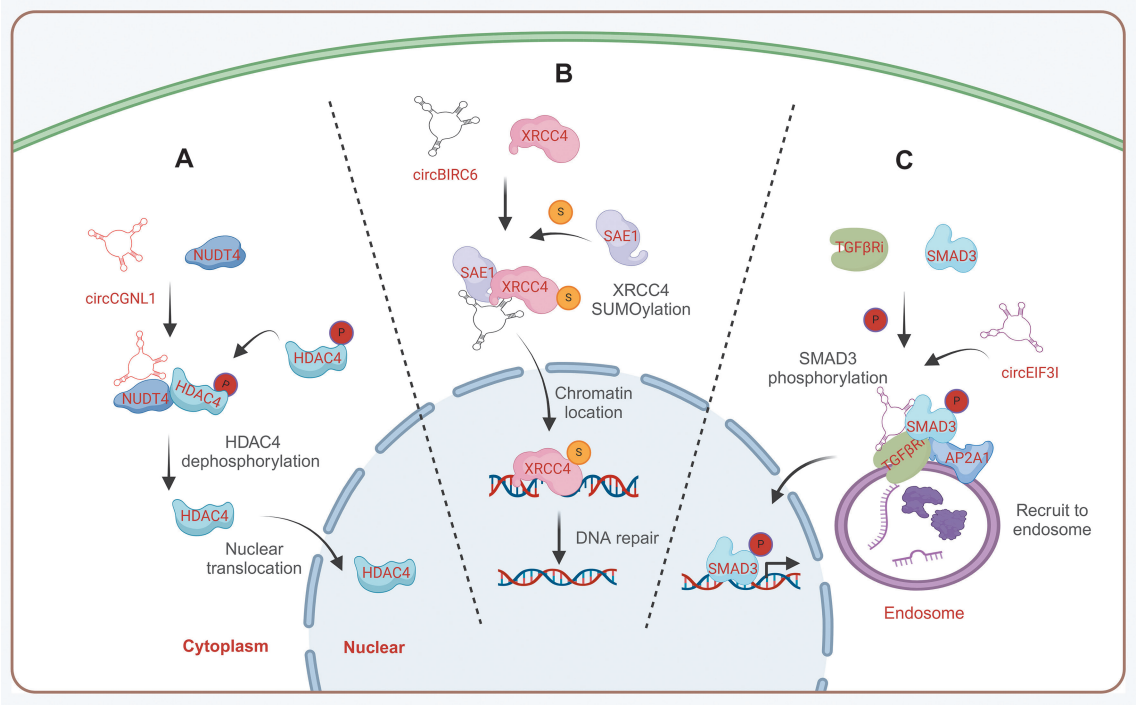

Figure 4: ncRNAs mediate protein translocation or redistribution to specific subcellular compartments. (A) circCGNL1 binds to the phosphorylase NUDT4 and HDAC4 in the cytoplasm, facilitating HDAC4 dephosphorylation and subsequent nuclear translocation. (B) circBIRC6 interacts with XRCC4 and enhances its association with SAE1, promoting XRCC4 SUMOylation and subsequent localization to chromatin. (C) circEIF3I binds to AP2A1 and SMAD3 in the cytoplasm, promoting the recruitment of TGFβRi to early endosomes and increased phosphorylation of SMAD3. AP2A1: Adaptor related protein complex 2 subunit alpha 1; HDAC4: Histone deacetylase 4; ncRNA: Noncoding RNA; NUDT4: Nudix hydrolase 4; P: Phosphorylation modification; S: SUMOylation modification; SAE1: SUMO1 activating enzyme subunit 1; SMAD3: SMAD family member 3; TGFβRI: Transforming growth factor beta receptor 1; XRCC4: X-Ray repair cross complementing 4.

through affecting tumor growth, metastasis, cell death, drug resistance, metabolic remodeling, stemness, and immunosuppressive microenvironment.[8,19,107–109] Notably, different kinds of ncRNAs may coordinate to regulate the same biological functions, as they can influence the expression of genes converging on the common signaling pathway. Besides, ncRNAs may function as ceRNAs and share common interaction partners, thus being functional redundancy during evolution.[110] Here, we summarize and discuss the roles of ncRNA-protein interaction in the progression of pancreatic cancer [Figure 5].

Cancer growth

Cancer is characterized by the uncontrolled proliferation of cells. Typically, normal cell cycle progression is tightly controlled by the balance between intracellular programs and extracellular signals, but cancer cells disrupt this balance by evading from growth suppressors and maintaining persistent proliferative signals. The discovery of ncRNAs and their protein interaction add a new dimension to understanding how pancreatic cancer cells grow beyond control.

C-Myc is one of the most important transcription factors to control cell growth. It is common that c-Myc is upregulated in various types of cancers including pancreatic cancer and sustains cancer cell proliferation by enabling them to reenter the cell cycle and inhibiting cell-cycle checkpoints.[111] It can also alter cancer cell metabolism to support rapid growth and proliferation.[112] In pancreatic cancer, ncRNA-protein interaction may regulate c-Myc expression to enhance cancer proliferation. For

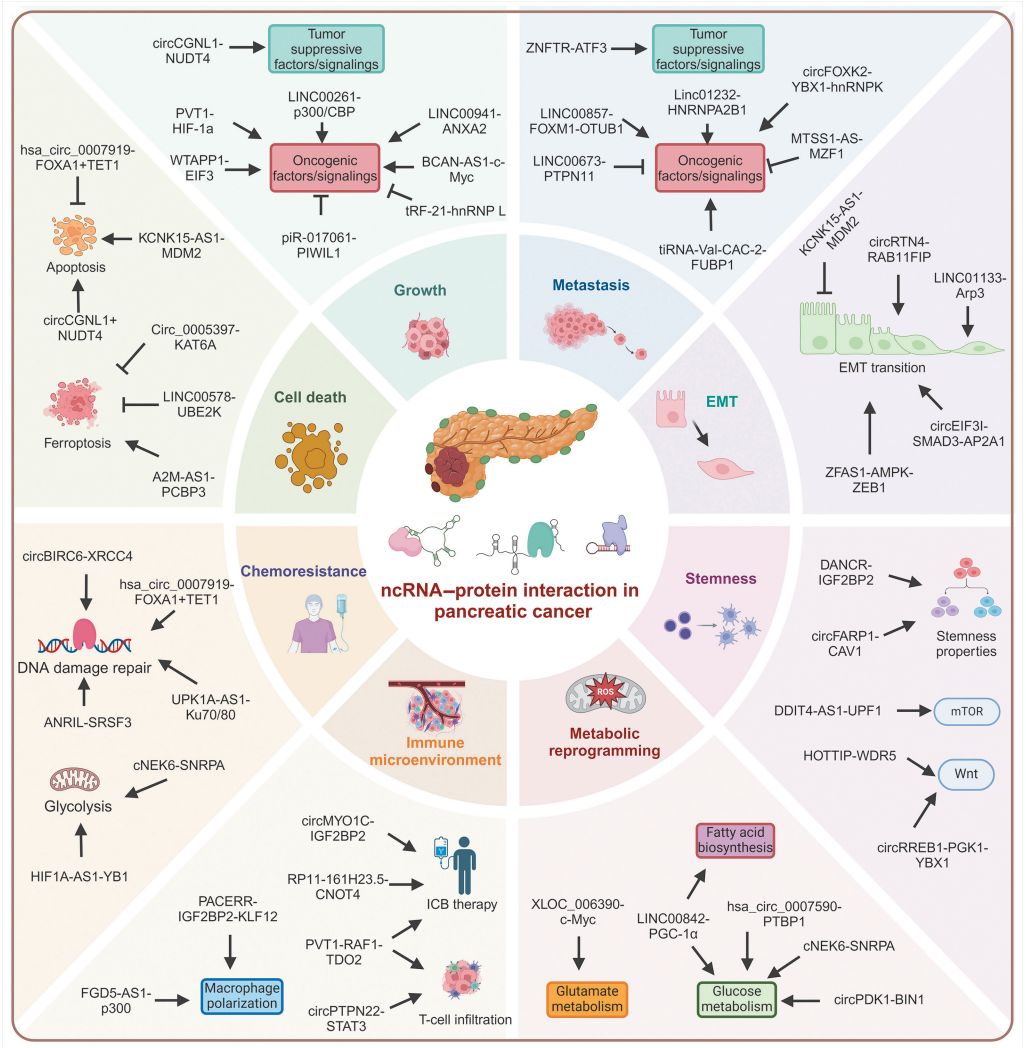

Figure 5: The functional roles of ncRNA-protein interactions in pancreatic cancer progression. ATF3: Activating transcription factor 3; ANXA2: Annexin A2; ARP3: Actin related protein 3; BIN1: Bridging integrator 1; CAV1: Caveolin 1; CBP: CREB binding protein; CNOT4: CCR4-NOT transcription complex subunit 4; EIF3: Eukaryotic translation initiation factor 3; FUBP1: Far upstream element binding protein 1; FOXA1: Forkhead box A1; FOXM1: Forkhead box M1; HNRNPA2B1: Heterogeneous nuclear ribonucleoprotein A2/B1; hnRNPK: Heterogeneous nuclear ribonucleoprotein K; hnRNP L: Heterogeneous nuclear ribonucleoprotein L; MZF1: Myeloid zinc finger 1; ncRNA: Noncoding RNA; NUDT4: Nudix hydrolase 4; KAT6A: Lysine acetyltransferase 6A; KLF12: KLF transcription factor 12; Ku70: 70 kDa subunit of Ku antigen; Ku80: 86 kDa subunit of Ku antigen; NUDT4: Nudix hydrolase 4; p300: E1A binding protein p300; PCBP3: Poly(RC) binding protein 3; PGC-1α: PPARG coactivator 1 alpha; PGK1: Phosphoglycerate kinase 1; PTBP1: Polypyrimidine tract binding protein 1; PTPN11: Protein tyrosine phosphatase non-receptor type 11; SNRPA: Small nuclear ribonucleoprotein polypeptide A; STAT3: Signal transducer and activator of transcription 3; SRSF3: Serine/arginine-rich splicing factor 3; TDO2: Tryptophan 2,3-dioxygenase; TET1: Tet methylcytosine dioxygenase 1; UBE2K: Ubiquitin conjugating enzyme E2 K; UPF1: UPF1 RNA helicase and ATPase; WDR5: WD repeat domain 5; XRCC4: X-Ray repair cross complementing 4; YB1: Y-Box binding protein 1.

instance, m^{6}A-modified lncRNA BCAN-AS acts as a scaffold to facilitate the formation of a ternary complex together with c-Myc and SNIP1, thus preventing c-Myc from SKP2-mediated ubiquitination and degradation.[113] On the contrary, LINC00261 binds to the acetylase complex p300/CBP and prevents its binding to the promoter of *c-Myc* gene, thus decreasing H3K27 acetylation and c-Myc transcription in pancreatic cancer cells.[74]

The PI3K/Akt signaling is frequently activated in human cancers and plays important roles in promoting cell survival and cell cycle progression.[114] PTEN is a negative regulator for the PI3K/Akt signaling. In pancreatic cancer, different kinds of ncRNAs are reported to coordinately regulate PTEN expression and PI3K/Akt signaling. For example, hsa_circ_0007590 promotes the proliferation of PDAC cells via downregulating PTEN expression and consequently activating PI3K/Akt signaling.[100] In contrast, the lncRNA KCNK15-AS1 upregulates PTEN expression to inactivate the Akt pathway and suppress the proliferation of pancreatic cancer cells.[115] Mechanically, KCNK15-AS1 binds to the E3 ubiquitin ligase MDM2 and transcription factor REST together, enhancing ubiquitination and degradation of REST, and transcriptionally promoting PTEN expression.

Cancer metastasis

Metastasis is a major cause of cancer-related death in pancreatic cancer. It is a complicated process and encompasses a series of biological events, including dissemination, dormancy, and colonization.[116] EMT, a shift of proliferative epithelial state to migratory mesenchymal state of cells, is considered an early and key step for tumor metastasis.[117] EMT triggers the disassociation of carcinoma cells from their primary sites and promotes their migration and dissemination to distant organs. Increasing reports demonstrate that ncRNAs are involved in EMT regulation in pancreatic cancer.

ZEB1 is a primary EMT-related transcription factor implicating cellular plasticity, dissemination and the dormant-to-proliferative phenotypic switch of cancer cells.[118] Under the metabolic stress of glucose or glutamine deprivation, pancreatic cancer cells undergo EMT and acquire increased migratory and invasion abilities. For example, the lncRNA ZFAS1 is induced by glucose/glutamine deprivation in pancreatic cancer cells, and its overexpression confers an EMT phenotype.[119] Mechanistically, ZFAS1 enhances the interaction between AMP-activated protein kinase (AMPK) and ZEB1, resulting in phosphorylation and subsequent stabilization of ZEB1 to induce EMT.

TGF-β signaling elicits a variety of context-dependent cellular responses, which induce cell growth arrest at the early stage but promote metastasis at the late stage during cancer progression.[120] In pancreatic cancer, TGF-β signaling is overactivated and associated with poor prognosis by facilitating EMT, angiogenesis, and cancer stemness.[121] Recently, ncRNAs have been reported to regulate TGF-β signaling and cancer metastasis. For example, circEIF3I is highly expressed in PDAC tissues and is associated with poor prognosis in patients with PDAC.[106] CircEIF3I directly binds to AP2A1 and SMAD3 and recruits TGFβRi on early endosomes, which leads to the activation of TGF-β signaling and metastasis of PDAC cells.

Cell death

Cells may undergo self-destruct to maintain biological homeostasis and prevent against harmful substances. Cell death can be genetically programmed, such as apoptosis, necroptosis, and pyroptosis, or induced by dysregulated metabolism, such as that in ferroptosis.[122,123] A hallmark of cancer cells is evading cell death, a feature crucial for drug treatment resistance and cancer recurrence. Increasing studies indicate that ncRNAs are important regulators for cell death in pancreatic cancer.

Apoptosis is a form of regulated cell death that is extensively studied. It functions as a natural barrier against malignancy. In pancreatic cancer, circCGNL1 is downregulated and its overexpression promotes apoptosis of pancreatic cancer cells via upregulating the expression of guanidinoacetate *N*-methyltransferase (GAMT), an essential enzyme in the creatine-biosynthesis pathway, and subsequently activating the proapoptotic AMPK-AKT-Bad signaling.[28] As mentioned earlier, hsa_circ_0007919 prevents gemcitabine-induced apoptosis by facilitating LIG1-dependent DNA damage repair.[82]

Ferroptosis is a form of cell death driven by iron-dependent lipid peroxidation.[124] Initially described as Ras-dependent cell death, ferroptosis is involved in drug resistance and progression of pancreatic cancer.[125,126] SLC7A11 is an important regulator of ferroptosis by regulating cystine import for glutathione biosynthesis and antioxidant defense. In pancreatic cancer, LINC00578 is elevated and inhibits ferroptosis events, including cell proliferation, reactive oxygen species (ROS) generation, and mitochondrial membrane potential (MMP) depolarization.[127] Mechanically, LINC00578 directly binds with the ubiquitin-conjugating enzyme UBE2K to decrease the ubiquitination of SLC7A11, thus promoting SLC7A11 expression. In addition, the lncRNA A2M-AS1 promotes ferroptosis in pancreatic cancer cells because it directly interacts with the poly (rC) binding protein 3 (PCBP3), which plays a pivotal role in iron metabolism, thus promoting p38 activation and inhibiting Akt-mTOR signaling.[128]

Chemoresistance

The FOLFIRINOX regimen and gemcitabine in combination with nab-paclitaxel represent the primary chemotherapeutic options for the treatment of advanced pancreatic cancer. However, the development of chemoresistance is a critical factor contributing to adverse clinical outcomes and poor prognosis.[129] Although the underlying mechanism for chemoresistance in pancreatic cancer remains obscure, ncRNAs are recently reported to be involved in the chemoresistance of pancreatic cancer.

Chemotherapeutic agents, including gemcitabine and oxaliplatin, exert their antitumor effects by inhibiting cell cycle progression and inducing DNA damage. Consequently, alterations in the DNA damage repair

machinery contribute to chemoresistance. For example, CAF^R is a cancer-associated fibroblast cell line derived from platinum-resistant pancreatic cancer patients. Paracrine IL-8 secreted by CAF^R induces Oxaliplatin resistance and upregulates the lncRNA UPK1A-AS1 in pancreatic cancer cells.[130] Mechanistically, UPK1A-AS1 promotes oxaliplatin resistance by strengthening the interaction between Ku70 and Ku80, two critical proteins involved in the repair of DNA double-strand break (DSB), to facilitate NHEJ and enhance DSB repair. SRSF3, a member of the serine/arginine-rich (SR) family of RNA-binding proteins, plays crucial roles in RNA splicing. In pancreatic cancer cells, SRSF3 confers resistance to gemcitabine by modulating the alternative splicing of the lncRNA ANRIL, leading to the production of the ANRIL-208 splice variant that enhance DNA homologous recombination repair (HR) capacity by forming a complex with Ring1b and EZH2.[80]

Alterations in tumor metabolism have been implicated in chemoresistance development in pancreatic cancer.[131,132] For example, the circRNA cNEK6 induces gemcitabine resistance by promoting glycolysis in PDAC cells.[133] cNEK6 binds to the RNA-binding protein SNRPA and prevents K48 ubiquitination of SNRPA from the BTRC, a ubiquitin E3 ligase. Then the accumulated SNRPA binds to the G-quadruplexes within the 5′ UTR of *PP2Ac* mRNAs, thus repressing *PP2Ac* translation and activating the mTORC1 pathway. Besides, the lncRNA HIF1A-AS1 promotes gemcitabine resistance of pancreatic cancer cells through enhancing HIF-1α-dependent glycolysis.[34] In detail, HIF1A-AS1 facilitates the interaction between the transcription factor YB1 and the kinase AKT to promote the phosphorylation of YB1 (pYB1). Meanwhile, HIF1A-AS1 recruited pYB1 to *HIF1α* mRNA that consequently promoted translation of HIF1α.

Cancer stemness

Stemness refers to the capacity of a cell to self-renew, differentiate into multiple cell types, and communicate with its microenvironment to maintain a balance between quiescence, proliferation, and regeneration.[134] Emerging evidence indicates the presence of pancreatic cancer stem cells (PCSCs), which exhibit stemness properties that drive tumor progression, chemoresistance, and recurrence.[135] Furthermore, some studies suggest the roles of ncRNA-protein interactions in regulating the stemness of pancreatic cancer cells.

In pancreatic cancer, circFARP1 is derived from CAFs, and positively correlated with gemcitabine resistance and poor survival in patients with advanced PDAC.[136] Mechanistically, circFARP1 promotes gemcitabine resistance of pancreatic cancer cells by enhancing stemness properties. Specifically, circFARP1 binds to caveolin 1 (CAV1) and blocks the interaction of CAV1 with the E3 ubiquitin ligase ZNRF1 to prevent CAV1 degradation, which increases the secretion of leukemia inhibitory factor (LIF) by CAFs. Given that LIF is a member of the IL-6 cytokine family to regulate stem cell identity and proliferation,[137] elevated LIF secretion reinforces stemness and gemcitabine resistance in pancreatic cancer cells.

The Wnt/β-catenin signaling is one of the key pathways to regulate development and stemness. Modulation of Wnt/β-catenin singling has been shown to influence the stemness properties of pancreatic cancer cells. For instance, circRREB1 is frequently upregulated in PDAC tissues, and its overexpression promotes glycolysis and enhances stemness in PDAC cells.[138] Mechanistically, circRREB1 directly interacts with the RNA-binding protein YBX1 and facilitates its nuclear translocation, thus promoting WNT7B transcription to activate Wnt/β-catenin signaling.

Metabolic reprogramming

Dysregulated metabolism is a hallmark of cancer, characterized by the reprogramming of metabolic processes to support uncontrolled proliferation and adaption to the hostile tumor microenvironment. Key metabolic alternations include (1) a shift from oxidative phosphorylation to aerobic glycolysis (the Warburg effect), (2) enhanced glutamate metabolism to facilitate NADPH regeneration, and (3) upregulation of lipid uptake and lipogenesis.[139] NcRNA-protein interactions have been implicated in mediating these metabolic reprogramming events in pancreatic cancer.

Altered energy metabolism is a biochemical hallmark of cancer cells, characterized by a preferential reliance on glycolysis. As previously discussed, dysregulation of glucose metabolism contributes to chemoresistance in pancreatic cancer. In addition, reprogramming of glucose metabolism drives tumor progression. For example, the hypoxia-induced circPDK1 promotes proliferation and metastasis of pancreatic cancer cells by enhancing aerobic glycolysis.[140] Mechanistically, circPDK1 interacts with the RNA-binding protein BIN1 to strengthen its interaction with the ubiquitin-conjugating enzyme UBE2O, thus promoting the ubiquitination and degradation of BIN1. The downregulation of BIN1 elevates c-Myc transcriptional activity, thereby further enhancing aerobic glycolysis and supporting tumor growth.

Glutamate metabolism plays an important role in supporting macromolecule biosynthesis and maintaining redox homeostasis, thereby facilitating cancer cell growth and survival.[141] In pancreatic cancer, the absence of lncRNA XLOC_006390 is associated with reduced levels of alpha-ketoglutarate (aKG), a key metabolite predominately controlled by glutamate dehydrogenase 1 (GDH1).[142] XLOC_006390 binds to c-Myc to prevent its ubiquitination and degradation, which in turn enhances the transcriptional activation of GDH1. Through the XLOC_006390/c-Myc axis, glutamate metabolism is upregulated and promotes tumor progression in pancreatic cancer.

Lipid metabolism, particularly fatty acid synthesis, plays an essential role in converting nutrients into metabolic intermediates for energy storage and membrane biogenesis. Emerging evidence indicates that enhanced fatty acid synthesis contributes to tumorigenesis and cancer progression.[143] For example, the lncRNA LINC00842 is upregulated under high glucose conditions, and its overexpression causes metabolic remodeling from

mitochondrial oxidative catabolic process to fatty acid synthesis. This shift promotes the malignant progression of PDAC cells.[14]

Immune microenvironment

Pancreatic cancer is among the most immune-resistant malignancies, exhibiting an immunologically "cold" tumor microenvironment characterized by impaired adaptive T-cell immunity, the accumulation of immunosuppressive cell populations, and resistance to immune checkpoint blockade (ICB) therapy.[144,145] Modulating the immunosuppressive tumor microenvironment is a promising strategy to overcome immune resistance and improve therapeutic outcomes in pancreatic cancer.

Recent evidences demonstrate that intratumoral T cells exhibit functional impairment due to multifaceted suppressive signals within the tumor microenvironment.[146] Prolonged antigen exposure within the tumor microenvironment induces T-cell exhaustion, characterized by a hierarchical loss of effector functions, reduced proliferation capacity, and altered transcriptional and metabolic profiles. Thus, reinvigoration of T-cell function by ncRNAs may offer an opportunity to promote antitumor therapy. For example, circPTPN22 is highly upregulated in pancreatic cancer tissues and its silencing enhances the infiltration and activation of cytotoxic $CD8^+$ T cells in the mice models bearing pancreatic cancer xenografts.[147] Mechanistically, circPTPN22 interacts with STAT3, a key regulator of anti-tumor immune responses, and promotes it acetylation by inhibiting its association with the deacetylase enzyme SIRT1. This modulation of STAT3 activity subsequently promotes antitumor T cell immunity. Besides, the upregulated lncRNA PVT1 in TAS cells promotes the excessive production of kynurenine to construct an immunosuppressive microenvironment in PDAC.[87] Moreover, depletion of TASc or PVT1 effectively sensitized PDAC to immunotherapy.

Current studies indicate that PD-1/PD-L1 blockade monotherapy has limited effect in pancreatic cancer, underscoring the need for combined therapeutic strategies.[148] Targeting functional ncRNAs may enhance the efficacy of PD-1/PD-L1 blockade and improve therapeutic outcomes in pancreatic cancer. For example, the lncRNA RP11-161H23.5 promotes the degradation of *HLA-A* mRNA and immune evasion of PDAC cells. Notably, targeting RP11-161H23.5 by engineered vesicle-loaded siRNA significantly enhances the sensitivity of dual ICB therapy (anti-PD-L1 and anti-CTLA-4).[90]

The M1/M2 macrophage polarization paradigm plays a crucial role in tumor progression. Polarization of macrophage toward M2 subtype is associated with anti-inflammatory responses, an immunosuppressive tumor microenvironment, and tumor-promoting effects.[149] Disruption of the balance between M1 and M2 macrophage polarization can contribute to PDAC progression. For instance, the highly expressed exosomal lncRNA FGD5-AS1 promotes M2 macrophage polarization by activating STAT3/NF-κB signaling, thus enhancing the proliferation and metastasis potential of pancreatic cancer cells.[86] In addition, the lncRNA PACERR is upregulated in TAMs and induces protumour macrophages. Moreover, increasing infiltration of $PACERR^+$ TAMs is correlated with poor clinical outcomes in PDAC patients.[76]

Diagnostic and Therapeutic Potential of NcRNAs in Pancreatic Cancer

Pancreatic cancer is frequently diagnosed at advanced stages due to its insidious onset and the anatomical complexity of the pancreas. Current noninvasive diagnostic methods, including abdominal computed tomography (CT), magnetic resonance imaging (MRI), and the pancreatic cancer-specific biomarker CA19-9, exhibit significant limitations in detecting the disease at early stages.[150,151] Therefore, there is an urgent need to develop novel biomarkers for pancreatic cancer diagnosis and treatment. As previously discussed, ncRNAs are dysregulated in pancreatic cancer, with their expression levels strongly correlating with disease progression. Furthermore, dysregulated ncRNAs can be detected in body fluids, such as plasma, urine, and saliva, highlighting their potential as noninvasive biomarkers.

NcRNAs as potential diagnostic and prognostic markers

Accumulating evidence indicates that ncRNAs are aberrantly expressed in pancreatic cancer tissues, and their expression levels exhibit significant correlations with disease severity, making them promising candidates for diagnostic and prognostic biomarkers. For instance, the expression of circ-LDLRAD3 is markedly upregulated in pancreatic cancer tissues and is positively associated with venous invasion, lymphatic invasion, and metastatic progression.[152] Circ-LDLRAD3 demonstrates potential as a diagnostic biomarker, with an AUC value of 0.67 when used alone, which increases to 0.87 when combined with the established biomarker CA19-9. Similarly, Ma *et al*[153] identified a panel of immune-related lncRNAs, including LINC02325 (AUC = 0.80), FNDC1-AS1 (AUC = 0.76), and ZEB2-AS1 (AUC = 0.75), in pancreatic cancer tissues. These lncRNAs exhibit strong predictive efficacy for the 5-year survival of pancreatic cancer patients.[153] Furthermore, Ørbeck *et al*[154] investigated the prognostic potential of circRNAs in PDAC using frozen tissue specimens and revealed that circ_02984 (AUC = 0.70), circPNLIP (AUC = 0.67), and circMBOAT2 (AUC = 0.64) hold promise as prognostic markers for patients with PDAC.

Liquid biopsy represents a widely utilized noninvasive approach for the real-time monitoring and diagnosis of cancer. Given that ncRNAs are frequently dysregulated and abundantly secreted into the tumor microenvironment in pancreatic cancer, they hold significant potential as biomarkers for liquid biopsy applications. For example, Xu *et al*[155] identified a panel of five circRNAs (hsa_circ_0060733, hsa_circ_0006117, hsa_circ_0064288, hsa_circ_0007895, and hsa_circ_0007367) in plasma-based liquid biopsies, which demonstrated robust performance in detecting PDAC and distinguishing between early-stage (stage I/II) and late-stage (stage III/IV) disease. The AUC values for this circRNA panel are 0.83 and 0.81

in the training and validation cohorts, respectively, and increased to 0.94 when combined with CA19-9. Similarly, Xie *et al*[156] identified salivary lncRNAs HOTAIR and PVT1 as novel biomarkers for the early detection of pancreatic cancer. Compared with healthy controls, HOTAIR and PVT1 exhibited AUC values of 0.880 and 0.870, respectively, and their combination further improved the AUC value to 0.909. Notably, these salivary lncRNAs are also capable of distinguishing pancreatic cancer from benign pancreatic tumors. In another study, Jin *et al*[51] identified two serum tsRNAs, tRF-ProAGG-004 and tRF-Leu-CAG-002, which demonstrated good diagnostic performance in differentiating pancreatic cancer patients from healthy controls. In a validation cohort comprising 150 pancreatic cancer patients and 100 healthy controls, the AUC values for tRF-ProAGG-004 and tRF-Leu-CAG-002 are 0.90 and 0.78, respectively, while their combination achieved an AUC value of 0.94.

NcRNAs as potential therapeutic targets

The involvement of aberrant ncRNA expression in cellular biological processes associated with pancreatic cancer suggests that targeting these ncRNAs could offer therapeutic potential. The most widely utilized strategies for targeting ncRNAs are small interfering RNAs (siRNAs) and antisense oligonucleotides (ASOs), which can be effectively delivered through different delivery systems, such as nanoparticles, exosomes, and liposomes.

The lncRNA RP11-161H23.5 has been shown to promote immune evasion in PDAC. To target RP11-161H23.5, engineered extracellular vesicles are used to deliver RP11-161H23.5-specific siRNA (siRP11). When combined with immune checkpoint inhibitors (anti-PD-L1 and anti-CTLA-4), the codelivery of these engineered extracellular vesicles significantly suppresses RP11-161H23.5 expression and enhances the efficacy of dual ICB therapy.[90] In addition, circBIRC6 has been linked to oxaliplatin resistance in patients with PDAC. An ASO inhibitor targeting circBIRC6 has been developed, and the combination of ASO-circBIRC6 with chemotherapy drugs such as olaparib and oxaliplatin significantly improves therapeutic outcomes in PDAC mouse models, highlighting its potential as a synergistic treatment strategy.[105]

Engineered circRNAs have recently emerged as a useful platform for protein expression and targeted therapy. The unique covalently closed-loop structure confers circRNAs resistance to exonucleases, thus exhibiting greater stability compared with linear RNAs. Notably, circRNAs possess the capacity to encode proteins, making them an attractive tool for targeted gene expression.[157,158] Furthermore, synthesized circRNAs exhibit minimal immunogenicity, which enhances their safety for *in vivo* applications.[159] A landmark study indicates the potential of engineered circRNAs as mRNA vaccines, exemplified by the development of a circRNA-based vaccine for SARS-CoV-2.[160] Beyond infectious diseases, circRNA vaccines have also shown promise in cancer immunotherapy. For instance, Amaya *et al*[161] developed a circOVA cancer vaccine that effectively activates dendritic cells and induces potent antitumor T-cell responses in a murine melanoma model. Recently, an *in vitro* transcribed engineered circRNA (called $GSDMD^{ENG}$ circRNA) has been designed and encapsulated in lipid nanoparticles (LNPs), effectively inhibiting $EIF4G2^{+}$/$PTBP1^{+}$ PDAC xenograft growth.[162]

Conclusions

The human genome harbors a vast number of non-coding genes that are actively transcribed into a diverse array of ncRNA molecules.[163] Advances in sequencing technologies and bioinformatics tools have led to the discovery of an increasing number of ncRNAs in recent years. To date, compelling evidence underscores the critical roles of ncRNAs in the pathogenesis and progression of pancreatic cancer. Although ncRNAs primarily exert their functions through interactions with proteins and other biomolecules, the tertiary structures of ncRNA-protein complexes remain poorly understood. In addition, RNA modifications have emerged as critical regulators for RNA stability and function. However, knowledge about ncRNA modifications—such as the crosstalk tween different RNA modifications, their dynamic change, and their effects on interactions with proteins—remains limited. Therefore, it is essential to develop novel technologies to elucidate the molecular mechanisms underlying ncRNA–protein interactions and to characterize their dynamic change during pancreatic cancer progression.

Although ncRNAs have shown considerable promise as diagnostic and prognostic biomarkers, as well as therapeutic targets for pancreatic cancer, several critical challenges must be addressed to advance their clinical translation. First, the clinical feasibility of ncRNAs as biomarkers requires further validation through large-scale, multicenter retrospective, and prospective studies involving diverse patient cohorts. Such studies are crucial to establish robust and reproducible evidence supporting their utility in clinical practice. Second, the lack of standardized and reliable protocols for ncRNA detection limits their widespread clinical application. Furthermore, a major obstacle to leveraging ncRNAs as therapeutic targets is the development of efficient delivery systems for ncRNA-based therapies, as current delivery platforms face limitations in specificity, stability, and cellular uptake efficiency. Addressing these challenges will be essential to realizing the full potential of ncRNA-based diagnostics and therapeutics in pancreatic cancer.

Acknowledgement

All figures in this review article are created with BioRender.com.

Funding

This study is supported by grants from the 1.3.5 Project for Disciplines of Excellence from West China Hospital of Sichuan University (No. ZYGD23027) and the Natural Science Foundation of Sichuan (No. 2023NSFSC1843).

Conflicts of interest

None.

References

1. Hu JX, Zhao CF, Chen WB, Liu QC, Li QW, Lin YY, *et al*. Pancreatic cancer: A review of epidemiology, trend, and risk factors. World J Gastroenterol 2021;27:4298–4321. doi: 10.3748/wjg.v27.i27.4298.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–249. doi: 10.3322/caac.21660.
3. Park W, Chawla A, O'Reilly EM. Pancreatic cancer: A review. JAMA 2021;326:851–862. doi: 10.1001/jama.2021.13027.
4. Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, *et al*. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004;350:1200–1210. doi: 10.1056/NEJMoa032295.
5. Orlandi E, Citterio C, Anselmi E, Cavanna L, Vecchia S. FOLFIRINOX or gemcitabine plus nab-paclitaxel as first line treatment in pancreatic cancer: A real-world comparison. Cancer Diagn Progn 2024;4:165–171. doi: 10.21873/cdp.10303.
6. Cicenas J, Kvederaviciute K, Meskinyte I, Meskinyte-Kausiliene E, Skeberdyte A, Cicenas J. KRAS, TP53, CDKN2A, SMAD4, BRCA1, and BRCA2 mutations in pancreatic cancer. Cancers (Basel) 2017;9:42. doi: 10.3390/cancers9050042.
7. Sempere LF, Powell K, Rana J, Brock AA, Schmittgen TD. Role of non-coding RNAs in tumor progression and metastasis in pancreatic cancer. Cancer Metastasis Rev 2021;40:761–776. doi: 10.1007/s10555-021-09995-x.
8. Sharma GG, Okada Y, Von Hoff D, Goel A. Non-coding RNA biomarkers in pancreatic ductal adenocarcinoma. Semin Cancer Biol 2021;75:153–168. doi: 10.1016/j.semcancer.2020.10.001.
9. Xiao Y, Hu Y, Liu S. Non-coding RNAs: A promising target for early metastasis intervention. Chin Med J 2023;136:2538–2550. doi: 10.1097/CM9.0000000000002619.
10. Feigin ME, Garvin T, Bailey P, Waddell N, Chang DK, Kelley DR, *et al*. Recurrent noncoding regulatory mutations in pancreatic ductal adenocarcinoma. Nat Genet 2017;49:825–833. doi: 10.1038/ng.3861.
11. Huang X, Ding L, Bennewith KL, Tong RT, Welford SM, Ang KK, *et al*. Hypoxia-inducible mir-210 regulates normoxic gene expression involved in tumor initiation. Mol Cell 2009;35:856–867. doi: 10.1016/j.molcel.2009.09.006.
12. Deng SJ, Chen HY, Zeng Z, Deng S, Zhu S, Ye Z, *et al*. Nutrient stress-dysregulated antisense lncRNA GLS-AS impairs GLS-mediated metabolism and represses pancreatic cancer progression. Cancer Res 2019;79:1398–1412. doi: 10.1158/0008-5472.CAN-18-0419.
13. Wang D, Wang S, Jin M, Zuo Y, Wang J, Niu Y, *et al*. Hypoxic exosomal circPLEKHM1-mediated crosstalk between tumor cells and macrophages drives lung cancer metastasis. Adv Sci (Weinh) 2024;11:e2309857. doi: 10.1002/advs.202309857.
14. Huang X, Pan L, Zuo Z, Li M, Zeng L, Li R, *et al*. LINC00842 inactivates transcription co-regulator PGC-1alpha to promote pancreatic cancer malignancy through metabolic remodelling. Nat Commun 2021;12:3830. doi: 10.1038/s41467-021-23904-4.
15. Peng JF, Zhuang YY, Huang FT, Zhang SN. Noncoding RNAs and pancreatic cancer. World J Gastroenterol 2016;22:801–814. doi: 10.3748/wjg.v22.i2.801.
16. Reese M, Dhayat SA. Small extracellular vesicle non-coding RNAs in pancreatic cancer: molecular mechanisms and clinical implications. J Hematol Oncol 2021;14:141. doi: 10.1186/s13045-021-01149-4.
17. Dalmasso B, Ghiorzo P. Long Non-coding RNAs and metabolic rewiring in pancreatic cancer. Cancers (Basel) 2023;15:3486. doi: 10.3390/cancers15133486.
18. Xie W, Chu M, Song G, Zuo Z, Han Z, Chen C, *et al*. Emerging roles of long noncoding RNAs in chemoresistance of pancreatic cancer. Semin Cancer Biol 2022;83:303–318. doi: 10.1016/j.semcancer.2020.11.004.
19. Bao H, Li J, Dong Q, Liang Z, Yang C, Xu Y. Circular RNAs in pancreatic cancer progression. Clin Chim Acta 2024;552:117633. doi: 10.1016/j.cca.2023.117633.
20. Chen Q, Li J, Shen P, Yuan H, Yin J, Ge W, *et al*. Biological functions, mechanisms, and clinical significance of circular RNA in pancreatic cancer: A promising rising star. Cell Biosci 2022;12:97. doi: 10.1186/s13578-022-00833-3.
21. Li J, Sun D, Pu W, Wang J, Peng Y. Circular RNAs in cancer: Biogenesis, function, and clinical significance. Trends Cancer 2020;6:319–336. doi: 10.1016/j.trecan.2020.01.012.
22. Tan S, Gou Q, Pu W, Guo C, Yang Y, Wu K, *et al*. Circular RNA F-circEA produced from EML4-ALK fusion gene as a novel liquid biopsy biomarker for non-small cell lung cancer. Cell Res 2018;28:693–695. doi: 10.1038/s41422-018-0033-7.
23. Stoll L, Rodriguez-Trejo A, Guay C, Brozzi F, Bayazit MB, Gattesco S, *et al*. A circular RNA generated from an intron of the insulin gene controls insulin secretion. Nat Commun 2020;11:5611. doi: 10.1038/s41467-020-19381-w.
24. Huang S, Li X, Zheng H, Si X, Li B, Wei G, *et al*. Loss of super-enhancer-regulated circRNA Nfix induces cardiac regeneration after myocardial infarction in adult mice. Circulation 2019;139:2857–2876. doi: 10.1161/CIRCULATIONAHA.118.038361.
25. Memczak S, Jens M, Elefsinioti A, Torti F, Krueger J, Rybak A, *et al*. Circular RNAs are a large class of animal RNAs with regulatory potency. Nature 2013;495:333–338. doi: 10.1038/nature11928.
26. Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, *et al*. Natural RNA circles function as efficient microRNA sponges. Nature 2013;495:384–388. doi: 10.1038/nature11993.
27. Piwecka M, Glazar P, Hernandez-Miranda LR, Memczak S, Wolf SA, Rybak-Wolf A, *et al*. Loss of a mammalian circular RNA locus causes miRNA deregulation and affects brain function. Science 2017;357:eaam8526. doi: 10.1126/science.aam8526.
28. Yuan H, Chen C, Li H, Qu G, Chen L, Liu Y, *et al*. Role of a novel circRNA-CGNL1 in regulating pancreatic cancer progression via NUDT4-HDAC4-RUNX2-GAMT-mediated apoptosis. Mol Cancer 2024;23:27. doi: 10.1186/s12943-023-01923-7.
29. Gao X, Xia X, Li F, Zhang M, Zhou H, Wu X, *et al*. Circular RNA-encoded oncogenic E-cadherin variant promotes glioblastoma tumorigenicity through activation of EGFR-STAT3 signalling. Nat Cell Biol 2021;23:278–291. doi: 10.1038/s41556-021-00639-4.
30. Cabili MN, Trapnell C, Goff L, Koziol M, Tazon-Vega B, Regev A, *et al*. Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses. Genes Dev 2011;25:1915–1927. doi: 10.1101/gad.17446611.
31. Iyer MK, Niknafs YS, Malik R, Singhal U, Sahu A, Hosono Y, *et al*. The landscape of long noncoding RNAs in the human transcriptome. Nat Genet 2015;47:199–208. doi: 10.1038/ng.3192.
32. Mattick JS, Amaral PP, Carninci P, Carpenter S, Chang HY, Chen LL, *et al*. Long non-coding RNAs: definitions, functions, challenges and recommendations. Nat Rev Mol Cell Biol 2023;24:430–447. doi: 10.1038/s41580-022-00566-8.
33. Zhang F, Yang Y, Chen X, Liu Y, Hu Q, Huang B, *et al*. The long non-coding RNA betaFaar regulates islet beta-cell function and survival during obesity in mice. Nat Commun 2021;12:3997. doi: 10.1038/s41467-021-24302-6.
34. Xu F, Huang M, Chen Q, Niu Y, Hu Y, Hu P, *et al*. LncRNA HIF1A-AS1 promotes gemcitabine resistance of pancreatic cancer by enhancing glycolysis through modulating the AKT/YB1/HIF1alpha pathway. Cancer Res 2021;81:5678–5691. doi: 10.1158/0008-5472.CAN-21-0281.
35. Statello L, Guo CJ, Chen LL, Huarte M. Gene regulation by long non-coding RNAs and its biological functions. Nat Rev Mol Cell Biol 2021;22:96–118. doi: 10.1038/s41580-020-00315-9.
36. Kallen AN, Zhou XB, Xu J, Qiao C, Ma J, Yan L, *et al*. The imprinted H19 lncRNA antagonizes let-7 microRNAs. Mol Cell 2013;52:101–112. doi: 10.1016/j.molcel.2013.08.027.
37. Mondal T, Subhash S, Vaid R, Enroth S, Uday S, Reinius B, *et al*. MEG3 long noncoding RNA regulates the TGF-beta pathway genes through formation of RNA-DNA triplex structures. Nat Commun 2015;6:7743. doi: 10.1038/ncomms8743.
38. Peng Y, Croce CM. The role of MicroRNAs in human cancer. Signal Transduct Target Ther 2016;1:15004. doi: 10.1038/sigtrans.2015.4.
39. Slack FJ, Chinnaiyan AM. The role of non-coding RNAs in oncology. Cell 2019;179:1033–1055. doi: 10.1016/j.cell.2019.10.017.
40. Zhang J, Bai R, Li M, Ye H, Wu C, Wang C, *et al*. Excessive miR-25-3p maturation via N(6)-methyladenosine stimulated by cigarette smoke promotes pancreatic cancer progression. Nat Commun 2019;10:1858. doi: 10.1038/s41467-019-09712-x.
41. Singh PK, Brand RE, Mehla K. MicroRNAs in pancreatic cancer metabolism. Nat Rev Gastroenterol Hepatol 2012;9:334–344. doi: 10.1038/nrgastro.2012.63.
42. Madadjim R, An T, Cui J. MicroRNAs in pancreatic cancer: Advances in biomarker discovery and therapeutic implications. Int J Mol Sci 2024;25:3914. doi: 10.3390/ijms25073914.

43. Pal A, Ojha A, Ju J. Functional and potential therapeutic implication of microRNAs in pancreatic cancer. Int J Mol Sci 2023;24:17523. doi: 10.3390/ijms242417523.
44. Rachagani S, Kumar S, Batra SK. MicroRNA in pancreatic cancer: Pathological, diagnostic and therapeutic implications. Cancer Lett 2010;292:8–16. doi: 10.1016/j.canlet.2009.11.010.
45. Uddin MH, Al-Hallak MN, Philip PA, Mohammad RM, Viola N, Wagner KU, *et al*. Exosomal microRNA in pancreatic cancer diagnosis, prognosis, and treatment: From bench to bedside. Cancers (Basel) 2021;13:2777. doi: 10.3390/cancers13112777.
46. Li J, Zhu L, Cheng J, Peng Y. Transfer RNA-derived small RNA: A rising star in oncology. Semin Cancer Biol 2021;75:29–37. doi: 10.1016/j.semcancer.2021.05.024.
47. Kuhle B, Chen Q, Schimmel P. tRNA renovatio: Rebirth through fragmentation. Mol Cell 2023;83:3953–3971. doi: 10.1016/j.molcel.2023.09.016.
48. Zhang S, Gu Y, Ge J, Xie Y, Yu X, Wu X, *et al*. tRF-33-P4R8Y-P9LON4VDP inhibits gastric cancer progression via modulating STAT3 signaling pathway in an AGO2-dependent manner. Oncogene 2024;43:2160–2171. doi: 10.1038/s41388-024-03062-9.
49. Xiong Q, Zhang Y, Xu Y, Yang Y, Zhang Z, Zhou Y, *et al*. tiRNA-Val-CAC-2 interacts with FUBP1 to promote pancreatic cancer metastasis by activating c-MYC transcription. Oncogene 2024;43:1274–1287. doi: 10.1038/s41388-024-02991-9.
50. Zhu L, Li J, Gong Y, Wu Q, Tan S, Sun D, *et al*. Exosomal tRNA-derived small RNA as a promising biomarker for cancer diagnosis. Mol Cancer 2019;18:74. doi: 10.1186/s12943-019-1000-8.
51. Jin F, Yang L, Wang W, Yuan N, Zhan S, Yang P, *et al*. A novel class of tsRNA signatures as biomarkers for diagnosis and prognosis of pancreatic cancer. Mol Cancer 2021;20:95. doi: 10.1186/s12943-021-01389-5.
52. Xue M, Shi M, Xie J, Zhang J, Jiang L, Deng X, *et al*. Serum tRNA-derived small RNAs as potential novel diagnostic biomarkers for pancreatic ductal adenocarcinoma. Am J Cancer Res 2021;11:837–848. doi.
53. Girard A, Sachidanandam R, Hannon GJ, Carmell MA. A germline-specific class of small RNAs binds mammalian Piwi proteins. Nature 2006;442:199–202. doi: 10.1038/nature04917.
54. Lau NC, Seto AG, Kim J, Kuramochi-Miyagawa S, Nakano T, Bartel DP, *et al*. Characterization of the piRNA complex from rat testes. Science 2006;313:363–367. doi: 10.1126/science.1130164.
55. Sai Lakshmi S, Agrawal S. piRNABank: A web resource on classified and clustered Piwi-interacting RNAs. Nucleic Acids Res 2008;36:D173–D177. doi: 10.1093/nar/gkm696.
56. Xie J, Xing S, Shen BY, Chen HT, Sun B, Wang ZT, *et al*. PIWIL1 interacting RNA piR-017061 inhibits pancreatic cancer growth via regulating EFNA5. Hum Cell 2021;34:550–563. doi: 10.1007/s13577-020-00463-2.
57. Saha B, Chakravarty S, Ray S, Saha H, Das K, Ghosh I, *et al*. Correlating tissue and plasma-specific piRNA changes to predict their possible role in pancreatic malignancy and chronic inflammation. Biomed Rep 2024;21:186. doi: 10.3892/br.2024.1874.
58. Zhong Y, Tian Y, Wang Y, Bai J, Long Q, Yan L, *et al*. Small extracellular vesicle piR-hsa-30937 derived from pancreatic neuroendocrine neoplasms upregulates CD276 in macrophages to promote immune evasion. Cancer Immunol Res 2024;12:840–853. doi: 10.1158/2326-6066.CIR-23-0825.
59. Chauhan W, Sudharshan S, Kafle S, Zennadi R. SnoRNAs: Exploring Their implication in human diseases. Int J Mol Sci 2024;25:7202. doi: 10.3390/ijms25137202.
60. Balakin AG, Smith L, Fournier MJ. The RNA world of the nucleolus: two major families of small RNAs defined by different box elements with related functions. Cell 1996;86:823–834. doi: 10.1016/s0092-8674(00)80156-7.
61. Dupuis-Sandoval F, Poirier M, Scott MS. The emerging landscape of small nucleolar RNAs in cell biology. Wiley Interdiscip Rev RNA 2015;6:381–397. doi: 10.1002/wrna.1284.
62. Dieci G, Preti M, Montanini B. Eukaryotic snoRNAs: a paradigm for gene expression flexibility. Genomics 2009;94:83–88. doi: 10.1016/j.ygeno.2009.05.002.
63. Brown JW, Marshall DF, Echeverria M. Intronic noncoding RNAs and splicing. Trends Plant Sci 2008;13:335–342. doi: 10.1016/j.tplants.2008.04.010.
64. Wajahat M, Bracken CP, Orang A. Emerging Functions for snoRNAs and snoRNA-Derived Fragments. Int J Mol Sci 2021;22:10193. doi: 10.3390/ijms221910193.
65. Cui L, Nakano K, Obchoei S, Setoguchi K, Matsumoto M, Yamamoto T, *et al*. Small nucleolar noncoding RNA SNORA23, up-regulated in human pancreatic ductal adenocarcinoma, regulates expression of spectrin repeat-containing nuclear envelope 2 to promote growth and metastasis of xenograft tumors in mice. Gastroenterology 2017;153:292–306 e292. doi: 10.1053/j.gastro.2017.03.050.
66. Kitagawa T, Taniuchi K, Tsuboi M, Sakaguchi M, Kohsaki T, Okabayashi T, *et al*. Circulating pancreatic cancer exosomal RNAs for detection of pancreatic cancer. Mol Oncol 2019;13:212–227. doi: 10.1002/1878-0261.12398.
67. Consortium ITP-CAoWG. Pan-cancer analysis of whole genomes. Nature 2020;578:82–93. doi: 10.1038/s41586-020-1969-6.
68. Zheng J, Huang X, Tan W, Yu D, Du Z, Chang J, *et al*. Pancreatic cancer risk variant in LINC00673 creates a miR-1231 binding site and interferes with PTPN11 degradation. Nat Genet 2016;48:747–757. doi: 10.1038/ng.3568.
69. Chang TC, Wentzel EA, Kent OA, Ramachandran K, Mullendore M, Lee KH, *et al*. Transactivation of miR-34a by p53 broadly influences gene expression and promotes apoptosis. Mol Cell 2007;26:745–752. doi: 10.1016/j.molcel.2007.05.010.
70. Hu Y, Wang F, Xu F, Fang K, Fang Z, Shuai X, *et al*. A reciprocal feedback of Myc and lncRNA MTSS1-AS contributes to extracellular acidity-promoted metastasis of pancreatic cancer. Theranostics 2020;10:10120–10140. doi: 10.7150/thno.49147.
71. Ren X, Chen C, Luo Y, Liu M, Li Y, Zheng S, *et al*. lncRNA-PLACT1 sustains activation of NF-kappaB pathway through a positive feedback loop with IkappaBalpha/E2F1 axis in pancreatic cancer. Mol Cancer 2020;19:35. doi: 10.1186/s12943-020-01153-1.
72. Zhu Y, Wu F, Gui W, Zhang N, Matro E, Zhu L, *et al*. A positive feedback regulatory loop involving the lncRNA PVT1 and HIF-1alpha in pancreatic cancer. J Mol Cell Biol 2021;13:676–689. doi: 10.1093/jmcb/mjab042.
73. Roalso MTT, Hald OH, Alexeeva M, Soreide K. Emerging role of epigenetic alterations as biomarkers and novel targets for treatments in pancreatic ductal adenocarcinoma. Cancers (Basel) 2022;14:546. doi: 10.3390/cancers14030546.
74. Liu S, Zheng Y, Zhang Y, Zhang J, Xie F, Guo S, *et al*. Methylation-mediated LINC00261 suppresses pancreatic cancer progression by epigenetically inhibiting c-Myc transcription. Theranostics 2020;10:10634–10651. doi: 10.7150/thno.44278.
75. Modali SD, Parekh VI, Kebebew E, Agarwal SK. Epigenetic regulation of the lncRNA MEG3 and its target c-MET in pancreatic neuroendocrine tumors. Mol Endocrinol 2015;29:224–237. doi: 10.1210/me.2014-1304.
76. Liu Y, Shi M, He X, Cao Y, Liu P, Li F, *et al*. LncRNA-PACERR induces pro-tumour macrophages via interacting with miR-671-3p and m6A-reader IGF2BP2 in pancreatic ductal adenocarcinoma. J Hematol Oncol 2022;15:52. doi: 10.1186/s13045-022-01272-w.
77. Guan H, Tian K, Luo W, Li M. m(6)A-modified circRNA MYO1C participates in the tumor immune surveillance of pancreatic ductal adenocarcinoma through m(6)A/PD-L1 manner. Cell Death Dis 2023;14:120. doi: 10.1038/s41419-023-05570-0.
78. Hu X, Peng WX, Zhou H, Jiang J, Zhou X, Huang D, *et al*. IGF2BP2 regulates DANCR by serving as an N6-methyladenosine reader. Cell Death Differ 2020;27:1782–1794. doi: 10.1038/s41418-019-0461-z.
79. Yuan H, Liu J, Zhao L, Wu P, Chen G, Chen Q, *et al*. Prognostic risk model and tumor immune environment modulation of m5C-related LncRNAs in pancreatic ductal adenocarcinoma. Front Immunol 2021;12:800268. doi: 10.3389/fimmu.2021.800268.
80. Wang ZW, Pan JJ, Hu JF, Zhang JQ, Huang L, Huang Y, *et al*. SRSF3-mediated regulation of N6-methyladenosine modification-related lncRNA ANRIL splicing promotes resistance of pancreatic cancer to gemcitabine. Cell Rep 2022;39:110813. doi: 10.1016/j.celrep.2022.110813.
81. Kong Y, Luo Y, Zheng S, Yang J, Zhang D, Zhao Y, *et al*. Mutant KRAS mediates circARFGEF2 biogenesis to promote lymphatic metastasis of pancreatic ductal adenocarcinoma. Cancer Res 2023;83:3077–3094. doi: 10.1158/0008-5472.CAN-22-3997.
82. Xu L, Ma X, Zhang X, Zhang C, Zhang Y, Gong S, *et al*. hsa_circ_0007919 induces LIG1 transcription by binding to FOXA1/TET1 to enhance the DNA damage response and promote gemcitabine resistance in pancreatic ductal adenocarcinoma. Mol Cancer 2023;22:195. doi: 10.1186/s12943-023-01887-8.

83. Li Y, Egranov SD, Yang L, Lin C. Molecular mechanisms of long noncoding RNAs-mediated cancer metastasis. Genes Chromosomes Cancer 2019;58:200–207. doi: 10.1002/gcc.22691.
84. Tsai MC, Manor O, Wan Y, Mosammaparast N, Wang JK, Lan F, *et al*. Long noncoding RNA as modular scaffold of histone modification complexes. Science 2010;329:689–693. doi: 10.1126/science.1192002.
85. Du WW, Yang W, Liu E, Yang Z, Dhaliwal P, Yang BB. Foxo3 circular RNA retards cell cycle progression via forming ternary complexes with p21 and CDK2. Nucleic Acids Res 2016;44:2846–2858. doi: 10.1093/nar/gkw027.
86. He Z, Wang J, Zhu C, Xu J, Chen P, Jiang X, *et al*. Exosome-derived FGD5-AS1 promotes tumor-associated macrophage M2 polarization-mediated pancreatic cancer cell proliferation and metastasis. Cancer Lett 2022;548:215751. doi: 10.1016/j.canlet.2022.215751.
87. Sun C, Ye Y, Tan Z, Liu Y, Li Y, Hu W, *et al*. Tumor-associated nonmyelinating Schwann cell-expressed PVT1 promotes pancreatic cancer kynurenine pathway and tumor immune exclusion. Sci Adv 2023;9:eadd6995. doi: 10.1126/sciadv.add6995.
88. Pereira B, Billaud M, Almeida R. RNA-binding proteins in cancer: Old players and new actors. Trends Cancer 2017;3:506–528. doi: 10.1016/j.trecan.2017.05.003.
89. Deng J, Zhang J, Ye Y, Liu K, Zeng L, Huang J, *et al*. N(6)-methyladenosine-mediated upregulation of WTAPP1 promotes WTAP translation and Wnt signaling to facilitate pancreatic cancer progression. Cancer Res 2021;81:5268–5283. doi: 10.1158/0008-5472.CAN-21-0494.
90. Yao H, Huang C, Zou J, Liang W, Zhao Y, Yang K, *et al*. Extracellular vesicle-packaged lncRNA from cancer-associated fibroblasts promotes immune evasion by downregulating HLA-A in pancreatic cancer. J Extracell Vesicles 2024;13:e12484. doi: 10.1002/jev2.12484.
91. Zhao S, Allis CD, Wang GG. The language of chromatin modification in human cancers. Nat Rev Cancer 2021;21:413–430. doi: 10.1038/s41568-021-00357-x.
92. Qu T, Cha L, Liu H, Tian L, Hu X, Zou H, *et al*. Circ_0005397 inhibits ferroptosis of pancreatic cancer cells by up-regulating PCBP2 through KAT6A/H3K9Ac. FASEB J 2024;38:e70028. doi: 10.1096/fj.202401151R.
93. Corley M, Burns MC, Yeo GW. How RNA-binding proteins interact with RNA: Molecules and mechanisms. Mol Cell 2020;78:9–29. doi: 10.1016/j.molcel.2020.03.011.
94. Lee S, Kopp F, Chang TC, Sataluri A, Chen B, Sivakumar S, *et al*. Noncoding RNA NORAD regulates genomic stability by sequestering PUMILIO proteins. Cell 2016;164:69–80. doi: 10.1016/j.cell.2015.12.017.
95. Elguindy MM, Mendell JT. NORAD-induced Pumilio phase separation is required for genome stability. Nature 2021;595:303–308. doi: 10.1038/s41586-021-03633-w.
96. Zhao Q, Liu J, Deng H, Ma R, Liao JY, Liang H, *et al*. Targeting mitochondria-located circRNA SCAR alleviates NASH via reducing mROS output. Cell 2020;183:76–93 e22. doi: 10.1016/j.cell.2020.08.009.
97. Wong CH, Lou UK, Fung FK, Tong JHM, Zhang CH, To KF, *et al*. CircRTN4 promotes pancreatic cancer progression through a novel CircRNA-miRNA-lncRNA pathway and stabilizing epithelial-mesenchymal transition protein. Mol Cancer 2022;21:10. doi: 10.1186/s12943-021-01481-w.
98. Zhang Y, Liu X, Wang Y, Lai S, Wang Z, Yang Y, *et al*. The m(6)A demethylase ALKBH5-mediated upregulation of DDIT4-AS1 maintains pancreatic cancer stemness and suppresses chemosensitivity by activating the mTOR pathway. Mol Cancer 2022;21:174. doi: 10.1186/s12943-022-01647-0.
99. Li L, Chen H, Gao Y, Wang YW, Zhang GQ, Pan SH, *et al*. Long noncoding RNA MALAT1 promotes aggressive pancreatic cancer proliferation and metastasis via the stimulation of autophagy. Mol Cancer Ther 2016;15:2232–2243. doi: 10.1158/1535-7163.MCT-16-0008.
100. Zheng D, Chen W, Peng J, Huang X, Zhang S, Zhuang Y. Hsa_circ_0007590/PTBP1 complex reprograms glucose metabolism by reducing the stability of m(6)A-modified PTEN mRNA in pancreatic ductal adenocarcinoma. Cancer Gene Ther 2024;31:1090–1102. doi: 10.1038/s41417-024-00786-4.
101. Li W, Han S, Hu P, Chen D, Zeng Z, Hu Y, *et al*. LncRNA ZNFTR functions as an inhibitor in pancreatic cancer by modulating ATF3/ZNF24/VEGFA pathway. Cell Death Dis 2021;12:830. doi: 10.1038/s41419-021-04119-3.
102. Mao C, Wang X, Liu Y, Wang M, Yan B, Jiang Y, *et al*. A G3BP1-interacting lncRNA promotes ferroptosis and apoptosis in cancer via nuclear sequestration of p53. Cancer Res 2018;78:3484–3496. doi: 10.1158/0008-5472.CAN-17-3454.
103. Du WW, Yang W, Chen Y, Wu ZK, Foster FS, Yang Z, *et al*. Foxo3 circular RNA promotes cardiac senescence by modulating multiple factors associated with stress and senescence responses. Eur Heart J 2017;38:1402–1412. doi: 10.1093/eurheartj/ehw001.
104. Du WW, Yang W, Li X, Fang L, Wu N, Li F, *et al*. The circular RNA circSKA3 binds integrin beta1 to induce invadopodium formation enhancing breast cancer invasion. Mol Ther 2020;28:1287–1298. doi: 10.1016/j.ymthe.2020.03.002.
105. Zheng S, Tian Q, Yuan Y, Sun S, Li T, Xia R, *et al*. Extracellular vesicle-packaged circBIRC6 from cancer-associated fibroblasts induce platinum resistance via SUMOylation modulation in pancreatic cancer. J Exp Clin Cancer Res 2023;42:324. doi: 10.1186/s13046-023-02854-3.
106. Zhao Z, Yang W, Kong R, Zhang Y, Li L, Song Z, *et al*. circEIF3I facilitates the recruitment of SMAD3 to early endosomes to promote TGF-beta signalling pathway-mediated activation of MMPs in pancreatic cancer. Mol Cancer 2023;22:152. doi: 10.1186/s12943-023-01847-2.
107. Ashrafizadeh M, Rabiee N, Kumar AP, Sethi G, Zarrabi A, Wang Y. Long noncoding RNAs (lncRNAs) in pancreatic cancer progression. Drug Discov Today 2022;27:2181–2198. doi: 10.1016/j.drudis.2022.05.012.
108. Li J, Hou S, Ye Z, Wang W, Hu X, Hang Q. Long non-coding RNAs in pancreatic cancer: biologic functions, mechanisms, and clinical significance. Cancers (Basel) 2022;14:2115. doi: 10.3390/cancers14092115.
109. Seimiya T, Otsuka M, Fujishiro M. Roles of circular RNAs in the pathogenesis and treatment of pancreatic cancer. Front Cell Dev Biol 2022;10:1023332. doi: 10.3389/fcell.2022.1023332.
110. Salmena L, Poliseno L, Tay Y, Kats L, Pandolfi PP. A ceRNA hypothesis: The Rosetta Stone of a hidden RNA language? Cell 2011;146:353–358. doi: 10.1016/j.cell.2011.07.014.
111. Dhanasekaran R, Deutzmann A, Mahauad-Fernandez WD, Hansen AS, Gouw AM, Felsher DW. The MYC oncogene: The grand orchestrator of cancer growth and immune evasion. Nat Rev Clin Oncol 2022;19:23–36. doi: 10.1038/s41571-021-00549-2.
112. Dong Y, Tu R, Liu H, Qing G. Regulation of cancer cell metabolism: oncogenic MYC in the driver's seat. Signal Transduct Target Ther 2020;5:124. doi: 10.1038/s41392-020-00235-2.
113. Wu G, Su J, Zeng L, Deng S, Huang X, Ye Y, *et al*. LncRNA BCAN-AS1 stabilizes c-Myc via N(6)-methyladenosine-mediated binding with SNIP1 to promote pancreatic cancer. Cell Death Differ 2023;30:2213–2230. doi: 10.1038/s41418-023-01225-x.
114. Glaviano A, Foo ASC, Lam HY, Yap KCH, Jacot W, Jones RH, *et al*. PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer. Mol Cancer 2023;22:138. doi: 10.1186/s12943-023-01827-6.
115. He Y, Yue H, Cheng Y, Ding Z, Xu Z, Lv C, *et al*. ALKBH5-mediated m(6)A demethylation of KCNK15-AS1 inhibits pancreatic cancer progression via regulating KCNK15 and PTEN/AKT signaling. Cell Death Dis 2021;12:1121. doi: 10.1038/s41419-021-04401-4.
116. Gerstberger S, Jiang Q, Ganesh K. Metastasis. Cell 2023;186:1564–1579. doi: 10.1016/j.cell.2023.03.003.
117. Nieto MA, Huang RY, Jackson RA, Thiery JP. Emt: 2016. Cell 2016;166:21–45. doi: 10.1016/j.cell.2016.06.028.
118. Drapela S, Bouchal J, Jolly MK, Culig Z, Soucek K. ZEB1: A critical regulator of cell plasticity, dna damage response, and therapy resistance. Front Mol Biosci 2020;7:36. doi: 10.3389/fmolb.2020.00036.
119. Zhuo W, Zeng Z, Hu Y, Hu P, Han S, Wang D, *et al*. Metabolic stress-induced reciprocal loop of long noncoding RNA ZFAS1 and ZEB1 promotes epithelial-mesenchymal transition and metastasis of pancreatic cancer cells. Cancer Sci 2023;114:3623–3635. doi: 10.1111/cas.15905.
120. Massague J, Sheppard D. TGF-beta signaling in health and disease. Cell 2023;186:4007–4037. doi: 10.1016/j.cell.2023.07.036.
121. Zhao M, Mishra L, Deng CX. The role of TGF-beta/SMAD4 signaling in cancer. Int J Biol Sci 2018;14:111–123. doi: 10.7150/ijbs.23230.
122. Newton K, Strasser A, Kayagaki N, Dixit VM. Cell death. Cell 2024;187:235–256. doi: 10.1016/j.cell.2023.11.044.
123. Gong L, Huang D, Shi Y, Liang Z, Bu H. Regulated cell death in cancer: From pathogenesis to treatment. Chin Med J 2023;136:653–665. doi: 10.1097/CM9.0000000000002239.

124. Jiang Q, Wan R, Jiang J, Li T, Li Y, Yu S, *et al*. Interaction between macrophages and ferroptosis: Metabolism, function, and diseases. Chin Med J 2024. doi: 10.1097/CM9.0000000000003189.
125. Stockwell BR. Ferroptosis turns 10: Emerging mechanisms, physiological functions, and therapeutic applications. Cell 2022;185:2401–2421. doi: 10.1016/j.cell.2022.06.003.
126. Liu J, Kang R, Tang D. The art of war: Ferroptosis and pancreatic cancer. Front Pharmacol 2021;12:773909. doi: 10.3389/fphar.2021.773909.
127. Li H, Wei Y, Wang J, Yao J, Zhang C, Yu C, *et al*. Long noncoding RNA LINC00578 inhibits ferroptosis in pancreatic cancer via regulating SLC7A11 ubiquitination. Oxid Med Cell Longev 2023;2023:1744102. doi: 10.1155/2023/1744102.
128. Qiu X, Shi Q, Zhang X, Shi X, Jiang H, Qin S. LncRNA A2M-AS1 promotes ferroptosis in pancreatic cancer via interacting with PCBP3. Mol Cancer Res 2022;20:1636–1645. doi: 10.1158/1541-7786.MCR-22-0024.
129. Zhang J, Wang Y, Wang L, You L, Zhang T. Pancreatic ductal adenocarcinoma chemoresistance: From metabolism reprogramming to novel treatment. Chin Med J 2024;137:408–420. doi: 10.1097/CM9.0000000000002758.
130. Zhang X, Zheng S, Hu C, Li G, Lin H, Xia R, *et al*. Cancer-associated fibroblast-induced lncRNA UPK1A-AS1 confers platinum resistance in pancreatic cancer via efficient double-strand break repair. Oncogene 2022;41:2372–2389. doi: 10.1038/s41388-022-02253-6.
131. Xi Y, Yuan P, Li T, Zhang M, Liu MF, Li B. hENT1 reverses chemoresistance by regulating glycolysis in pancreatic cancer. Cancer Lett 2020;479:112–122. doi: 10.1016/j.canlet.2020.03.015.
132. Zeng Z, Zhao Y, Chen Q, Zhu S, Niu Y, Ye Z, *et al*. Hypoxic exosomal HIF-1alpha-stabilizing circZNF91 promotes chemoresistance of normoxic pancreatic cancer cells via enhancing glycolysis. Oncogene 2021;40:5505–5517. doi: 10.1038/s41388-021-01960-w.
133. Li G, She FF, Liao CY, Wang ZW, Wang YT, Wu YD, *et al*. cNEK6 induces gemcitabine resistance by promoting glycolysis in pancreatic ductal adenocarcinoma via the SNRPA/PPA2c/mTORC1 axis. Cell Death Dis 2024;15:742. doi: 10.1038/s41419-024-07138-y.
134. Aponte PM, Caicedo A. Stemness in cancer: Stem cells, cancer stem cells, and their microenvironment. Stem Cells Int 2017;2017:5619472. doi: 10.1155/2017/5619472.
135. Zhao Y, Qin C, Zhao B, Wang Y, Li Z, Li T, *et al*. Pancreatic cancer stemness: Dynamic status in malignant progression. J Exp Clin Cancer Res 2023;42:122. doi: 10.1186/s13046-023-02693-2.
136. Hu C, Xia R, Zhang X, Li T, Ye Y, Li G, *et al*. circFARP1 enables cancer-associated fibroblasts to promote gemcitabine resistance in pancreatic cancer via the LIF/STAT3 axis. Mol Cancer 2022;21:24. doi: 10.1186/s12943-022-01501-3.
137. Onishi K, Zandstra PW. LIF signaling in stem cells and development. Development 2015;142:2230–2236. doi: 10.1242/dev.117598.
138. Rong Z, Xu J, Yang J, Wang W, Tang R, Zhang Z, *et al*. CircRREB1 mediates metabolic reprogramming and stemness maintenance to facilitate pancreatic ductal adenocarcinoma progression. Cancer Res 2024;84:4246–4263. doi: 10.1158/0008-5472.CAN-23-3596.
139. Schiliro C, Firestein BL. Mechanisms of metabolic Reprogramming in cancer cells supporting enhanced growth and proliferation. Cells 2021;10:1056. doi: 10.3390/cells10051056.
140. Lin J, Wang X, Zhai S, Shi M, Peng C, Deng X, *et al*. Hypoxia-induced exosomal circPDK1 promotes pancreatic cancer glycolysis via c-myc activation by modulating miR-628-3p/BPTF axis and degrading BIN1. J Hematol Oncol 2022;15:128. doi: 10.1186/s13045-022-01348-7.
141. Jin L, Alesi GN, Kang S. Glutaminolysis as a target for cancer therapy. Oncogene 2016;35:3619–3625. doi: 10.1038/onc.2015.447.
142. He J, Li F, Zhou Y, Hou X, Liu S, Li X, *et al*. LncRNA XLOC_006390 promotes pancreatic carcinogenesis and glutamate metabolism by stabilizing c-Myc. Cancer Lett 2020;469:419–428. doi: 10.1016/j.canlet.2019.11.021.
143. Rohrig F, Schulze A. The multifaceted roles of fatty acid synthesis in cancer. Nat Rev Cancer 2016;16:732–749. doi: 10.1038/nrc.2016.89.
144. Binnewies M, Roberts EW, Kersten K, Chan V, Fearon DF, Merad M, *et al*. Understanding the tumor immune microenvironment (TIME) for effective therapy. Nat Med 2018;24:541–550. doi: 10.1038/s41591-018-0014-x.
145. Bear AS, Vonderheide RH, O'Hara MH. Challenges and opportunities for pancreatic cancer immunotherapy. Cancer Cell 2020;38:788–802. doi: 10.1016/j.ccell.2020.08.004.
146. Thommen DS, Schumacher TN. T cell dysfunction in cancer. Cancer Cell 2018;33:547–562. doi: 10.1016/j.ccell.2018.03.012.
147. He Y, Han P, Chen C, Xie S, Zhang H, Song Y, *et al*. circPTPN22 attenuates immune microenvironment of pancreatic cancer via STAT3 acetylation. Cancer Gene Ther 2023;30:559–566. doi: 10.1038/s41417-021-00382-w.
148. Feng M, Xiong G, Cao Z, Yang G, Zheng S, Song X, *et al*. PD-1/PD-L1 and immunotherapy for pancreatic cancer. Cancer Lett 2017;407:57–65. doi: 10.1016/j.canlet.2017.08.006.
149. Boutilier AJ, Elsawa SF. Macrophage polarization states in the tumor microenvironment. Int J Mol Sci 2021;22:6995. doi: 10.3390/ijms22136995.
150. Yang J, Huang J, Zhang Y, Zeng K, Liao M, Jiang Z, *et al*. Contrast-enhanced ultrasound and contrast-enhanced computed tomography for differentiating mass-forming pancreatitis from pancreatic ductal adenocarcinoma: A meta-analysis. Chin Med J 2023;136:2028–2036. doi: 10.1097/CM9.0000000000002300.
151. Zhang D, Cui F, Zheng K, Li W, Liu Y, Wu C, *et al*. Single-cell RNA sequencing reveals the process of CA19-9 production and dynamics of the immune microenvironment between CA19-9 (+) and CA19-9 (-) PDAC. Chin Med J 2024;137:2415–2428. doi: 10.1097/CM9.0000000000003130.
152. Yang F, Liu DY, Guo JT, Ge N, Zhu P, Liu X, *et al*. Circular RNA circ-LDLRAD3 as a biomarker in diagnosis of pancreatic cancer. World J Gastroenterol 2017;23:8345–8354. doi: 10.3748/wjg.v23.i47.8345.
153. Ma Y, He X, Di Y, Liu S, Zhan Q, Bai Z, *et al*. Identification of prognostic immune-related lncRNAs in pancreatic cancer. Front Immunol 2022;13:1005695. doi: 10.3389/fimmu.2022.1005695.
154. Orbeck SV, Jakobsen T, Garcia-Rodriguez JL, Burton M, Rasmussen LG, Ewald JD, *et al*. Exploring the prognostic value of circular RNAs in pancreatic ductal adenocarcinoma using genome-wide expression profiling. Pancreatology 2024;24:706–718. doi: 10.1016/j.pan.2024.04.004.
155. Xu C, Jun E, Okugawa Y, Toiyama Y, Borazanci E, Bolton J, *et al*. A Circulating panel of circRNA biomarkers for the noninvasive and early detection of pancreatic ductal adenocarcinoma. Gastroenterology 2024;166:178–190 e116. doi: 10.1053/j.gastro.2023.09.050.
156. Xie Z, Chen X, Li J, Guo Y, Li H, Pan X, *et al*. Salivary HOTAIR and PVT1 as novel biomarkers for early pancreatic cancer. Oncotarget 2016;7:25408–25419. doi: 10.18632/oncotarget.8323.
157. Chen R, Wang SK, Belk JA, Amaya L, Li Z, Cardenas A, *et al*. Engineering circular RNA for enhanced protein production. Nat Biotechnol 2023;41:262–272. doi: 10.1038/s41587-022-01393-0.
158. Wu P, Mo Y, Peng M, Tang T, Zhong Y, Deng X, *et al*. Emerging role of tumor-related functional peptides encoded by lncRNA and circRNA. Mol Cancer 2020;19:22. doi: 10.1186/s12943-020-1147-3.
159. Liu CX, Guo SK, Nan F, Xu YF, Yang L, Chen LL. RNA circles with minimized immunogenicity as potent PKR inhibitors. Mol Cell 2022;82:420–434 e426. doi: 10.1016/j.molcel.2021.11.019.
160. Qu L, Yi Z, Shen Y, Lin L, Chen F, Xu Y, *et al*. Circular RNA vaccines against SARS-CoV-2 and emerging variants. Cell 2022;185:1728–1744.e16. doi: 10.1016/j.cell.2022.03.044.
161. Amaya L, Grigoryan L, Li Z, Lee A, Wender PA, Pulendran B, *et al*. Circular RNA vaccine induces potent T cell responses. Proc Natl Acad Sci USA 2023;120:e2302191120. doi: 10.1073/pnas.2302191120.
162. Feng Z, Zhang X, Zhou J, Li Q, Chu L, Di G, *et al*. An in vitro-transcribed circular RNA targets the mitochondrial inner membrane cardiolipin to ablate EIF4G2(+)/PTBP1(+) pan-adenocarcinoma. Nat Cancer 2024;5:30–46. doi: 10.1038/s43018-023-00650-8.
163. Gerstein MB, Kundaje A, Hariharan M, Landt SG, Yan KK, Cheng C, *et al*. Architecture of the human regulatory network derived from ENCODE data. Nature 2012;489:91–100. doi: 10.1038/nature11245.

How to cite this article: Li Z, Zhang TT, Yang XJ, Peng Y. Role of noncoding RNA and protein interaction in pancreatic cancer. Chin Med J 2025;138:1019–1036. doi: 10.1097/CM9.0000000000003587