Non-coding RNAs in pancreatic ductal adenocarcinoma: New approaches for better diagnosis and therapy

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignancies with a 5-year survival rate less than 8%, which has remained unchanged over the last 50 years. Early detection is particularly difficult due to the lack of disease-specific symptoms and a reliable biomarker. Multimodality treatment including chemotherapy, radiotherapy (used sparingly) and surgery has become the standard of care for patients with PDAC. Carbohydrate antigen 19–9 (CA 19–9) is the most common diagnostic biomarker; however, it is not specific enough especially for asymptomatic patients. Non-coding RNAs are often deregulated in human malignancies and shown to be involved in cancer-related mechanisms such as cell growth, differentiation, and cell death. Several micro, long non-coding and circular RNAs have been reported to date which are involved in PDAC. Aim of this review is to discuss the roles and functions of non-coding RNAs in diagnosis and treatments of PDAC.

Keywords: Non-coding RNAs; MicroRNA; Long non-coding RNA; Circular RNA; Pancreatic ductal adenocarcinoma

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a major cause of cancer-associated deaths in Western countries and is the eighth main source of cancer-related deaths globally, with the median survival rate of 3–10 months [1,2]. The complex biology and aggressive features of PDAC have been associated with the limited efficiency of treatments, especially in advanced stages of PDAC [3]. PDAC cases present significant heterogeneity of somatic DNA modifications, and alterations in genetic pathways [4]. Therefore, a substantial number of complex genetic networks and transcriptomics have been correlated with the development of PDAC [5]. The progression of PDAC can be divided into three major PDAC precursor lesions: pancreatic intraepithelial neoplasia (PanIN I, II, III); mucinous cystic neoplasm (MCN), and intraductal papillary mucinous neoplasm (IPMN) [6]. Each of these PDAC precursor lesions presents unique clinical, pathological and molecular features [6]. The most frequent genetic alterations that are associated with PDAC development are mutations of *KRAS* and overexpression of human epidermal growth factor receptor (*HER-2*/neu) [7]. Furthermore, at later stages, inactivation of tumour suppressor genes (TS) such as cyclin-dependant kinase inhibitor 2A (*CDKN2A*), tumour protein 53 (*TP53)* and SMAD family number 4 (*SMAD4*) have been closely linked to pathogenesis and metastasis of PDAC [7]. Carbohydrate antigen 19–9 (CA 19–9), carcinoembryonic antigen (CEA) and duke pancreatic monoclonal antigen type 2 (DUPAN2) are the most commonly used biomarkers for PDAC [8,9]. However, even CA 19–9, the best biomarker available, cannot be characterized as a PDAC-specific biomarker, especially for asymptomatic patients [10], as the false-positive rate of CA19–9 is relatively high at 20–30% [11]. Hence, these biomarkers are most commonly utilized to monitor during and post-treatment, and assess prognosis, but are not robust enough [12]. There is an urgent need for novel non-invasive biomarkers for the early diagnosis and prognosis [13], which could be used to ascertain follow-up strategies for PDAC. Molecular modifications, genetic and epigenetic factors could be a crucial for the early diagnosis of PDAC [14]. Technological advances have prompted a new era of "omics" based research for the establishment of circulating biomarkers, including proteins, cell-free DNAs, non-coding RNAs, circulating tumour cells (CTCs), and exosomes' molecular content [15]. In terms of the treatment, currently, combination chemotherapies such as FOLFIRINOX (5-FU, irinotecan, oxaliplatin and leucovorin) and gemcitabine-nab-paclitaxel are considered superior to gemcitabine monotherapy for advanced pancreatic cancer [16].

Non-coding RNAs (ncRNAs) are a class of RNA molecules that cannot be translated into protein and are classified into subtypes based on their length [17]. Most commonly studied ncRNAs are long non-coding RNA (lncRNAs: longer than 200 nucleotides) and microRNAs (miRs: 18–24 nucleotides long) however, small interfering RNAs (siRNAs), tRNA-derived stress-induced RNAs (tiRNAs), enhancer non-coding RNAs (eRNAs) and circular RNAs (circRNAs) are also classified as ncRNAs [18]. ncRNAs are key regulators in several physiological cellular and biological processes, which involve the modulation of gene expressions both transcriptionally and post-transcriptionally [19]. Recent studies showed that ncRNAs play a crucial role in cancer prognosis by controlling both cellular and biological processes including chromatin remodelling, transcription, post-transcriptional modifications and signal transduction [20, 21]. ncRNAs can act both as tumour suppressors and oncogenic drivers in numerous malignancies including PDAC, and correlation between aberrant expression levels of several ncRNAs in PDAC has been reported [22,23]. Therefore, the aim of this review is to evaluate the expression profiles of ncRNAs to determine the most significant miR, lncRNA and circRNA signatures, which could be critical both for the early diagnosis and effective therapy strategies of PDAC.

miRNAs as Diagnostic and Prognostic Biomarkers for PDAC

miRs, are small (18 to 24 nucleotides in length), endogenous, non-coding, evolutionary conserved, single-stranded RNA molecules that can moderate gene expression at the post-transcriptional level through binding to the complementary sequences of their target mRNAs at 3′ untranslated regions (UTRs) [24]. Epigenetic alterations, which are regulated by miRs have been suggested to be implicated in the prognosis of PDAC may explain its complexity [25]. The aberrant expression of miRs plays a significant role in initiation, proliferation, induction of the epithelial to mesenchymal transition (EMT), metastasis, and chemo-resistance of PDAC cells [26]. Stable miR expression was detected in tissues, blood plasma and several body fluids such as serum, urine, and breast milk [27]. Thus, miRs can be characterized as "circulating microRNAs", which can be found encapsulated in cell-secreted vesicles or vesicle-free [27]. miRs can act as oncogenes (oncomiR) or tumour suppressor genes (tsmiRNA) in PDAC [28, 29]. The aberrant expression of miRs can be the result of amplification or deletion in a genomic region where miRs genes are expressed [30]. Even though the biological functions of the identified miRs present considerable ambiguity, the examination of the expression profiles of these biomarkers can provide useful information regarding

their regulation and function [31]. Despite the narrow knowledge of these molecules, a plethora of miRs can be characterized as vital biomarkers not only for the early prognosis and diagnosis of PDAC but also for better management of therapeutics [32].

Oncogenic miRs in PDAC

miR-376a and miR-301 are upregulated in tissues while miR-23a and miR-23b over expressions were detected in saliva of PDAC patients [33,34]. Moreover, miR-21, is one of the most studied miRs, along with miR-20a, miR-24, miR-25, miR-99a, miR-185 and miR-191 and, due to their increased expression levels in PDAC, were suggested as potential diagnostic markers [34–36]. Interestingly, miRs that identified as biomarkers showed an accuracy of 83.6% compared to CA 19–9, which is only 56.4% [37–39]. Another study reported increased expressions of miR-1246, miR-4644, miR-3976 and miR-4306 in serum derived exosomes of PDAC patients [40], whereas miR-221 and miR-18a were also found to be upregulated in plasma of PDAC patients [41–43]. miR-221 is associated with distant metastasis, interestingly, miR-221 and miR-18a expression levels were reduced after surgery [41–43]. Therefore, both miR-221 and miR-18a could be effective diagnostic and prognostic biomarkers [41–43]. Furthermore, miR-194 expression levels were significantly elevated and linked with the poor prognosis of PDAC [44], while Bloomston *et al.* (2007) suggested the overexpression of miR-155, miR-181a, b, c, d and miR-196a in PDAC cases [45]. Moreover, miR-10a, miR-17–5p and miR-92 expressions were significantly upregulated in PDAC cases [46]. Lin *et al.* (2014) also showed the overexpression of miR-1238, miR-4290 and miR-483–5p in PDAC patients [47]. miR-486–5p and miR-938 have been proposed as potential diagnostic serum biomarkers for PDAC [48]. Further studies have suggested the upregulation of miR-203, miR-210, miR-222 [49], miR-196b and miR-196a [50]. Wang *et al.* (2013) also showed that the upregulation of miR-27a-3p effectively discriminated PDAC cases from benign pancreatic/peri-pancreatic diseases (BPD) [51]. Conclusively, miR-135b, which is also overexpressed in PDAC, can be characterized as a potential diagnostic biomarker for PDAC due to the fact that it presented high sensitivity and specificity for the discrimination of PDAC cases [52] (Table 1, Fig. 1).

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Table 1

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Oncogenic miRs associated with PDAC.

miRs	Expression in PDAC	Clinical Values	Functional Involvement in PDAC	Detected	Biology Tested	Control	Number of Patients	Group Tested	References(s)
miR-376a	Up	D	Increase cell proliferation, invasion, migration	Tissue + Panc-1, HS766T, MIA PaCa-2, BxPC3, Panc10.05 cell lines	Cells, Patients	6 Normal pancreatic tissue	28	Stage II, III	[33]
miR-301	Up	D	Increase cell growth	Tissue +Panc-1, HS766T, MIA PaCa-2, BxPC3, Panc10.05 cell lines	Cells, Patients	6 Normal pancreatic tissue	28	Stage II, III	[33]
miR-21	Up	D, P, T	Inhibition of apoptosis, increase gemcitabine resistance, aggressiveness	Saliva, Blood, Tissue	Patients, Animals	4 Healthy controls	7	Locally advanced and unresectable PDAC	[34,36,41,45, 53,54,55]
miR-23a	Up	D, T	Inhibition of apoptosis	Saliva	Patients, Animals	4 Healthy controls	7	Locally advanced and unresectable PDAC	[34,36,56]
miR-23b	Up	D, T	Inhibition of apoptosis, Radioresistance	Saliva	Patients, Animals	4 Healthy controls	7	Locally advanced and unresectable PDAC	[34,57]
miR-24	Up	D, P	Inhibition of apoptosis	Blood-Serum	Patients	158 Healthy controls	197	Stages I, II, III, IV	[35,37,58]
miR-25	Up	D, P	Inhibition of apoptosis	Blood-serum	Patients	158 Healthy controls	197	Stages I, II, III, IV	[35,37,58]
miR-99a	Up	D, P	Increase cell proliferation, invasion, migration	Blood-serum	Patients	158 Healthy controls	197	Stages I, II, III, IV	[35,37,58]
miR-185	Up	D, P	Increase invasion, migration	Blood-serum	Patients	158 Healthy controls	197	Stages I, II, III, IV	[35, 37, 58]
miR-191	Up	D, P	Inhibition of cell differentiation	Blood-serum	Patients	158 Healthy controls	197	Stages I, II, III, IV	[35,37,58]
miR-1246	Up	D, T	Increase chemoresistance, cell invasion and migration	Serum	Patients	12 Healthy controls	131	Stages I, II, III, IV	[40,59]
miR-4644	Up	D	Increase cell invasion and migration	Serum	Patients	12 Healthy controls	131	Stages I, II, III, IV	[40]
miR-3976	Up	D	Increase cell invasion and migration	Serum	Patients	12 Healthy controls	131	Stages I, II, III, IV	[40]
miR-4306	Up	D	Increase cell invasion and migration	Serum	Patients	12 Healthy controls	131	Stages I, II, III, IV	[40]
miR-221	Up	D, P, T	Increase cell proliferation, migration, EMT	Plasma, Tissue +Panc-1 cell line	Patients, Cell lines	30 Healthy volunteers	47	Stages I, II, III, IV	[42,45]
miR-18a	Up	D, P, T	Inhibition of apoptosis, increase cell growth	Plasma, Tissue + Panc-1	Patients, Cell	30 Healthy controls	36	Stages I, II, IV	[41]

					lines				
miR-194	Up	D, P	Increase tumour growth and invasion	Tissue + Panc-1, BxPC3, AsPC-1, Capan-1, MIA Paca-2, SW1990 cell line	Patients, Cell lines	3 Adjacent non-cancerous tissues	9	PDAC patients with surgical resection	[44]
miR-155	Up	D, P, T	Decrease apoptosis, Increase cell invasion, migration, metastasis, generation of reactive oxygen species	Plasma, Tissue	Patients	Adjacent non-cancerous tissues	65	PDAC patients with surgical resection	[45,36,60,61]
miR-181a, b, c, d	Up	D, T	Increase migration and metastasis	Plasma, Tissue	Patients	Adjacent non-cancerous tissues	65	PDAC patients with surgical resection	[45,62,58]
miR-196a	Up	D, P	Increase invasion and migration	Plasma, Tissue	Patients	Adjacent non-cancerous tissues	65	PDAC patients with surgical resection	[45,50,58]
miR-10a	Up	D, T	Increase chemoresistance and metastasis	Tissue +Panc-1, BxPC3, AsPC-1, Capan-1, MIA Paca-2, SW1990, HDPE cell line	Cell lines	HDPE	15 Cell lines	Primary tumours	[63,64]
miR-17–5p	Up	D, P, T	Increase cell growth apoptosis, decreased chemosensitivity to gemcitabine	Tissue +Panc-1, BxPC3, AsPC-1, Capan-1, MIA Paca-2, SW1990, HDPE cell line	Cell lines	HDPE	15 Cell lines	Primary tumours	[36,63,65]
miR-92	Up	D	Increase cell growth, inhibition of cell differentiation	Tissue +Panc-1, BxPC3, AsPC-1, Capan-1, MIA Paca-2, SW1990, HDPE cell line	Cell lines	HDPE	15 Cell lines	Primary tumours	[63]
miR-1238	Up	D	Inhibition of apoptosis	Serum	Patients	27 Matched Healthy controls	49	Stages I, II, III, IV	[47]
miR-4290	Up	D	Inhibition of cell differentiation	Serum	Patients	27 Matched Healthy controls	49	Stages I, II, III, IV	[47]
miR-483–5p	Up	D	Increase proliferation and colony formation *in vitro*	Serum	Patients	27Matched Healthy controls	49	Stages I, II, III, IV	[47]
miR-486–5p	Up	D	Increase cell proliferation, migration and invasion	Plasma	Patients	5 Healthy controls	7	Pre-operative PDAC	[48]
miR-938	Up	D	Increase cell proliferation, migration and invasion	Plasma	Patients	5 Healthy controls	7	Pre-operative PDAC	[48]
miR-203	Up	D, P	Increase cell proliferation, migration, invasion, decrease apoptosis	Tissue	Patients	7 Normal pancreatic tissue	10	Stage III, IV	[49,36,60]
miR-210	Up	D, P	Promotes invasion and EMT	Plasma, Tissue	Patients	7 Normal pancreatic tissue	10	Stage III, IV	[49,36,58,60]
miR-222	Up	D, P	Increase cell proliferation, migration, invasion, decrease apoptosis	Tissue	Patients	7 Normal pancreatic tissue	10	Stage III, IV	[36,49,60]
miR-196b	Up	D, P	Increase invasion and migration	Tissue	Patients	35 Normal pancreatic tissue	165	Stage IA, IB, IIA, IIB	[66]
miR-27a-3p	Up	D, T	Increase growth, migration, and colony formation *in vitro*	Blood	Patients	20 Healthy controls	20	Stage IA, IB, IIA, IIB, III, IV	[51,56]
miR-135b	Up	D, P	Increase tumour growth, promote cell adaptation to metabolic stress, suppress glycolysis	Tissue	Patients	Normal pancreatic tissue	52	-	[52]
miR-212	Up	D, P	Increase proliferation	Tissue + MIA Paca-2, AsPC1 cell line	Patients, Cell lines	Normal pancreatic tissue	41	PDAC patients with surgical resection	[67]
miR-182	Up	D, P	Increase tumour growth, invasion and migration	Plasma	Patients	Healthy controls	109	Stages I, II, III, IV	[68]

D: diagnostic biomarker, P: prognostic biomarker, T: therapeutic target

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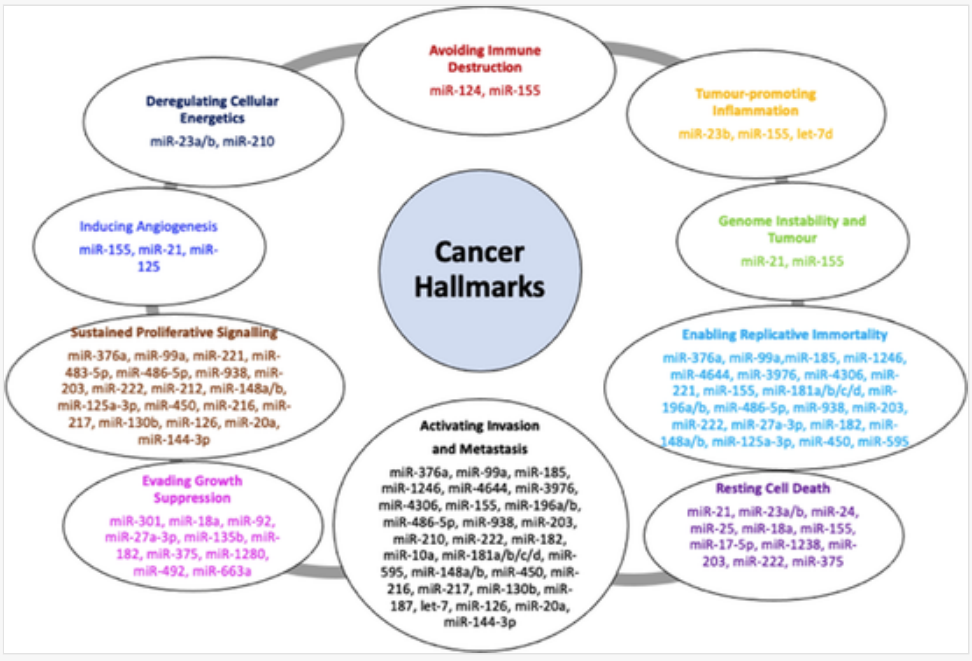
Fig. 1



Involvement of miRs in PDAC progression. miRs are classified both as oncogenes and tumour suppressors by moderating several key downstream gene targets which control different cellular and biological processes involved in cancer progression.

Tumour suppressor miRs and PDAC

Downregulation of miR-148a, b, and miR-375 expression could be used to differentiate PDAC, normal pancreatic and pancreatitis tissues [45]. Reduced expression of miR-125a-3p was correlated with EMT and gemcitabine resistance in PDAC [69,70]. Another study reported that both miR-450 and miR-205 aberrantly expressed in PDAC [63], while Lin *et al.* (2014) suggested that the downregulation of miR-1280, miR-492, miR-595 and miR-663a in PDAC patients [47]. Specifically, miR-663a is found to be closely correlated with the tumour-node-metastasis (TNM) stages in PDAC. Thus, these novel non-invasive biomarkers could be utilized for the prognosis of PDAC [47], while a combined miR panel could be a valuable diagnostic and prognostic strategy for PDAC. miR-216 and miR-217 were down regulated in PDAC samples and hence could be used as diagnostic biomarkers for PDAC patients [49]. Moreover, the expression levels of three miRs, which are transcribed from the miR-216/-217 miR family, were decreased in the $P48^{+/Cre}$;$LSL\text{-}KRAS^{G12D}$, PDX-1-Cre;$LSL\text{-}KRAS^{G12D}$, and ELa-$Kras^{G12D}$ mice [71]. Similarly, reduced expression of miR-216a, miR-216b and miR-217 were detected in the pancreas of $P48^{+/Cre}$;$LSL\text{-}KRAS^{G12D}$ mice [72]. Further studies indicate that miR knockout mouse models increased the lethality in mice [73,74]. miR-130b also considerably downregulated in PDAC cases and was closely related to poor prognosis, elevated tumour size, late TNM stage, lymphatic invasion and distant metastasis [75] (Table 2, Fig. 1).

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Table 2

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Tumour suppressor miRs are identified in PDAC.

miRs	Expression in PDAC	Clinical Values	Biological processes involved	Detected	Biology Tested	Control	Number of patients	Group Tested	References
miR-148a	Down	D, P, T	Cell proliferation, invasion, migration	Plasma, Tissue	Patients	Matched Adjacent non-cancerous tissues	65	PDAC patients with surgical resection	[45,50,76,77]
miR-148b	Down	D, T	Cell proliferation, invasion, migration, inhibition of chemo-sensitization	Plasma, Tissue	Patients	Matched Adjacent non-cancerous tissues	65	PDAC patients with surgical resection	[45,78]
miR-375	Down	D, P	Tumour growth and apoptosis	Plasma, Tissue	Patients	Matched Adjacent non-cancerous tissues	65	PDAC patients with surgical resection	[45,49]
miR-125a-3p	Down	D, T, P	Cell proliferation and migration, chemosensitivity, EMT	Blood	Patients, Panc-1, BxPC3, AsPC-1, Capan-2, MIA-PaCa-2 cell lines	Adjacent non-cancerous tissues	421	Advanced PDAC cases	[69,70,79]
miR-450	Down	D	Cell differentiation, proliferation, migration and invasion		Panc-1, BxPC3, AsPC-1, Capan-2, MIA-PaCa-2 cell lines		15 PDAC cell lines	Primary tumours	[63]
miR-1280	Down	D, P	Tumour growth	Blood	Patients	27 Healthy controls	49	Stages I, II, III, IV	[47]
miR-492	Down	D, P	Tumour growth and stage	Blood	Patients	27 Healthy controls	49	Stages I, II, III, IV	[47]
miR-595	Down	D, P	Migration, metastasis	Blood	Patients	27 Healthy controls	49	Stages I, II, III, IV	[47]
miR-663a	Down	D, P	Tumour growth and stage	Blood	Patients	27 Healthy controls	49	Stages I, II, III, IV	[47]
miR-216	Down	D, T	Increase cell proliferation, invasion	Tissue	Patients, +3 Cell Lines	Normal Pancreatic tissue	10	Stage III, IV	[49,80]
miR-217	Down	D, T	Increase cell proliferation, migration, invasion, DNA damage, stress responses, genome stability	Tissue	Patients, +3 Cell Lines	Normal Pancreatic tissue	10	Stage III, IV	[49,80]

			and cell survival					
miR-130b	Down	D, P, T	Cell proliferation, invasion	Tissue	Patients, Panc-1, BxPC3, AsPC-1, SW1990, MIA-PaCa-2 cell lines	Matched Normal Pancreatic tissue	52	Stage I, II III, IV	[75]
miR-187	Down	D, P	Invasion, migration	Tissue	Patients	Normal Pancreatic tissue	170	Stages IA, IB, IIA, IIB	[76]
let-7	Down	D, P, T	EMT, invasion	Tissue	Patients	Normal Pancreatic tissue	170	Stages IA, IB, IIA, IIB	[76]
miR-205	Down	D, T	Chemoresistance	Pancreatic Juice	Patients	19 Non-healthy (NPNH) controls	50	Advanced PDAC cases	[50,79,81,82]
miR-126	Down	D, P	Cell proliferation, migration, invasion	Tissue	Patients	Normal Pancreatic tissue	455	Stages O, I, II, III, IV	[36]
miR-20a	Down	D, P	Proliferation, invasion	Blood-plasma	Patients	Healthy individuals	197	Stages I, II, III, IV	[35,37,58]
miR-144–3p	Down	D, P	Cell cycle arrest, migration, invasion, metastasis, cell proliferation	Tissue	Patients + Panc-1 cell line	Paired adjacent non-tumour tissues	10	Stages IA, IB, II, III	[83]

D: diagnostic biomarker, P: prognostic biomarker, T: therapeutic target.

Early stage of PDAC associated miRs

It was suggested that miR-1290 could be used to determine low-stage PDAC with high sensitivity and specificity [84]. Besides, it was demonstrated that in addition to miR-16, miR-155 and miR-181a, miR-181b and miR-210 were overexpressed in the plasma of PDAC patients compared to normal controls [58]. Therefore, miR combination panels presented high specificity and sensitivity for the diagnosis of PanIN-I PDAC patients [58]. miR-16, especially, presented a sensitivity of 92.0% and a specificity of 95.6% for the determination of PDAC cases between normal samples [85]. miR-19a-3p was shown to be overexpressed in PDAC and could be utilized not only as an early non-invasive diagnostic biomarker for PDAC but also as a prognostic biomarker for patients with poor overall survival rate [86]. Another study identified the upregulation of miR-29a, miR-29b, miR-103 and miR-320 as early diagnostic predictors of PDAC and therefore it can be proposed that these miRs could be also utilized for the early diagnosis of PDAC [35] (Table 3, Fig. 2).

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Table 3

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Deregulated miRs in PDAC lesions.

PDAC Lesion	Overexpressed miRs	Down Regulated miRs	References
PanIN-I	miR-21, miR-155, miR-182, miR-200a, miR-200b, miR-221, miR-1290, miR-181a, miR-181b, miR-210, miR-103, miR-145, miR-193b, miR-320	miR-296–5p, miR-107, miR-181c	[33,58,84,85,86]
PanIN-II	miR-21, let-7, miR-155, miR-200, miR-205, miR-222, miR-10b, miR-196a, miR-196b, miR-29b/a, miR-486–3p, miR-425, miR-708, miR-874, miR-145, miR-200a, miR-200b, miR-200c, miR-193a-3p	miR-296–5p, miR-148, miR-217	[23,68,85,87,88,89,90]
PanIN-III	let-7, miR-18a, miR-21, miR-155, miR-145, miR-196b, miR-200, miR-222, miR-338–3p, miR-486–3p, miR-29b, miR-425, miR-708, miR-874, miR-10b, miR-196a, miR-182, miR-205, miR-221	miR-125b, miR-126, miR-218, miR-296–5p, miR-452, miR-148, miR-217	[68,85,87,89,91,92,93,94]

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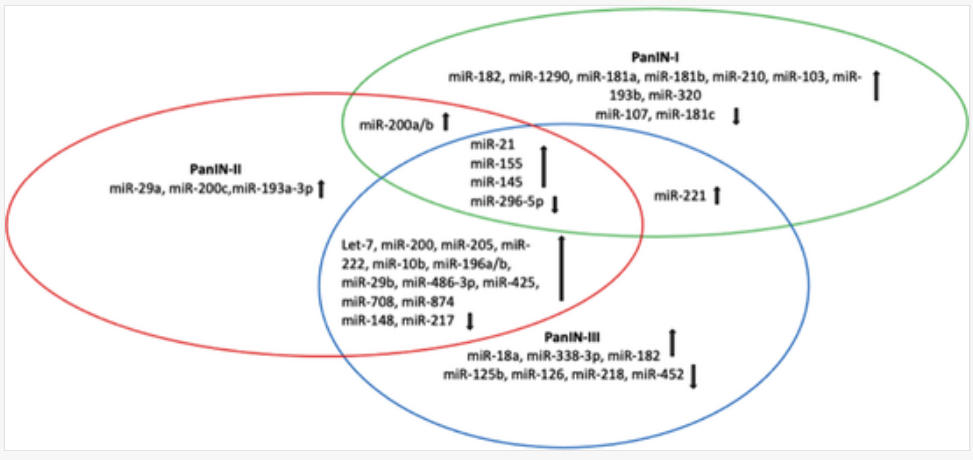
Fig. 2



Venn diagram shows the overlap between differentially expressed miRs in different lesions of PDAC. It can be noted that miR-21, miR-155, miR-145 and miR-296–5p are presented in all PanIN lesions, while miR-200a/b in both PanIN-I and II. miR-221 are detected only in PanIN-I and III.

Late stage of PDAC associated miRs

Both miR-196a and miR-196b were found to be overexpressed in PDAC patients with PanIN-II & III lesions and correlated with poor survival [87]. In particular, miR-196a and miR-196b presented 100% sensitivity and specificity in the discrimination of PDAC cases compared to healthy controls [87]. Significantly, miR-196a is an effective prognostic biomarker, due to the fact that patients with unresectable PDAC (stages III and IV) had considerable higher expression levels of miR-196a in comparison with patients in the early stages of the disease (stages I and II), which presented lower levels [85]. miR-182 was overexpressed in PDAC patients in correlation

to healthy controls and was linked to advanced clinical stages and lymph node metastasis [68]. Furthermore, overexpressed miR-21 has been associated with advanced stages of PDAC metastasis to lymph nodes and liver, increased gemcitabine-resistant and poor survival in PDAC patients [88–90]. Previous studies indicated that miR-21, miR-29b, miR-146a, miR-182, miR-193a-3p, miR-193b, miR-200a, miR-200b, miR-425, miR-486–3p, miR-708 and miR-874 were significantly dysregulated in PanIN-II & III lesions in comparison to PanIN-I lesions and normal pancreatic tissues [91,92]. Besides, Ryu and colleagues (2010) noted that miR-155 was upregulated in PanIN-II and III in comparison to PanIN-I and healthy controls [88]. Thus, a large body of evidence strongly suggests the utility of specific miRs profiles as potential effective early diagnostic and prognostic tools for PDAC subtypes (Table 3, Fig. 2).

Prognostic miRs in PDAC

Upregulated miR-132 [95], miR-21 [54] and downregulated miR-96 [96], miR-34a [97] are aberrantly expressed in PDAC tissues, in relation to normal adjacent tissue, and are associated with poor overall survival [98]. A study by Giovannetti *et al.* (2010) demonstrated that miR-21 expression could identify shorter overall survival rates in PDAC patients, who have undergone gemcitabine therapy [99]; miR-21 upregulation is also associated with poor survival rate in 79% of PDAC cases [54,100]. Another study indicated that PDAC tissues containing hypermethylated miR-124–1, miR-124–2 and miR-124–3, were related to poor survival rate in PDAC [101].

Further examples of miRs with considerable prognostic impact in PDAC are miR-451a and miR-1290 and tissue miR-10b, miR-17–5p, miR-29c, miR-126, miR-155, miR-203, miR-218, miR-221 and miR-222 [36]. In particular, miR-21, miR-451a, miR-23a, miR-155 and miR-218 presented the highest prognostic impact in PDAC patients and linked to poor survival [36]. Frampton *et al.* (2014) confirmed the prognostic impact of miR-23a and miR-27a in PDAC patients, who have undergone surgical resection [56]. In addition, upregulation of miR-200c was also linked with limited survival in PDAC patients through the reduction in the levels of mucin 4 (*MUC4)* and mucin 16 (*MUC16)* [102]. Similarly, the overexpression of miR-210 is associated with poor survival rate in PDAC patients [60]. miR-4521 down regulation is linked with uncontrolled proliferation of PDAC cells and poor overall survival rate [103]. Matrix metallopeptidase 7 (MMP7) is highly expressed in PDAC tissues and associated with metastasis, while it can be targeted with the upregulation of miR-144–3p, which leads to longer survival rates [83]. Upregulation in miR-182 presented shorter disease-free survival and overall survival compared to patients with low expression levels [68]. Similarly, Schultz *et al.* (2012) designated that the upregulation of miR-212 and miR-675 and down-regulation of miR-148a, miR-187 and let-7 g were linked to a worse prognosis in PDAC cases [104]. On the contrary, oncogenic miR-30a-3p, miR-105, miR-127, miR-187, miR-452 and miR-518a-2 are associated with a better prognosis of PDAC patients [45], whereas Greither *et al.* (2010) noted that miR-200c and miR-302 are related to PDAC patients' outcomes and poor survival [60]. Besides, it has been suggested that downregulated miR-506 is associated with poor prognosis in PDAC [105, 106]. A further study revealed that miR-6075, miR-4294, miR-6880–5p, miR-6799–5p, miR-125a-3p, miR-4530, miR-6836–3p and miR-4476 presented a higher accuracy for the diagnosis of PDAC in correlation with CA19–9 and CEA [78]. Further examples of miRs with better survival rates are the upregulated miR-142 and miR-204 [46], while downregulated miR-19a-3p corresponds to higher survival impact [86]. Hence, miRs could act as effective prognostic biomarkers.

LncRNAs in PDAC

Long non-coding RNAs (lncRNAs) have emerged as a class of factors that are of importance in regulating normal development and cancer pathology [107,108]. Although less functionally characterised than miRs, lncRNAs accounts for 25% of the total RNA distribution in the human cell, are more abundant than miRs and are accepted as an important class of pervasive ncRNAs [109]. The interplay between lncRNAs and their target molecules are involved in a wide range of fundamental and critical biological processes, deregulation of which is widely implicated in carcinogenesis [110–113]. Notably, lncRNAs are confirmed to play important roles including transcriptional and post-transcriptional regulation, epigenetic regulation, chromatin remodelling, organ or tissue development, cell differentiation and apoptosis, cell cycle control, cellular transport, metabolic processes and chromosome dynamics [110,114]. The intrinsic ability of lncRNAs to interact with DNA, RNA and proteins allows them to regulate gene expression at almost every stage by taking the role as guides, scaffolds, signals, and decoys [112,115]. A mounting number of studies have demonstrated that deregulation of lncRNAs is a critical factor in malignant transformation performing in either oncogenic or tumour-suppressive capacities and have potential to contribute to precise diagnosis and individualised therapy for cancers including PDAC [116]. Based on their different features and functional mechanisms, lncRNAs could be classed as: (**1**) long intergenic ncRNAs (lincRNAs); (**2**) long intronic ncRNAs [117]; (**3**) transcribed ultra-conserved regions; (**4**) transcribed pseudogenes [118]; (**5**) natural antisense transcripts (NATs); (**6**) promoter-associated long RNAs; (**7**) promoter upstream transcripts; (**8**) repetitive element-associated ncRNAs, and (**9**) enhancer-like ncRNAs [114] . lncRNAs can either act as "miR sponges" or competitive endogenous RNAs (ceRNAs) that regulate miR activity and consequently gene expression [111]. There are several widely recognised dysregulated lncRNAs in other cancers apart from PDAC, which have been functionally characterised and are shown to be promising diagnostic and prognostic biomarkers as well as novel therapeutic targets (*e.g.*, H19, HULC, HOTAIR, HOTTIP & MALAT-1) [119]. However, functional elucidation of the lncRNAs have only recently been identified as being linked specifically to PDAC tumorigenesis, including the identification of their target molecules (*e.g.*, miRs), and may have the potential to serve as early diagnostic tools for cancer risk, sub-typing and prognosis as well as targeted therapeutics [120].

Oncogenic lncRNAs mediated in PDAC

LncRNA H19 was not only found to be up-regulated in PDAC, compared to adjacent normal pancreatic tissues, but also promoted PDAC cell invasion and migration by increasing high mobility group AT-hook 2 (*HMGA2*)-mediated EMT through antagonising let-7 [121]. Additionally, H19 contributes to metastasis by promoting PDAC stem-like cell adhesion by up-regulating the expression of integrin and CD24 [122]. H19 may act as a sponge of miR-675 to promote PDAC cell proliferation by enhancing *E2F-1* expression and is crucial for regulating the growth and progression of PDAC [123]. H19 may be a good prognostic tool for the overall survival of PDAC patients [124] as well as sensitivity diagnostic marker for chemotherapy response [114]. Feng and colleagues (2018) showed that the over-expression of HULC activated PI3K/AKT pathway in Panc-1 cells by downregulating miR-15a while the suppression of HULC had opposite effects and dramatically induced Panc-1 cell apoptosis [125] . Another recent study revealed that miR-133b targets HULC directly and attenuates PDAC cell invasion and migration by inhibiting HULC expression highlighting its value as a potential therapeutic target for PDAC [126]. Moreover, overexpression of miR-622, which was significantly downregulated by transforming growth factor beta (TGF-β) in a panel of PDAC cells, significantly reduced cell invasion and migration whereas inhibition of miR-622 increased HULC expression and promoted EMT signalling, invasion, and migration of PDAC cells [127]. Upregulation of HULC was significantly correlated with large tumour size, advanced lymph node metastasis, and vascular invasion; it may serve as an independent predictor for overall survival in PDAC [128]. Overexpression of HOX Antisense Intergenic RNA (HOTAIR) has been linked to susceptibility, metastasis and/or poor prognosis of pancreatic cancers [129]. Li and associates (2016) demonstrated that lncRNA HOTAIR can physically interact with the miR-34a promoter and use its enhancer of zeste homologue 2 (*EZH2)*-interacting regions to guide *EZH2* in targeting miR-34a gene and its consequent silencing [130]. HOTAIR epigenetically regulates the expression of miR-663b via the histone modification [131], while Cai *et al.* (2019) showed that stable over-expression of miR-613 or knock-down of HOTAIR suppressed tumour growth and also reduced the expression of *Notch3* suggesting that HOTAIR functions as a ceRNA to regulate Notch3 expression via sponging miR-613 in PDAC [132]. In addition, HOTAIR may be induced by gemcitabine and acts as a tumour promoter by inhibiting the chemosensitivity and promoting the self-renewal capacity, proliferation and migration of Panc-1 cancer stemness [133]. Yang *et al.* (2017) showed that epigenetic modulation of the death receptor 5 (*DR5)* gene by HOTAIR regulates the resistance of PDAC cells to TRA-8-induced apoptosis, which may contribute to TNF-related apoptosis-inducing ligand (TRAIL) resistance [134]. It has also been indicated that HOTAIR knockdown promotes radiosensitivity of PDAC by regulating autophagy via autophagy related 7 (*Atg7*) gene expression [135]. The growing interest in HOTAIR as an important pro-oncogenic lncRNA is justified since it has been shown to be detectable in serum [136] as well as in saliva, making it a suitable candidate for a non-invasive biomarker [137].

HOXA transcript at the distal tip (HOTTIP) is another HOX-associated lncRNA that shows oncogenic-like activity in PDAC [120]. Overexpression of HOTTIP is significantly correlated with lymph node metastasis and overall survival, which can be detected through plasma-based HOTTIP-005, one of the most stable spice variants of HOTTIP in PDAC tissues [138]. Additionally, HOTTIP promotes gemcitabine resistance by regulating HOXA13 in PDAC, which suggests the HOTTIP/HOXA13 axis

as a potential therapeutic target for ‘chemo gene’ therapy [136,139]. Recently, it has also been shown that silencing HOTTIP reverses cisplatin resistance of PDAC cells by promoting miR-137 expression [140]. The oncogenic property of widely expressed lncRNA (MALAT-1) has also been found in PDAC [141–144] and its up-regulation significantly associated with tumour size, advanced stages, deeper invasion [145] and poor overall survival [146]. Zhou and associates (2018) demonstrated that downregulation of MALAT1 to suppress proliferation, migration and invasion, and induce apoptosis of pancreatic cancer cells by regulating the expression of *LATS1* and *YAP1* in the Hippo-YAP signalling [147]. They also showed that downregulation of MALAT1 inhibited the tumour growth of PDAC *in vivo* highlighting the crucial role MALAT1 played in PDAC progression [147]. MALAT1 acts as a ceRNA to regulate K-RAS protein expression by sponging miR-217 [148]. MALAT1 knockdown does not directly affect cellular miR-217 expression but decreases the miR-217 nucleus/cytoplasm ratio, suggesting that MALAT1 inhibits the translocation of miR-217 from the nucleus to the cytoplasm [148,149]. In addition, overexpressed PVT1 is also a negative regulator of gemcitabine sensitivity in PDAC [124] and can be used to predict patient outcomes [150]. PVT1 functions as a ceRNA for miR-448 binding to regulate the miRNA target *serpine1 mRNA binding protein 1 (SERBP1)* and therefore promote the proliferation and migration of PDAC cells [151]. The expression level of PVT1 was positively correlated with *SERBP1* in PDAC tissues [151]. *SERBP1* is a known transcription factor of lipogenic genes, *ACC, FASN* and *SCD1*, which plays important roles in regulating de novo lipogenesis, and is crucial for PDAC tumorigenesis [152]. It has also been reported that PVT1 up-regulated the expression of both *Pygo2* and *ATG14* and thus regulated Wnt/β-catenin signalling and autophagic activity to overcome gemcitabine resistance through sponging miR-619–5p [153]. PVT1 has also been shown to be readily detectable in patient saliva samples making it a versatile and non-invasive biomarker for early diagnosis and gemcitabine response [137]. Furthermore, high expression of lncRNA AFAP1 antisense RNA 1 (AFAP1-AS1) may act as a negative prognostic factor in PDAC patients with surgical resection [154]. Ye and associates (2015) indicated that the overall survival and progression-free survival was significantly worse in PDAC patients with higher AFAP1-AS1 expression in their tumour tissues as their levels correlated strongly with lymph node metastasis and perineural invasion [154]. AFAP1-AS1 could regulate the progression of pancreatic cancer by acting as a ceRNA for miR-133a [155]. The insulin like growth factor 1 receptor (*IGF1R)* oncogene, which is an important regulator of MEK/ERK signalling pathway, was positively regulated by AFAP1-AS1 through ameliorating miR-133a-mediated *IGF1R* repression in PDAC [155]. *IGF1R* has been shown to coordinate the regulation of multiple cellular pathways involved in survival, proliferation, metastasis, EMT, apoptosis and cell cycle signalling [156]. Interestingly, miR-133a has also been shown to down-regulate the expression of XIST, another long non-coding RNA implicated in PDAC [157]. Over-expression of X inactive-specific transcript (XIST) has been shown to significantly promote proliferation, migration and invasion, and suppressed cell apoptosis in PDAC cells [158]. Wei and associates (2017) showed that XIST and miR-133a reciprocally inhibited each other in PDAC cells [157]. Moreover, they showed that miR-133a bound to XIST and the 3′UTR of epidermal growth factor receptor (*EGFR)* by direct targeting, and that XIST expression was positively correlated with *EGFR* expression [157]. *EGFR* overexpression is thought to confer poor survival, correlating with a more advanced stage and the presence of metastases in PDAC [157]. XIST has also been demonstrated to act as a sponge for miR-429 to modulate zinc finger E-box binding homeobox 1 (*ZEB1)* expression, promoting migration, invasion and EMT [159]. Additionally, it has also been demonstrated that overexpression of XIST accelerates cell migration and invasion in PDAC by directly targeting and suppressing tumour-suppressor miR-34a-5p, and that miR-34a-5p mimics inhibited this acceleration induced by XIST [160]. Zou and colleagues (2020) demonstrated that XIST promotes *TGF-β1*-induced EMT by regulating the miR-34a/*YAP*/*EGFR* axis in PDAC [161]. Moreover, XIST also directly interacts with miR-141–3p, which negatively regulates *TGF-β2* expression [160]. LincRNA 152 (LINC00152) has recently been identified to be upregulated in PDAC [162] not only as a potential biomarker but also a novel therapeutic target [163]. Specifically, Yuan and colleagues (2020), showed that LINC00152 promotes PDAC cell proliferation, migration and invasion via targeting miR-150 which in turn directly targets *ZEB1* [164]. *ZEB1* is a transcriptional repressor that has been identified as an inducer of EMT and has been shown to be associated with drug resistance of pancreatic cancer cells [165]. Further examples of oncogenic lncRNAs in PDAC are described in Table 4 and Fig. 3.

alt-text: Table 4

Table 4

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Oncogenic LncRNAs in PDAC listed with their functions and miR interactions.

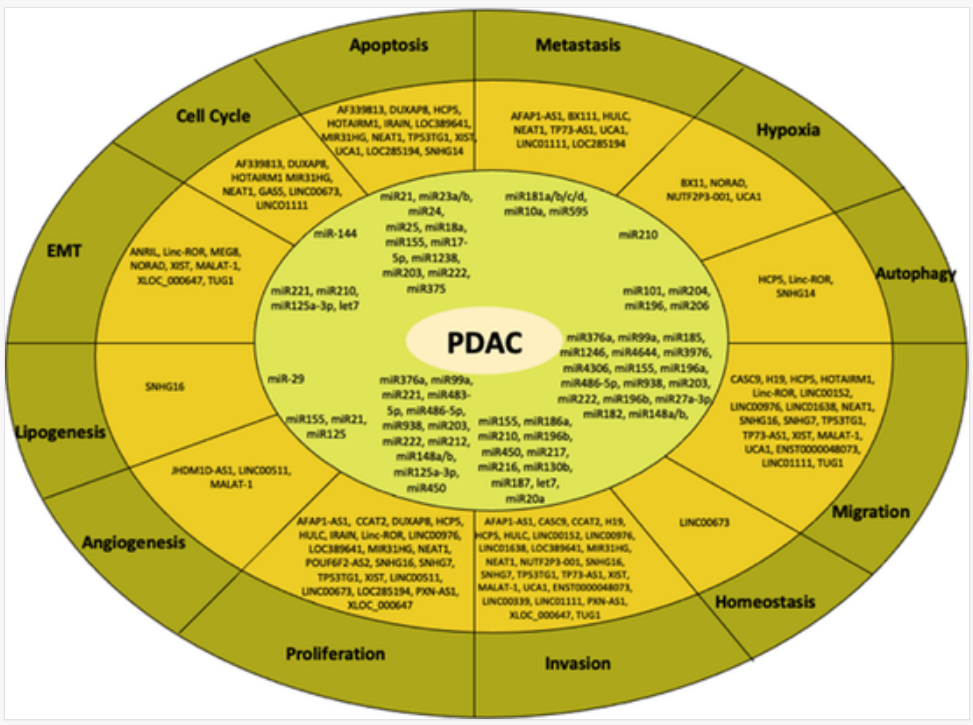
lncRNA	Expression in PDAC	miR Interactions in PDAC	Clinical Values	Functional Involvement	References
AF339813	up	-	D, T	cell cycle regulation and apoptotic escape	[166]
AFAP1-AS1	up	miR-133a	P	cell proliferation, lymph node metastasis and perineural invasion	[154,155,162,167]
ANRIL	up	-	P	EMT	[168]
BX111 (□lncRNA-BX111887)	up	-	T	hypoxia and cancer metastasis	[169]
CASC9	up	-	P	cell migration and invasion	[170]
CCAT1	up	-	P, T	cell proliferation, cell cycle □at G0/G1 stage, migration and EMT	[171]
CCAT2	up	-	D, T	cell proliferation, tumourigenesis and invasion	[172]
DUXAP8	up	-	P, T	epigenetic regulation of cell proliferation, cell cycle and apoptosis	[173]
H19	up	miR-675, miR-194, let 7	P, T	cell invasion and migration	[114,121,122,123,124]
HCP5	up	miR-214–3p, miR-29b-3p, miR-29c-3p, miR-140–5p	P, T	cell proliferation, invasion, migration, apoptosis and autophagy	[174–176]
HOTAIRM1	up	-	T	cell cycle regulation at G0/G1 phase, apoptosis and migration	[177]
HULC	up	miR-372, miR-15a, miR-133b, miR-622	D, P	cell proliferation, metastasis and invasion	[126–128]
IRAIN	up	-	T	cell proliferation and apoptotic escape	[178]
Linc-ROR	up	miR-145, miR-124, Let 7 family	D, P, T	cell proliferation, migration, invasion, EMT and autophagy	[179,180,181]
LINC00152	up	miR-150	D, P, T	cell migration and invasion	[162,163,164,167]
LINC00976	up	miR-137	P	cell proliferation, migration and invasion	[182]
LINC01638	up	-	D, T	migration and invasion	[183]

LOC389641	up	-	D, P	cell proliferation, invasion and apoptotic escape	[184]
MEG8	up	miR-34a, miR-203	P, T	EMT	[185]
MIR31HG	up	miR-193b	P, T	cell proliferation, cell cycle progression, invasion and apoptotic escape	[186]
NEAT1	up	□miR-506–3p, miR-335–5p	D, P, T	cell proliferation, cell cycle progression, migration, invasion, metastasis and apoptotic escape	[187–189]
NORAD	up	miR-125a-3p	D, P, T	hypoxia induced EMT	[190]
NUTF2P3–001	up	miR-3923	P, T	hypoxia, cell □proliferation and invasion	[191]
POU6F2-AS2	up	-	D	unknown; implicated in other cancers	□~~[192–193]~~ [192][193]
SNHG16	up	miR-218–5p, □miR-195, miR-200a-3p, miR-302b-3p	D, P, T	cell □proliferation, migration, invasion and lipogenesis	[194–197]
SNHG7	up	miR-342–3p	T	cell □proliferation, migration and invasion	[198]
TP53TG1	up	miR-96	T	cell □proliferation, migration and invasion and apoptotic escape	[199]
TP73-AS1	up	miR-141–3p	P, T	cell □migration, invasion and metastasis	[200]
XIST	up	miR-133a, miR-429, miR-34a-5p, miR-141–3p, miR-137	P, T	cell proliferation, migration, invasion, EMT and apoptotic escape	[157–160,201]
XLOC_006390	up	-	P, T	□glutamate metabolism and tumour progression	[202]
□JHDM1D-AS1	up	-	T	angiogenesis in response to nutrient starvation	[203]
LINC00511	up	miR-29b-3p, miR-29c-3p	P, T	cell proliferation, invasion and tumour angiogenesis	[204–205]
MALAT-1	up	miR-216a, miR-217	D, P, T	cell proliferation, angiogenesis, migration, invasion and EMT	[141–145]
UCA1	up	miR-509–3p, □miR-135a, □miR-96–5p, □miR-107,	P, T	cell proliferation, invasion, migration, metastasis, hypoxia, apoptotic escape, stemness and angiogenesis	[167,206]

D: diagnostic biomarker, P: prognostic biomarker, T: therapeutic target.

alt-text: Fig 3

Fig. 3



Biological processes and their related ncRNAs involved in PDAC progression. Both lncRNAs and miRs are aberrantly expressed in several biological processes during PDAC development including metastasis, cell proliferation, invasion, homoeostasis, migration, autophagy, hypoxia, apoptosis, cell cycle arrest, EMT, lipogenesis and angiogenesis. miR-21 is the most known oncogenic miR and is involved in both cell proliferation and apoptosis, while a well-described lncRNA known as HOTAIRM1 contributes to migration, apoptosis and cell cycle arrest.

Tumour suppressive lncRNAs in PDAC

Downregulation of growth arrest-specific 5 (GAS5) in PDAC has been shown to affect cell proliferation by negatively regulating cyclin dependant kinase 6 (*CDK6)* expression *in vitro* and *in vivo* [207]. GAS5 has also been shown to antagonise the chemoresistance of pancreatic cancer cells through down-regulation of miR-181c-5p, consequently regulating the Hippo signalling pathway [208]. Another study demonstrated that GAS5 reverses EMT and tumour stem cell-mediated gemcitabine resistance and metastasis in PDAC by functioning as a ceRNA for miR-221 in the miR-221/SOCS3 pathway [209]. In addition, GAS5 acts as a molecular switch for regulating quiescence and growth arrest in CD133+ population, a typical representation of the tumour initiating cells that is responsible for tumour recurrence suggesting that GAS5 is a key tumour suppressive lncRNA in PDAC that has clinical value [210]. Moreover, downregulation of long intergenic non-protein coding RNA, p53 induced transcript, which is known as Linc-pint is involved in tumour cell viability and proliferation. Specifically, Linc-pint expression levels in plasma could be used for monitoring and predicting tumour recurrence, whereas tissue Linc-pint levels could be used for predicting patient prognosis [211]. LINC01111 has negatively correlated with the TNM stage but positively correlated with the survival of PDAC patients [212]. It has been reported that overexpression of LINC01111 upregulated dual specificity phosphatase 1 (*DUSP1*) levels by sequestering miR-3924, resulting in the blockage of *SAPK* phosphorylation and the inactivation of the SAPK/JNK signalling pathway in PDAC cells and inhibiting aggressiveness [212]. ENST00000480739 expression level was remarkably decreased in PDAC in response to hypoxia and is negatively associated with lymph node metastasis and may serve as an independent prognostic factor of PDAC patient survival following surgery [206,213] (Table 5, Fig. 3).

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Table 5

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Tumour suppressive LncRNAs in PDAC.

lncRNA	Expression in PDAC	miR Interactions in PDAC	Clinical Values	Functional Involvement	References
BC008363	down	-	P, T	tumour growth and drug resistance	[214]
ENST00000480739	down	-	P, T	cell proliferation, migration and invasion	[213]
GAS5	down	miR-181c-5p, miR-221, miR-32–5p	D, P, T	cell cycle progression and cell proliferation	[207–210,215]
HNF1A-AS1	down	-	D, P, T	unknown; implicated in other cancers and shown to be detectable in exosomes	[162,~~216–223~~][216][217][218][219][220][221][222][223]
Linc-pint	down	-	D, P	tumour cell viability and proliferation	[211]
LINC00339	down	miR-497–5p	-	cell proliferation and invasion	[224]
LINC00673	down	miR-504, miR-23	D	cell homoeostasis, proliferation and cell cycle progression	[162,206,225]
LINC01111	down	miR-3924	D, P, T	cell proliferation, cell cycle, invasion, migration, tumourigenesis and metastasis	[212]
LOC285194	down	miR-34a	P, T	cell proliferation, lymph node metastasis, liver metastasis and apoptotic regulation in vascular smooth muscle cells	[226–228]
PXN-AS1	down	miR-3064	D, T	cell proliferation, invasion and sphere formation	[229]
XLOC_000647	down	-	P, T	cell proliferation, invasion, and EMT	[230]

D: diagnostic biomarker, P: prognostic biomarker, T: therapeutic target.

Role of lncRNAs in metastasis, proliferation, angiogenesis and apoptosis

Small Nucleolar RNA Host Gene (SNHG16) is another lncRNA that is upregulated in PDAC and was linked to the TNM stage, distant metastasis, tumour differentiation, and poor overall survival [194]. High levels of oncogenic LncRNA TP73 antisense RNA 1T (TP73-AS1) correlated with poor clinicopathological characteristics and shorter overall survival [200]. Targeting the miR-141/BDH2 axis, TP73-AS1 knockdown significantly inhibited the migration and invasion of PDAC cells, while the miR-141 inhibitor significantly restored the migration and invasion making this a potential biomarker and therapeutic target for PDAC [200]. Markedly up regulated in PDAC, the MIR31 host gene (MIR31HG) functions as an oncogenic lncRNA that promotes tumour progression with strong involvement and inverse correlation with miR-193b [186]. LINC00339 has been shown to be markedly overexpressed in PDAC tissues and cells and promoted cell proliferation, invasion, and migration via sponging miR-497–5p, thereby increasing the expression of its target gene *IGF1R* [224]. Lei *et al.* (2019) demonstrated that LINC00976 enhances the proliferation and invasion ability of PDAC cells by interacting with miR-137 and consequently upregulating its target *OTUD7B,* a mediator of the *EGFR* and mitogen-activated protein kinase (MAPK) signalling pathways [182]. The small nucleolar RNA host gene 14 (SNHG14) was significantly overexpressed in PDAC tissues compared to normal tissues and these levels negatively correlated with miR-101 [231]. Moreover, SNHG14 knockdown and miR-101 mimics both led to attenuation of gemcitabine resistance-PDAC cell viability and promoted cell apoptosis rate, as well as the reduction of autophagy-related proteins RAB5A and ATG4D [231]. SNHG14 has been demonstrated to modulate annexin A2 (*ANXA2)* expression by acting as a ceRNA for miR-613 [232] and to affect E-cadherin expression via an interaction with *EZH2* [232]. High expression of SNHG14 has been associated with poor tumour differentiation, advanced TNM stage and nodal metastasis in pancreatic cancer patients and can be utilised as a prognostic tool [232,233]. High lncRNA taurine up-regulated gene 1 (TUG1) expression was associated with high TNM staging, lymphatic invasion, unfavourable prognosis, and distal metastasis of PDAC and can promote the migration, invasion, EMT and apoptotic escape in PDAC cells and xenograft models [234]. Mechanistically, TUG1 has been shown to function as an oncogenic lncRNA promoting tumour progression through its function as an endogenous sponge competing for miR-382, miR-299–3p and miR-29c, consequently regulating their targets: Notch1 pathway [234]; *EZH2* [235]; and *ITGB1, MMP2* and *MMP9* [236] respectively. Microvascular invasion in hepatocellular carcinoma (MVIH) lncRNA also serves as a potential therapeutic target, which regulates multiple oncogenic pathways in PDAC including Hippo signalling pathway, FoxO signalling pathway and AGE-RAGE signalling pathway by activating *MMP2* and *MMP9*, downregulating miR-199a, or binding to AT-rich interaction domain 1A (*ARID1A).* Consequently, MVIH can accelerate tumour growth and metastasis [237]. Specifically, MVIH decreased the secretion of phosphoglycerate kinase 1 (*PGK1)* to enhance microvessel density and accelerated angiogenesis in PDAC cells [237] (Fig. 3).

CircRNAs as diagnostic and prognostic biomarkers for PDAC

circRNAs are a new, novel type of endogenous ncRNAs, which act as miR sponges that suppress the ability of miRs to bind to their target mRNAs [238–240]. circRNAs are a class of stable, diverse and conserved RNA molecules [241–242], that have been considered to be involved in the development of several malignancies such as bladder cancer [243], oesophageal squamous cell carcinoma [244], basal cell carcinoma [245], colorectal cancer [246] and PDAC [247]. Moreover, numerous circRNAs have presented tissue/developmental stage-specific expression [241,242,248,249], whereas previous studies have shown that circRNAs are linked to neuronal differentiation, synaptogenesis, neurological disorders, angiogenesis, prion disease and cancer [250–255]. circRNAs are aberrantly expressed in PDAC. Specifically, circ-LDLRAD3 was not only significantly upregulated in PDAC tissues, plasma, and PDAC cell lines but also related to venous and lymphatic invasion [256]. circ-LDLRAD3 directly targets miR-137–3p, which further controls proliferation, migration and invasion of PDAC cells through the miR-137–3p/pleiotrophin (PTN) axis [257]. circ_0030235 is linked to advanced tumour stage and positive lymph node metastasis in PDAC [247,258], while it also acts as a miR-sponge of miR-1253 and miR-1294 [258]. circ_0007534 is overexpressed in PDAC tissues and is associated with aggressiveness of PDAC [259], while their miRs-targets, miR-625 and miR-892b, promote cell proliferation, migration, and invasion in PDAC cell lines [259]. circ-PDE8A, is correlated with poor prognosis and acts as a sponge of miR-338 [260]. circ-IARS is also highly expressed in PDAC patients and is related with vessel invasion, liver and tumour-node metastasis [261] through the absorption of miR-122 [261]. ciRS-7 is another oncogenic circRNA in PDAC, which acts as miR-7 sponge, while ciRS-7 knockdown resulted to the reduction in both *EGFR* and *STAT3* expression, which led to the suppression of proliferation and decrease invasion of PDAC cells [262]. It has also been reported that circRHOT1 regulates proliferation, invasion and metastasis through the binding to miR-26b, miR-125a, miR-330, and miR-382 in PDAC [263]; circZMYM2 promote PDAC progression through the inhibition of *JMJD2C* expression levels via acting as miR-355–5p sponges [264]. Furthermore, has_circ_0001649 is not only associated with tumour stage and differentiation grade, but also with prognosis of PDAC patients who had undergone surgery [265]. Conclusively, Qu *et al.* (2015) demonstrated that the tumour suppressors circRNAs including hsa_circ_0006913, hsa_circ_0000257, hsa_circ_0005785, hsa_circ_0041150 and hsa_circ_0008719 are contributed to PDAC initiation and progression [266]. Therefore, it can be noted that numerous studies have shown the role of circRNAs in PDAC progression and hence these molecules could be used as potential novel diagnostic biomarkers in PDAC. However, the biological functions of circRNAs in PDAC, remain to be clarified (Fig. 4).

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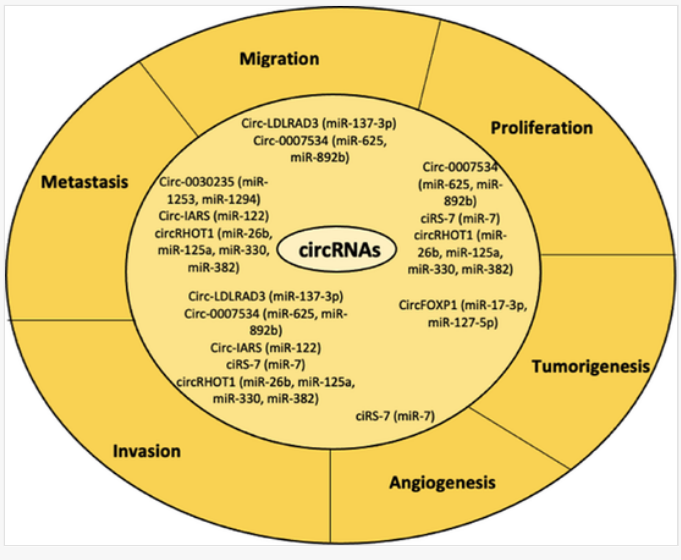
Fig. 4



Biological processes and their related circRNAs involved in PDAC development. circRNAs are also linked to several biological processes, which are related to PDAC progression. Especially, aberrant expression of these ncRNAs subtype is associated with invasion, metastasis, angiogenesis, tumorigenesis, migration, proliferation. ciRS-7 is a well-known circRNA, which is highly correlated to angiogenesis, invasion and proliferation, while circRHOT1 with invasion, metastasis and proliferation.

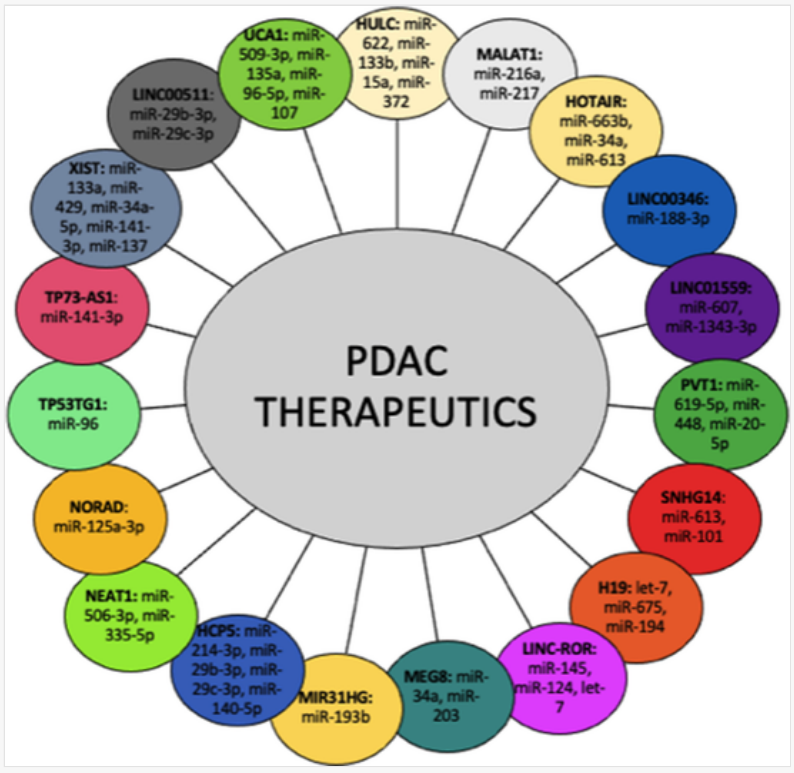
Current & potential therapy approaches by using non-coding RNAs in PDAC

miRNA therapeutic targets

Several researchers have examined the regulation of miR activity for the development of beneficial therapeutics strategies for PDAC [100]; current therapies have limited impact on median overall survival of PDAC patients [267]. miRs can promote the generation of tailored treatment strategies for individual PDAC cases [268]. Consequently, miR-targeting approaches can induce alterations in both chemosensitivity and radiosensitivity of PDAC cells [100]. A handful of studies have indicated that antisense targeting of both miR-21 and miR-221 can promote an improvement in the chemosensitivity of gemcitabine and inhibition of cell proliferation [55]. Moreover, transfection of miR-21 could elevate the activity of phosphatase and tensin homologue (*PTEN)* [269], which further results in the enhancement of gemcitabine-induced cell apoptosis. Another study suggested that the inhibition of miR-21 using a lentivirus vector can inhibit cell proliferation [270]. Additionally, the inhibition of miR-21 led to apoptosis and reduced PDAC cell proliferation [271], while low miR-21 expression levels correlated with higher chemosensitivity to 5-fluorouracil (5-FU) [272]. It has also been suggested that miR-181b inhibition resulted in a high sensitivity to gemcitabine and higher levels of apoptosis [62]. miR-17−5p inhibition in PDAC cells causes reduced cell growth, elevated caspase-3 activation and a higher chemosensitivity to gemcitabine via the overexpression of *Bim* [65]. miR-205 mimics could promote the restoration of chemosensitivity to gemcitabine and a minimized expression of stem cell markers *OCT3/4* and *CD44* [81]. Furthermore, expression of tumour suppressor miR-205 decreased PDAC cell invasion and the restoration of gemcitabine chemosensitivity [82]. An elevated expression level of miR-23b leads to the inhibition of radiation-induced autophagy and sensitization of PDAC cells to radiation [57]. The restoration of let-7 in PDAC cells showed an inhibition of cell proliferation, *KRAS* expression and *MAPK* activation [273], while Zhao *et al.* (2010) denoted that the transfection of PDAC cells with miR-217 resulted in a significant suppression of cell growth through the reduction in K-RAS protein levels and decreased downstream activation of the AKT pathway [80]. Moreover, upregulated miR-148b resulted in the suppression of PDAC cell growth, which further led to the induction of apoptosis and cell-cycle arrest at S phase, inhibition of invasion and enhancement of chemosensitivity of PDAC cells [77]. In addition, miR-137 mimic resulted in reduced cell invasion, tumour growth *in vivo* and an elevated sensitivity to fluorouracil in PDAC cells [274]. Similarly, miR-216a upregulation can have as an outcome the targeting of the JAK2/STAT3 signalling pathway and xenograft tumour growth *in vivo* in PDAC cells [275]. Another study showed that when miR-218 expression is restored, cell migration and invasion reduced in PDAC [276]. miR-34a and miR-143/145 expressions showed a therapeutic efficacy, inhibition of tumour growth and induction of apoptosis in PDAC subcutaneous and orthotopic xenograft models, through the downregulation of sirtuin 1 (*SIRT1), CD44*, aldehyde dehydrogenase (ALDH), *KRAS*, and Ras responsive element binding protein 1 (*RREB1)* [277]. Particularly, miR-34a nanocomplexes can considerably result in the suppression of PDAC cell growth and in the elevation of apoptosis through the downregulation of *E2F3, Bcl-2, c-myc* and *cyclin D1* [278]. Therefore, miR-34a nanocomplexes could be nominated as novel therapeutic strategies for PDAC [278]. Further studies revealed that inhibition of miR-155 expression led re-expression of TP53INP1 and enhanced apoptosis [61]. Moreover, when miR-27a was targeted, reduced cell growth, colony formation and migration was seen in PDAC [279]. Anti-miR-371−5p treatment can result in the inhibition of cell proliferation [280], whereas combined inhibition of miR-21, miR-23a and miR-27a can have as a synergistic result in decreased cell proliferation, which could be utilized for the development of effective PDAC therapies [56]. Additionally, ectopic expression of miR-96 could inhibit *KRAS*, which promotes apoptosis, reduces tumour growth *in vivo*, invasion and migration *in vitro* [96]. It has been also suggested that miR-506 can result in the enhancement of chemosensitivity in PDAC through the targeting of cell proliferation and the induction of cell cycle arrest at the G_1/S transition [281]. The knockdown of miR-1246 caused a gemcitabine sensitivity in gemcitabine-resistant PDAC cell lines [56]; upregulation of transcription factor–activating protein 2γ, which is negatively controlled by miR-10a-5p, can lead to the re-sensitization of PDAC cells to gemcitabine [64]. miR-34b could be used as an effective therapeutic agent, due to the fact that it negatively regulates oncogenic *SMAD3* [282]. miR-101 expression can promote E-cadherin and thus decrease PDAC tumour growth [283]. miR-204 expression leads to downregulation of myeloid cell leukaemia-1 (*Mcl-1*) as well as apoptosis [284]. Furthermore, targeting miR-31 *in vitro* reduces cell proliferation, migration and invasion [285]. Besides, targeting both miR-132 and miR-212 by antisense miRNA oligonucleotides led to the inhibition of PDAC tumour growth through the action on the retinoblastoma tumour suppressor (*Rb1*) [95]. The restoration of miR-150 could inhibit cell growth in PDAC cells [286]. Conclusively, it can be suggested that miR-based therapeutics could be a pioneer and effective therapeutic approach for PDAC [287]. However, specific issues, including the specificity in the delivery to certain cells of interest and safety, should be also addressed [288] (Fig. 5).

alt-text: Fig 5

Fig. 5



Role of lncRNAs with their target miRs in PDAC therapy. Interactions between miRs and lncRNAs have prompted novel therapeutic strategies for PDAC. Specifically, MALAT1, PVT1 and HOTAIR together with their target miRs could be used for the prediction of gemcitabine-based chemotherapy efficacy as first-line treatment of PDAC patients.

LncRNA therapeutic strategies

In a similar approach to the therapies based on miRNA modulation, lncRNAs could also potentially be custom applied specifically to regulate gene expression based on the genomic profile of the patient [289]. Due to their restricted spatio-temporal expression and capability of modulating the function and/or expression of key genes or their interacting partners, lncRNAs represent an ideal therapeutic target for PDAC [119]. There are a few therapeutic approaches for regulating lncRNAs either by transcript targeting or functional inhibition including (1) small interfering RNA/short hairpin RNA, (2) CRISPR-Cas9, (3) antisense oligonucleotides, (4) morpholino oligonucleotides, (5) Locked Nucleic Acid Gapmers, (6) small molecule inhibitors, (7) exploiting lncRNA promoters [119]. In a recent study, Takahashi and associates (2020) showed that overexpression of miR-622 via miR mimics, as a miR downregulated by *TGF-β*, could downregulate HULC and suppress invasion and migration by inhibiting EMT signalling via extracellular vesicle transfer [127]. In contrast, inhibition of miR-622 increased HULC expression and promoted epithelial-mesenchymal transition signalling, invasion, and migration of PDAC cells [127]. The potential of using the aforementioned strategies that would induce gain/loss-of-function to target lncRNAs is promising and enormous although modifying the expression levels of functional lncRNAs *in vivo* may present another level of difficulty due to their secondary structures [127]. Nevertheless, the most appealing therapeutic strategy when it comes to immediate clinical translatability is chemogene therapy [290].

There are several lncRNAs demonstrated to be involved in chemoresistance, and especially gemcitabine resistance, including those detailed in Table 6. LncRNA SLC7A11-AS1 promotes chemoresistance through reducing intracellular reactive oxygen species (ROS) by stabilizing nuclear factor erythroid-2-related factor 2 (*NRF2*), the key regulator in antioxidant defence [291]. SLC7A11-AS1 knockdown has been shown to weaken PDAC stemness and sensitises resistant PDAC cells toward gemcitabine *in vitro* and *in vivo* [291]. Similarly, downregulating the levels of oncogenic lncRNAs including HOTAIR [292], PVT1 [153,292], Linc-ROR [293], MALAT-1 [144], TUG1 ~~[264]~~[294] may revert the gemcitabine resistance in PDAC. It has been demonstrated that levels of MALAT1, HOTTIP and PVT1 in PDAC patient serum can be utilised to predict the efficacy of gemcitabine-based chemotherapy as first-line treatment of pancreatic cancer patients [133]. In addition, it has been shown that miR-216a can silence MALAT1 expression consequently inducing apoptosis both in the presence and absence of gemcitabine in PDAC cells [144]. Interestingly, curcumin has been shown to sensitise pancreatic cancer cells to gemcitabine by attenuating *PRC2* subunit *EZH2*, and the lncRNA PVT1 expression [295]. On the other hand, upregulating the expression of tumour suppressive lncRNAs such as GAS5 [209] and MEG3 [296] may also have the same effect. Ma and associates (2018) demonstrated that forced expression of MEG3 in PDAC cells attenuated cell proliferation, cell migration and invasion, EMT, decreased the sphere-forming ability and cancer stem cell properties, and increased the chemosensitivity to gemcitabine *in vitro* [296]. Moreover, in experiments conducted in PDAC animal models, the sequential administration of the H19-promoter-targeted vector BC-819 (also known as DTA-H19) and gemcitabine has been shown to have better antitumour activity as compared to the effect of each of them alone [297]. These suggest that the lncRNAs involved in conferring chemoresistance to PDAC and their functional involvements warrant further investigation to be able to be utilised as therapeutic targets in PDAC (Fig. 5).

alt-text: Table 6:

Table 6

The table layout displayed in this section is not how it will appear in the final version. The representation below is solely purposed for providing corrections to the table. To preview the actual presentation of the table, please view the Proof.

LncRNAs implicated in chemoresistance in PDAC.

lncRNA	Expressionin PDAC	Detected	miR Interactions in PDAC	Clinical Value(s)	Functional Involvement	References
HOTAIR	up	Plasma, Tissue, Saliva	miR-34a, miR-663b, miR-613	D, P, T	cell proliferation, cell cycle progression, apoptotic escape and gemcitabine resistance	[129–131,133–135, 137]
HOTTIP	up	Tissue, Serum	miR-137	P, T	cell proliferation, migration, apoptotic escape, cisplatin resistance and PCSC stemness	[120,136,138–140, 167]
LINC00346	up	Tissue	miR-188–3p	P, T	gemcitabine resistance, cell proliferation and cell cycle regulation at the G2/M-phase	[298–300]
LINC01559	up	Tissue	miR-607, □miR-1343–3p	D, T	cell proliferation, migration, invasion, metastasis, autophagy and gemcitabine resistance	[301–303]
MEG3	down	Tissue	-	P, T	cell proliferation, cell migration and invasion, EMT, cancer stem cell properties and chemosensitivity	[296]
PVT1	up	Saliva	miR-619–5p, miR-448,	D, P, T	EMT, cell proliferation, migration and gemcitabine resistance	[137,151,153,162,

			miR-20–5p			167,295]
SLC7A11-AS1	up	Tissue	-	P, T	PDAC stemness and gemcitabine resistance	[291]
SNHG14	up	Tissue	miR-613, □miR-101	T	cell proliferation, invasion, apoptosis escape, gemcitabine resistance and autophagy	[231–233]

D: diagnostic biomarker, P: prognostic biomarker, T: therapeutic target.

CircRNAs as therapeutic biomarkers for PDAC

Recent studies have suggested the role of specific circRNAs in chemotherapy-resistant PDAC including ciRS-7 and circHIPK3 [262,304]. Specifically, ciRS-7 increased gemcitabine resistance as an outcome of impaired moderation of *EGFR/STAT3* signalling pathway [262]. Furthermore, the upregulation of circHIPK3 has been linked to gemcitabine resistance in PDAC cell lines through the negative regulation of RASSF1 through sponging miR-330–5p [304].

Conclusion

Despite the latest efforts and breakthroughs to develop better, more effective therapeutic strategies for PDAC, it still remains one of the most fatal cancers with high mortality rates. ncRNAs expressions found to be significant and specific to cancer in general and miRs, lncRNAs and circRNAs found to be differentially expressed in PDAC. ncRNAs involve crucial regulation on cell proliferation, invasion and apoptosis and hence the strategy of altering their expression and activity in order to prevent cancer development and progression is promising. Several approaches to date have been used to mimic or inhibit ncRNAs expressions *in vitro* and *in vivo*. However, further studies are needed to understand their precise role in PDAC with regards to diagnosis, prognosis and therapeutics.

KRAS mutations and the overexpression of *HER-2/neu* [305] are common mutations in PDAC, while in more advanced stages, *CDKN2A, TP53* and *SMAD4* [305,306] are key regulators of PDAC pathogenesis [307]. Specifically, *KRAS* mutations have been detected in more than 90% [308,309], whereas *HER2* upregulation in 4–50% of PDAC cases [310]. *SMAD4* mutations are found in 60% of PDAC cases [311] and loss of *TP53* in more than 70% of PDAC patients [312]. *CDKN2A* tumour suppressor gene alterations have been found in 95% of PDAC cases [313]. Furthermore, previous studies have indicated that 12 main signalling pathways including *KRAS* signalling, Hedgehog signalling, apoptosis, control of G1/S phase transition and TGF-β signalling are altered in more than 80% of PDAC patients [312,314,315]. The recent discovery of ncRNAs has procured further insights regarding not only pathophysiology but also a better diagnosis and intervention of PDAC [316]. More recent evidence has shown that the aberrant expressions of ncRNAs play a considerable role in numerous human tumours and especially in initiation, proliferation and chemoresistance of PDAC [26]. ncRNAs are aberrantly expressed in numerous malignancies, while they can act as oncogenes or tumour suppressors [28]. ncRNAs research has emerged a significant interest, which is developed in all the fields of biological science for the examination of ncRNAs for human applications. Particularly, new advances in precision medicine have transpired the ability of the differentiation of distinct ncRNAs expression profiles, which could further discriminate between subtypes of normal and malignant tissues [317]. Especially, progressions in technology such as the use of next generation sequencing (NGS) have procured advances in ncRNAs expression profiles for PDAC diagnosis [318]. This could minimize the number of PDAC-associated deaths through the development of an improved understanding of PDAC biology. Despite the narrow knowledge of these molecules, ncRNAs can be characterized as vital biomarkers not only for the early prognosis and diagnosis of PDAC but also for a better management of therapeutics specimens [32]. These new approaches have remarked both cell and tissue specific ncRNAs expression models and thus not only clinical but also translational research have suggested the use of ncRNAs as early diagnostic, prognostic and therapeutic tools. However, there is a long way to go before the establishment of ncRNAs in the early diagnosis and treatment of PDAC and subsequently further evaluation of all the ncRNAs targets, silencing mechanisms and networks is required [319]. In this review, we elucidated the roles of ncRNAs in PDAC prognosis and metastasis and evaluated the recent developments in ncRNAs-based therapies in PDAC, which have shown substantial promise in controlling tumour progression and metastasis. However, more advanced preclinical and clinical trials are needed to overcome certain challenges such as adverse effects of ncRNA-based therapies.

Author contributions

Conceptualization, MM, ZT, EDA, HK and PUO; writing—original draft preparation, MM, ZT, EDA, HK and PUO; writing—review and editing, MM, ZT, EDA, HK and PUO supervision, PUO. All authors have read and agreed to the published version of the manuscript.

Uncited references

Q2 [192,193,216–223,294].

Declaration of Competing Interest

Authors declare that there is no financial/personal interest or belief that could affect the results, discussions or conclusions, which are reported in this work.

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Graphical abstract

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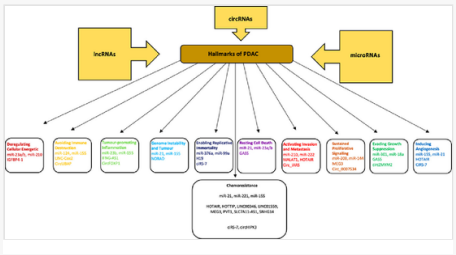

Highlights

- Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies, which is usually diagnosed at an advanced stage.
- Non-coding RNAs (ncRNAs) have been recognized to play a central role in PDAC pathogenesis and could be used as biomarkers for PDAC.
- microRNAs (miRs) can act either as oncogenes or tumour suppressors in PDAC.
- Long non-coding RNAs (lncRNAs) are around 25% of the total RNA distribution in the human cell and their deregulation is widely implicated in PDAC carcinogenesis.
- Circular RNAs (circRNAs) can be potential novel biomarkers and therapeutic targets for PDAC diagnosis and treatment via their function as miR molecular "sponges", RNA-binding protein (RBP) sponges, protein translators and gene transcription regulators.

Queries and Answers

Q1

Query: Please confirm that givennames and surnames have been identified correctly.

Answer: Yes

Q2

Query: This section comprises references that occur in the reference list but not in the body of the text. Please position each reference in the text or, alternatively, delete it.

Answer: We have positioned each reference in the text.