Review Article

Emerging potential value of long non-coding RNAs as biomarkers and therapeutic targets in pancreatic cancer

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Abstract: Pancreatic cancer (PC) is often asymptomatic in its early stages and is usually diagnosed late and in advanced stages, which can make treatment difficult and usually patients do not have a good prognosis, so early diagnosis of this disease is very important. Long non-coding RNAs (lncRNAs) have been shown to play an important role in the proliferation of cancer cells, metastasis and invasion. The lncRNAs are predicted to have a wide range of functions in cellular processes, and may be useful as biomarkers for early detection and therapeutic target in treatment of PC. The recent application of next-generation sequencing has nowadays provided a novel inside on gene profiling in multiple tumors and revealed the potential value of aberrant expression of lncRNAs with PC. In this study, 160 articles were reviewed, and lncRNAs associated with PC diagnosis, prognosis, and treatment were identified independently. Furthermore, the levels of expression of various lncRNAs in PC as well as the effective molecular pathways were described and discussed. This study hopes to help researchers identify lncRNAs that can be used as biomarkers for diagnostic and prognostic purposes, as well as discover the details of the cellular mechanisms underlying these lncRNAs in order to develop treatments that can be taken advantage of.

Keywords: Pancreatic cancer (PC); long non-coding RNAs (lncRNAs); biomarker; therapeutic; prognosis

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Introduction

Pancreatic cancer (PC) is often asymptomatic in its early phases and hence it is diagnosed in the advanced stages; it has a poor prognosis and has a high prevalence (1). PC was recently reported to be the 13th most common cancer globally, with 458,918 new cases per annum, and the 7th most common cause of cancer-related mortality, with 432,242 related deaths (2). According to the American Cancer Society report, approximately 60,430 new cases and 48,220 deaths from PC occurred in the United States in 2021, ranking third after lung and bronchus cancer and colorectal cancer (3). Early symptoms of PC are non-

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specific, including: epigastric bloating, abdominal bloating, general lethargy, diarrhea, vomiting, and constipation (4). However, as the tumor progresses, features include obstructive jaundice, weight loss, light stools, abdominal pain and fatigue develop (5). The highest mortality rate attributable to PC is observed in developed countries, and although the causes of PC are not well understood, factors such as smoking, family history, genetic problems, diabetes mellitus, alcohol, and inactivity can be considered as factors that cause (6). PC is age-dependent and its rate is slightly higher in men than in women (2). The causation of PC may involve non-protein-coding RNA (ncRNA). Non-coding RNAs are involved in the regulation of cancer cell proliferation, apoptosis, invasion and metastasis. They are abnormally expressed in human malignancies (7), and may potentially be used in the diagnosis, treatment and assessment of the prognosis of cancer, and may be used as cancer markers (8). Surgery, chemotherapy, endoscopic treatment and immunotherapy are used to treat PC; these treatments most often used in combination (9).

Only 2% of the human genome encodes proteins, with the remaining 98% of genes previously being considered non-functional "junk DNA" (10). However, the ENCODE project has revealed that part of the human genome, encodes ncRNAs that are not only relevant to fundamental biological processes such as growth and development but are also involved in a wide range of diseases, including cancer (11,12).

Non-coding RNAs can be classified into two groups based on their size. Short RNAs are less than 200 nucleotides in length, and may also be termed microRNAs (miRNAs); the other group are the long non-coding RNAs (lncRNAs) that are >200 nucleotides in length (13,14). Despite the extensive research on miRNAs and their role in gene regulation, the biological relevance of the vast majority of lncRNAs remains unclear. Their complexity relates to their ability to switch functions and be tissue/cell-specific (15,16). Many types of lncRNAs are categorized according to their genomic localization, mode of action, and function. LncRNAs can be transcribed from the introns of protein-coding genes (intronic lncRNAs), from intergenic regions between protein-coding genes (intergenic lncRNAs), or the antisense strand of a gene (natural antisense transcripts) depending on their genomic location (17-20). It is possible to categorize lncRNAs into four categories based on their function: signaling, decoying, guiding, and scaffolding properties (21). RNA polymerase II transcribes lncRNAs, which can be capped, spliced, and polyadenylated but lack an open reading frame (ORF) (22,23). There is a low degree of evolutionary constraint associated with most lncRNAs; therefore, they have differed significantly during evolution (24).

LncRNAs are aberrantly expressed in many different cancers, including PC (25). By comparing the expression of lncRNAs in tumor tissue and surrogate tissues between people with PC and healthy individuals, it is possible to develop a non-invasive method for early diagnosis and even stage prediction. Furthermore, since lncRNAs play a role in many processes involved in cancer development, including proliferation, apoptosis, metastasis, and angiogenesis, they are attractive therapeutic targets attracting researchers' attention (26). This article reviews the lncRNAs identified in recent years for their role in PC diagnosis, prognosis, and treatment.

Non-coding RNAs have been used for the prediction, diagnosis and assessing the prognosis of cancers (27). It has also been reported that lncRNAs are found in exosomes of tumors, which could provide a way to diagnose and treat PC (28). Non-coding RNAs may be involved in the development of PC by regulating gene expression at the chromatin, transcriptional, or post-transcriptional level (29). Among the therapeutic implications, it may be possible to suppress the expression of overexpressed lncRNAs. This may be through the use of RNAi methods, degradation of lncRNAs by RNase H, antisense oligonucleotides, or the use of the CRISPR/Cas9 genome editing method (30). Balancing the expression of different lncRNAs may be a viable method for treating PC. It has been shown that several lncRNAs including lncRNA-UFC1, RP11-263F15.1, ABHD11-AS1, LINC00675, HULC and C9orf139 can be used in the diagnosis of PC. Also, the expression of non-coding RNA can affect the expression of cancer. Things like RUNX1-IT1, ENSG00000254041.1, MALAT1, LOC285194 LncRNA-UFC1, RP11-263F15.1, BC008363, MEG3 and HULC are among the lncRNAs involved in this (26).

C9orf139 is another regulated lncRNA found in the tissues and sera of patients with PC and may have diagnostic value because the area under the curve (AUC) value of this lncRNA is estimated to be 0.923, and overexpression of this lncRNA is associated with a higher probability of cancer progressing to advanced stages and metastasis. It is related to lymph nodes and poor differentiation (31).

It is proposed that lncRNAs contribute to the pathobiology of PC through various mechanisms, including the modulation of cancer-related pathways such as JAK2/STAT3, EGFR/MAPK, ERK, NOTCH, and PTEN (26).

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The epithelial-mesenchymal transition (EMT) process is an important process in the progression of cancer metastasis, which has been found to affect several lncRNAs in PC (26). LINC00462, LINC00958, SNHG12, and OIP5-AS1 are among the lncRNAs that have been confirmed to play a role in EMT progression in PC (26). Many lncRNAs used as diagnostic markers also have the potential to be used for assessing prognosis. For example, in addition to being a diagnostic marker, UFC1 can also facilitate the prediction of PC. Therefore, UFC1 can be shown as an independent prognostic factor for PC (32) Attention to non-coding RNAs shows that MALAT-1, HOTAIR, HOXA13, H19, LINC01559, LINC00460, SNHG14, SNHG16, DLX6-AS1, MSC-AS1, ABHDDUXCRAP2, Regulating, DLRNAsl, are non-coding RNAs. Which have a positive effect on PC, while GAS5, HMlincRNA717, MIAT, LINC01111, lncRNA KCNK15-AS1 are down-regulated lncRNAs that inhibit pancreatic ductal adenocarcinoma (PDAC) invasion and progression (33).

LncRNAs are detected in most body fluids including blood, saliva, urine, and even pancreatic juice, and they can therefore serve as biomarkers for tumor diagnosis, targeted therapy, and improved patient prognosis (34).

Epigenetic and lncRNA

The main epigenetic mechanisms include the well-understood phenomenon of DNA methylation, histone modifications, and regulation by non-coding RNAs (35). LncRNA participates in the control of genomic transcription by interacting with epigenetic modifying complexes (36). Major epigenetic mechanisms include the well-understood phenomenon of DNA methylation, histone modifications, and regulation by non-coding RNAs. Complex 2 [polycomb repressive complex 2 (PRC2)] is one of the main histone modification complexes that is regulated by lncRNAs, and a large number of lncRNAs are associated with this complex (37). The first HOX-associated lncRNA, HOTAIR, was initially identified as a scaffold RNA associated with histone modification complexes, namely PRC2 and the LSD1/CoREST/REST complex (38). LncRNA HOXA distal transcript antisense RNA (HOTTIP) is a HOX-related lncRNA associated with chromatin remodeling complexes and promoting H3K27 trimethylation to repress the expression of multiple *HOXA* gene (25). *HOXA10* and *HOXA11* genes regulate the expression of matrix metalloproteinase 3 and 2 genes, which cause invasion of PC cells (39). HOTAIR plays a role in cell proliferation and metastasis and is associated with human EZH2, a component of the PRC2, and binds to the promoter region of miR-34 and causes trimethylation of histone 3 lysine 27 (H3K27), which ultimately leads to suppression of miR-34 transcription, increase in cell proliferation and decrease in apoptosis (25). Or, H19 promotes PC progression by downregulating target region let-7, which enhances HMGA-2-mediated EMT (33). MALAT-1 is a lncRNA overexpressed in several types of cancer. MALAT-1 engages the Hippo-YAP signaling pathway when highly expressed (40).

Diagnostic role of lncRNAs in PC

Detection and treatment of PC at an early stage can significantly reduce mortality. Recent technological advancement in high-throughput sequencing has made it possible for researchers to identify dysregulated expression of lncRNAs in various types of cancer (41). It is possible to use lncRNAs as sensitive biomarkers for diagnosing, predicting, and developing promising therapies for PC. It has been reported that some lncRNAs display tissue and cancer-specific expression patterns, making them potentially useful as biomarkers for diagnostic purposes (41). For example, prostate cancer antigen 3 (PCA3) is a prostate-specific gene highly expressed in prostate cancer (42). The detection of differential expression of lncRNAs in serum or plasma has become an important new diagnostic tool in noninvasive diagnostic procedures. One study used a colorimetric assay to detect lncRNA HOTTIP through RT-LAMP (reverse transcription loop-mediated isothermal amplification) to diagnose PC (43). Research on lncRNAs is expected to develop new diagnostic biomarkers for the early diagnosis of PC. For example, an increase in the C9orf139 level in tissue and serum of patients had clinical significance for PC diagnosis. There is a greater risk of progression to stage III+IV, lymph node metastasis, and poor differentiation in patients with high C9orf139 expression. Specifically, C9orf139 promotes PC cell growth by modulating the miR-663a/Sox12 axis (31) (*Table 1*).

A significant increase in CTBP1AS2 expression was observed in PC tissues and cell lines. Patients with high expression of CTBP1AS2 had advanced clinical stages and lymph node metastases. The lncRNA CTBP1AS2, therefore, may play an essential role in PC progression as well as a diagnostic biomarker by modulating miR1413p and USP22 expression (58).

MIR99AHG is another lncRNA that is distinctly

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Table 1 Overview of diagnostic significance of lncRNAs in pancreatic cancer

LncRNAs	Expression in PC	Relevant targets in PC	Reference
SNHG12	High	miR-320b	(44)
C9orf139 (LINC02908)	High	miR-663a/Sox12	(31)
GAS8-AS1	Down	miR-1179	(45)
H19	High	E2F1, let-7	(46)
LINC01197	Down	–	(47)
LINC00473 (C6orf176)	High	cAMP/β-catenin	(48)
AL109748.6	–	*HOXA13*, *RTN1* (hub genes)	(49)
AC125792.1	–	*HOXA13* (hub gene)	(49)
CTD-2292M14.1	–	*HOXA13* (hub gene)	(49)
AK027298	–	*HOXA13*, *RTN1* (hub genes)	(49)
AK094441	–	*HOXA13*, *RTN1* (hub genes)	(49)
BC084573	–	*RTN1* (hub gene)	(49)
RP11-288L9.1	–	*RTN1* (hub gene)	(49)
AC012005.5	–	*RTN1*, *CHRAC1* (hub genes)	(49)
NR_002827	–	*RTN1*, *CHRAC1* (hub genes)	(49)
NR_024058	–	*RTN1*, *CHRAC1* (hub genes)	(49)
NR_024427	–	*RTN1*, *CHRAC1* (hub genes)	(49)
AK056486	–	*RTN1*, *CHRAC1* (hub genes)	(49)
RP11-312H15.3	–	*CHRAC1* (hub gene)	(49)
AC006427.3	–	*CHRAC1* (hub gene)	(49)
BC035067	–	*CHRAC1* (hub gene)	(49)
CTD-2066L21.3	–	*CHRAC1* (hub gene)	(49)
CERS6-AS1	High	miR-217/YWHAG/RAF1 signaling	(50)
LINC00339	High	–	(51)
LINC-ROR	High	miR-124/PTBP1, ZEB1	(52)
MALAT1	High	IPO7/p53/miR-129-5p positive feedback loop	(53)
SBF2-AS1	High	miR-142-3p/TWF1, miR-122-5p/XIAP	(54)
UCA1	High	p27, miR-135a, miR-96, MOB1, Lats1, YAP	(55)
LINC01133	High	miR-216a-5p/TPT1	(56)
SNHG16	High	miR-302b-3p/SLC2A4	(57)
CTBP1-AS2	High	miR-141-3p/USP22	(58)
DGCR5	High	miR-3163/TOP2A/Wnt/β-catenin	(59)
LINC00152	High	miR-150	(60)
LINC00261	Down	miR-552-5p/FOXO3	(61)
LINC00514	High	miR-28-5p/Rap1b	(62)

Table 1 (*continued*)

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Table 1 (*continued*)

LncRNAs	Expression in PC	Relevant targets in PC	Reference
LINC00941	High	miR-335-5p	(63)
LINC01559	High	miR-1343-3p/RAF1	(64)
MIR99AHG	High	FOXA1/miR-3129-5p/ELAVL1/NOTCH2	(65)
NORAD	High	miR-202-5/ANP32E	(66)
SNHG15	High	EZH2/P15/KLF2	(67)
XIST	High	miR-137/Notch1	(68)
ZEB1-AS1	High	HIF-1a/ZEB1/HDAC1	(69)
ZFAS1	High	miR-497-5p/HMGA2	(70)
MCM3AP-AS1	High	miR-138-5p, FOXK1	(71)

LncRNA, long non-coding RNA; PC, pancreatic cancer.

overexpressed in PDAC cell lines. As a result of MIR99AHG deficiency, PC cells could not proliferate, migrate, and invade by activating the FOXA1/MIR99AHG/miR-3129-5p/ELAVL1/NOTCH2 axis. Through sequestering microRNA-3129-5p (miR-3129-5p) and recruiting ELAV-like RNA binding protein 1 (ELAVL1), MIR99AHG modulated notch receptor 2 (NOTCH2) expression and stimulated the Notch signaling pathway (65).

LINC00514 was reported to be upregulated in PC tissues, and its expression was significantly associated with clinical progression and prognosis. Rap1b was a downstream target of microRNA-28-5p, and LINC00514 acted as a sponge for miR-28-5p in PC (62).

It has been reported that LINC00941 and ROCK1 are highly expressed in PC. At the same time, miR-335-5p exhibits low expression, and high LINC00941 expression is strongly associated with larger tumors, lymph node metastasis, and poor prognosis in PC. Furthermore, LINC00941 was shown to function as a molecular sponge for miR-335-5p and a competitive endogenous RNA (ceRNA) for ROCK1, promoting ROCK1 upregulation and activation of the LIMK1/Cofilin-1 pathway. Therefore, LINC00941 may be helpful as a diagnostic and prognostic marker in patients with PC (63).

Prognostic value of lncRNAs in PC

Several recent studies have demonstrated that some lncRNAs are related to the clinicopathological characteristics and the prognosis of patients with PC. These lncRNAs were independent prognostic factors in patients with cancer and positively correlated with overall survival, suggesting that they could be helpful for the monitoring of high-risk populations, the prediction of prognosis, and the monitoring of recurrence of the disease (72) (*Table 2*).

Two lncRNAs TSPOAP1.AS1 and MIR600HG have been identified as cancer biomarkers predicting 3- and 5-year survival in patients with PC. There is potential for this two-lncRNA signature to serve as a new prognostic indicator for clinical outcomes (81).

The results of another study indicated that LINC00460 was upregulated in PC samples and was associated with a poorer survival rate among patients diagnosed with the disease. LINC00460 expression levels were significantly correlated with tumor size but not with age, sex, differentiation, lymph node metastasis, vascular invasion, or tumor stage. There is potential that LINC00460 targets the microRNA503/cyclin D1 axis and can be used as an independent prognostic biomarker for prostate cancer (82).

The expression of SNHG16 in PC tissues and cell lines was also significantly elevated and was associated with a poor prognosis for PC patients. In PC cells, SNHG16 acted as a sponge to regulate miR-302b-3p expression. Furthermore, miR-302b-3p directly targeted SLC2A4 (57).

A study also demonstrated that LINC00473 expressed highly in PC tissues and cells, and elevated LINC00473 levels were associated with larger tumor sizes, more advanced tumor, node, metastasis (TNM) stages, poorer tumor differentiation, and higher rates of perineural invasions and lymphatic invasions. The high level of LINC00473 suggests a worse prognosis for PC patients. There is a possibility that LINC00473 could promote the

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Table 2 Overview of prognosis significance of lncRNAs in pancreatic cancer

LncRNAs	Expression in PC	Relevant targets in PC	Reference
C9orf139 (LINC02908)	High	miR-663a/Sox12	(31)
GAS8-AS1	Down	miR-1179	(45)
H19	High	E2F1, let-7	(46)
LINC01197	Down	–	(47)
LINC00473 (C6orf176)	High	cAMP/β-catenin	(48)
CERS6-AS1	High	miR-217/YWHAG/RAF1 signaling	(50)
LINC-ROR	High	miR-124/PTBP1, ZEB1	(52)
SBF2-AS1	High	miR-142-3p/TWF1, miR-122-5p/XIAP	(54)
		miR-122-5p, XIAP	(73)
UCA1	High	p27, miR-135a, miR-96, MOB1, Lats1, YAP	(55)
LINC00152	High	miR-150	(60)
BC037916	High	JAK2/STAT3, TGF-β/smad2/3	(74)
HULC	High	–	(75)
GABPB1-AS1	High (cell lines)	mir-217	(76)
ST7-AS1	Down	mir-181a-5p	(76)
PSMG3-AS1	Down (cell lines)	mir-210-3p	(62)
RP11-48O20.4	High	–	(77)
AC009014.3	Down	–	(77)
LINC00476	Down	PTK2, FGF, MAPK and HIF-1 signaling pathway	(78)
C9orf163	Down	FNFSF	(78)
LINC00346	High	PLK1 and p53 signaling pathway	(78)
DSCR9	Down	Ras, p53, MAPK and PI3K/Akt signaling pathway	(78)
FLVCR1-DT	No changed	ULK3, CALCOCO2, MAPK8IP1, GABARAPL2	(79,80)
AC245041.2	High	LAMA3	(79,80)
AC006504.7	–	–	(81)
AC125494.2	Down	ULK1, MAP2K7, GABARAPL1, ATG4D, RPTOR, RAB24	(81,82)
AC012306.2	Down	WIPI2, TUSC1, STK11, RPTOR, RAB24, PEX14, MLST8, ARSA	(79,80)
ST20-AS1	–	–	(81)
AC036176.1	–	ATG16L1, Mir223	(81)
LINC01089	–	–	(81)
AC005696.1	–	–	(81)
LINC02257	High	RPTOR, miR-377-3p	(79,80)
TRPC7-AS1	–	–	(83)
AC092171.5	High	–	(80,84)

Table 2 (*continued*)

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Table 2 (*continued*)

LncRNAs	Expression in PC	Relevant targets in PC	Reference
DCST1-AS1	–	–	(83)
LINC02004	–	–	(83)
AC025165.1	–	–	(83)
CASC8	High	–	(83,85,86)
AC010615.2	–	–	(83)
AC090114.2	–	–	(83,86)
AGAP2-AS1	High	ANKRD1, ANGPTL4, EZH2	(87)
ATB	Down	–	(88,89)
DLX6-AS1	High	ZEB2, miR-181b	(90)
LINC00460	High	microRNA-503/cyclin D1	(82)
LINC01586	Down	SNAP25	(91)
LINP1	High (bad prognosis)	microRNA-491-3p	(85,92)
MIR600HG	Down	–	(81)
TSPOAP1-AS1	Down	–	(81)
NT5E	High	SYNCRIP	(93)
OIP5-AS1	High	miR-186-5p/NGFR	(94)
CYTOR	High	miR-205-5p/CDK6	(95)
DGCR5	Down	miR-27a-3p/BNIP3/p38 MAPK	(96)
RUNX1-IT1	High	*RUNX1* gene, C-FOS	(97)
AC006504.8	No changed	ATG10, BNIP1, BNIP3, GABARAP, GABARAPL2, MAP1LC3A, MAPK8IP1, PELP1, TSC1	(80)
AC005332.6	Down	GABARAPL2, GABARAPL1, TSC1, RPTOR, ETC.	(80)
AC002091.1	High	–	(84)
MEG9	High	–	(84)
ZNF236-DT	High (good prognosis)	–	(85)
PAN3-AS1	No changed	–	(85,86)
SH3PXD2A-AS1	High	–	(85,86)
AC015660.1	–	–	(86)
AC087501.4	–	–	(86)
LINC01133	High	–	(86)
AC009974.1	–	–	(86)
TRAF3IP2-AS1	No changed	–	(86)
AC083841.1	–	–	(86)
AC022098.1	–	–	(86)
AL161431.1	High	CDH1, CDH2, VIM	(98)

Table 2 (*continued*)

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Table 2 (*continued*)

LncRNAs	Expression in PC	Relevant targets in PC	Reference
DUXAP8	High	miR-448/WTAP/Fak Signaling	(99,100)
ELFN1-AS1	High	E-cadherin, N-cadherin, vimentin	(101)
HMGA2-AS1	High	HMGA2	(102)
LINC00261	Down	c-Myc	(103)
LINC01128	High	miR-561-5p/LDHA	(104)
NT5E	High	SYNCRIP	(93)
PART1	High	miR-122	(105)
SNHG15	High	microRNA-345-5p/RAB27B	(106)
XLOC_006390	High	c-Myc	(107)
LINC00671	Down	AKT/ERK signaling pathway	(108)
MCM3AP-AS1	High	miR-138-5p, FOXK1	(71)

LncRNA, long non-coding RNA; PC, pancreatic cancer.

proliferation and metastasis of PC cells by activating cAMP, which triggers the phosphorylation of β-catenin, possibly providing a new marker for the diagnosis and prognosis of PC patients (48).

Therapeutic role of lncRNAs in PC

LncRNAs are promising therapeutic targets for cancer therapy and offer many advantages as the novel, specific therapeutics. LncRNA is vital for the design of new drugs because of its role in apoptosis and proliferation of cancer. Selectively silencing oncogenic lncRNAs makes a new approach to cancer treatment possible. The manipulation of lncRNAs can be easily achieved through RNAi or LNA GapmeRs (43).

It is also important to note that ncRNAs play an essential role in drug resistance. As a consequence of their role in regulating the sensitivity of cancer cells to therapy, ncRNAs could influence the efficacy of cancer therapeutics, including chemotherapy, radiotherapy, immunotherapy, and other targeted therapies, which are used in the treatment of PC (41). A discussion of the lncRNAs which have promising therapeutic potential is provided in *Table 3*.

TTN-AS1 regulates SQLE expression by acting as a molecular sponge for miR-133b, and low levels of SQLE can promote PC progression by activating the ERK/NF-κB pathway. Another study demonstrated that TTN-AS1 and FOXP1 were upregulated in PC cell lines and tissues. TTN-AS1 acted as a molecular sponge for miR-5890-5p, and its mRNA expression level in PC tissues is inversely correlated with that of miR-589-5. Consequently, targeting the lncRNA-TTN-AS1/miR-133b/SQLE axis or the TTNAS1/miR5895p/FOXP1 feedback loop should provide new ideas for the treatment of patients with PC (159,160).

PVT1 is highly expressed in PC patients and plays a crucial role in disease progression by binding to the HIF-1a promoter and activating its transcription; it is also up-regulated in gemcitabine-resistant PC and promotes gemcitabine resistance of PC via miR-143/HIF-1α/VMP1 axis, or by activating Wnt/β-catenin and autophagy pathway through modulating the miR-619-5p/Pygo2 and miR-619-5p/ATG14 axes (154-156). Additionally, the lncRNA ANRIL is highly expressed in PC cells and increases chemotherapy resistance to gemcitabine through the miR-181a/HMGB1 pathway (124). Another study, which was particularly pronounced in gemcitabine-resistant PC tissues. There was a significant negative correlation between DBH-AS1 downregulation, PC tumor malignancy, and patient survival. Functional analysis revealed that DBH-AS1 suppressed PC cell growth through the METTL3-dependent m6A methylation of lncRNA. In addition, decreased DBH-AS1 expression in PC was linked to METTL3-dependent methylation of lncRNA. It appears that DBH-AS1 acts by sequestering miR-3163 and upregulating USP44 in PC cells, making them more sensitive to gemcitabine (129). As mentioned, lncRNAs can

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Table 3 LncRNAs with promising therapeutic potential for PC

LncRNAs	Expression in PC	Relevant targets in PC	Reference
SNHG12	High	miR-320b	(44)
LINC00473 (C6orf176)	High	cAMP/β-catenin	(48)
AL109748.6	–	*HOXA13*, *RTN1* (hub genes)	(49)
AC125792.1	–	*HOXA13* (hub gene)	(49)
CTD-2292M14.1	–	*HOXA13* (hub gene)	(49)
AK027298	–	*HOXA13*, *RTN1* (hub genes)	(49)
AK094441	–	*HOXA13*, *RTN1* (hub genes)	(49)
BC084573	–	*RTN1* (hub gene)	(49)
RP11-288L9.1	–	*RTN1* (hub gene)	(49)
AC012005.5	–	*RTN1*, *CHRAC1* (hub genes)	(49)
NR_002827	–	*RTN1*, *CHRAC1* (hub genes)	(49)
NR_024058	–	*RTN1*, *CHRAC1* (hub genes)	(49)
NR_024427	–	*RTN1*, *CHRAC1* (hub genes)	(49)
AK056486	–	*RTN1*, *CHRAC1* (hub genes)	(49)
RP11-312H15.3	–	*CHRAC1* (hub gene)	(49)
AC006427.3	–	*CHRAC1* (hub gene)	(49)
BC035067	–	*CHRAC1* (hub gene)	(49)
CTD-2066L21.3	–	*CHRAC1* (hub gene)	(49)
CERS6-AS1	High	miR-217/YWHAG/RAF1 signaling	(50)
LINC00339	High	–	(51)
LINC-ROR	High	miR-124/PTBP1, ZEB1	(52)
MALAT1	High	IPO7/p53/miR-129-5p positive feedback loop	(53)
RGMB-AS1	High	miR-574-3p/PIM3	(109)
SBF2-AS1	High	miR-142-3p/TWF1, miR-122-5p/XIAP	(54)
		miR-122-5p	(110)
UCA1	High	p27, miR-135a, miR-96, MOB1, Lats1, YAP	(55)
		miR-96-5p/AMOTL2	(111)
LINC01133	High	miR-216a-5p/TPT1	(56,86)
		miR-199b-5p/MYRF pathway	(112)
SNHG16	High	miR-302b-3p/SLC2A4	(57)
CRNDE	High	miR-451a/CDKN2D	(113)
CTBP1-AS2	High	miR-141-3p/USP22	(58)
DGCR5	High	miR-3163/TOP2A/Wnt/β-catenin	(59)
	Down	miR-27a-3p/BNIP3/p38 MAPK	(96)
LINC00152	High	miR-150	(60)

Table 3 (*continued*)

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Table 3 (*continued*)

LncRNAs	Expression in PC	Relevant targets in PC	Reference
LINC00261	Down	miR-552-5p/FOXO3	(61)
		c-Myc	(103)
		KLF13- mTOR-P70S6K1-S6 signaling pathway	(114)
		SCP2/FOXP3	(115)
LINC00514	High	miR-28-5p/Rap1b	(62)
LINC00941	High	miR-335-5p	(63)
LINC01094	High	miR-577/LIN28B/PI3K/AKT	(116)
LINC01559	High	miR-1343-3p/RAF1	(64)
		YAP	(117)
MIR99AHG	High	FOXA1/miR-3129-5p/ELAVL1/NOTCH2	(65)
NORAD	High	miR-202-5/ANP32E	(66)
SNHG15	High	EZH2/P15/KLF2	(67)
		microRNA-345-5p/RAB27B	(106)
XIST	High	miR-137/Notch1	(68)
ZEB1-AS1	High	HIF-1a/ZEB1/HDAC1	(69)
		miR-505-3p/TRIB2	(118)
ZFAS1	High	miR-497-5p/HMGA2	(70)
CYTOR	High	miR-205-5p/CDK6	(95)
RUNX1-IT1	High	*RUNX1* gene, C-FOS	(97)
AC245041.2	High	LAMA3	(79,80)
LINC02257	High	RPTOR, miR-377-3p	(79,80)
FLVCR1-DT	No changed	ULK3, CALCOCO2, MAPK8IP1, GABARAPL2	(79,80)
AC006504.8	No changed	ATG10, BNIP1, BNIP3, GABARAP, GABARAPL2, MAP1LC3A, MAPK8IP1, PELP1, TSC1	(80)
AC005332.6	Down	GABARAPL2, GABARAPL1, TSC1, RPTOR, ETC	(80)
AC012306.2	Down	WIPI2, TUSC1, STK11, RPTOR, RAB24, PEX14, MLST8, ARSA	(79,80)
AC125494.2	Down	ULK1, MAP2K7, GABARAPL1, ATG4D, RPTOR, RAB24	(81,82)
AC092171.5	High	–	(80,84)
AC002091.1	High	–	(84)
MEG9	High	–	(84)
AC015660.1	–	–	(86)
AC087501.4	–	–	(86)
AC009974.1	–	–	(86)
TRAF3IP2-AS1	No changed	–	(86)
AC083841.1	–	–	(86)

Table 3 (*continued*)

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Table 3 (*continued*)

LncRNAs	Expression in PC	Relevant targets in PC	Reference
AC022098.1	–	–	(86)
PAN3-AS1	No changed	–	(85,86)
SH3PXD2A-AS1	High	–	(85,86)
AC090114.2	–	–	(83,86)
CASC8	High	–	(86)
AL161431.1	High	CDH1, CDH2, VIM	(98)
ATB	Down	–	(89)
DUXAP8	High	miR-448/WTAP/Fak signaling	(99,100)
ELFN1-AS1	High	E-cadherin, N-cadherin, vimentin	(101)
HMGA2-AS1	High	HMGA2	(102)
LINC01128	High	miR-561-5p/LDHA	(104)
NT5E	High	SYNCRIP	(93)
XLOC_006390	High	c-Myc	(107)
CRNDE	High	miR-451a/CDKN2D	(113)
LINC01320	High	miR-324-3p	(119)
FGD5-AS1	High	miR-520a-3p/KIAA1522	(120)
PSMB8-AS1	High	miR-382-3p/STAT1/PD-L1	(121)
SNHG6	High	FUBP1/miR-26a-5p	(122)
ABHD11-AS1	High	miR-1231	(123)
ANRIL	High	miR-181a	(124)
CASC2	Down	miR-24/MUC6	(125)
CASC19	High	miR-148b/E2F7	(126)
CTD-3252C9.4	Down	IFI6	(127)
DANCR	High	miR-135a/NLRP37, miR-214-5p/E2F2, miR-33b/MMP-16	(128)
DBH-AS1	Down	miR-3163/USP44	(129)
DSCAM-AS1	High	miR-136-5p/PBX3	(130)
DLEU2	High	miR-455, SMAD2	(131)
FAM66C	–	miR-574-3p	(132)
FLVCR1-AS1	Down	KLF10	(133)
FTX	High	miR-513b-5p	(134)
GATA3-AS1	High	miR-30b-5p-Tex10	(135)
H19	High	miR-675-3p	(136)
HIF1A-AS1	High	HIF1α	(137)
HCP5	High	miR-140-5p/CDK8	(138)

Table 3 (*continued*)

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Table 3 (*continued*)

LncRNAs	Expression in PC	Relevant targets in PC	Reference
HOST2	High	–	(139)
HOTAIR	High (PC cells in mice)	Wnt/β-catenin signaling pathway	(140)
HOTTIP	High	miR-137	(141)
HOXA10-AS	High	miR-340-3p/HTR1D	(142)
HOXA-AS3	High	miR-29c/CDK6	(143)
LIFR-AS1	High	miRNA-150-5p/VEGFA	(144)
LINC00472	Down	miR-23a-3p/FOXO3/BID	(145)
LINC00491	High	miR-188-5p/ZFP91	(146)
LINC00657	High	miR-520h/CKS1B	(147)
LINC00671	Down	AKT/ERK signaling pathway	(108)
LINC00857	High	miR-130b/RHOA	(148)
Linc01232	High	HNRNPA2B1/A-Raf/MAPK	(149)
LNC00673	Down	miR-504/HNF1A	(150)
LOXL1-AS1	High	miR-28-5p/SEMA7A	(151)
MCM3AP-AS1	High	miR-138-5p, FOXK1	(71)
NEAT1	High	ELF3	(152)
OIP5-AS1	High	miR-342-3p	(153)
PVT1	High	miR-143/HIF-1α/VMP1	(154)
		HIF-1a	(155)
		miR-619-5p/Pygo2, miR-619-5p/ATG14	(156)
SNHG7	High	Notch1/Jagged1/Hes-1 signaling pathway	(157)
TP73-AS1	High	miRNA-128-3p/GOLM1	(158)
TTN-AS1	High	microRNA-589-5p/FOXP1	(159)
		miR-133b/SQLE	(160)

LncRNA, long non-coding RNA; PC, pancreatic cancer.

be used as therapeutic targets through various strategies; for example, in one study, CRISPR-dCas9 was proposed as an alternative technique to target HOXA-AS3. HOXA-AS3 was upregulated in PC cells and was able to promote PC cell proliferation through its regulation of miR-29c/CDK6 (143).

Conclusions

Studies have shown that lncRNA is significantly associated with the initiation and progression of PC. Also, some ncRNAs may act as biomarkers for PC. In this article, we have reviewed the types of ncRNAs and their potential roles in PC in terms of prognosis, diagnosis and treatment. Certainly, their clinical translation could contribute to the development of biomarkers in all types of cancer, and even in the future, lncRNA-based therapies may be an adjunctive option. Expanding our knowledge in this field will further improve diagnostic methods and develop treatment options.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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