Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Review Article

Turk J Med Sci
(2023) 53: 1552-1564
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doi:10.55730/1300-0144.5724

Long noncoding RNAs in pancreas cancer: from biomarkers to therapeutic targets

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Received: 21.05.2023 • **Accepted/Published Online:** 09.09.2023 • **Final Version:** 12.12.2023

Abstract: Long noncoding RNAs (lncRNAs) are noncoding RNA molecules with a heterogeneous structure consisting of 200 or more nucleotides. Because these noncoding RNAs are transcribed by RNA polymerase II, they have properties similar to messenger RNA (mRNA). Contrary to popular belief, the term "ncRNA" originated before the discovery of microRNAs. LncRNA genes are more numerous than protein-coding genes. They are the focus of current molecular research because of their pivotal roles in cancer-related processes such as cell proliferation, differentiation, and migration. The incidence of pancreatic cancer (PC) is increasing around the world and research on the molecular aspects of PC are growing. In this review, it is aimed to provide critical information about lncRNAs in PC, including the biological and oncological behaviors of lncRNAs in PC and their potential application in therapeutic strategies and as diagnostic tumor markers.

Key words: Long noncoding RNA, cancer, pancreas, pancreas cancer, biomarker

1. Introduction

Gene expression is an important step in the regulation of changes that occur during vital processes in cells and tissues. Genomic DNA is located in the nucleus of the cell and guides the correct processing of transcription for messenger RNAs (mRNAs). It then migrates to the cytoplasm and initiates the translation of proteins. In order to secure optimal processing, non-protein-coding RNAs are needed. In general, non-protein-coding RNAs are divided into RNA types such as small nuclear RNA (snRNA), carrier RNA (tRNA), and ribosomal RNA (rRNA), which have different end functions [1].

Long noncoding RNAs (lncRNAs) in the genome are responsible for gene regulation and the development of events in the cell, so they have many pivotal roles in the development of diseases. In addition, they undertake different functions in the cell, such as regulating chromatin remodeling, secondary structures attached to proteins, and epigenetic, transcriptional, and translational events [2,3].

The term "lncRNA" originated before the discovery of microRNA. The first lncRNA found in mammalian cells reported in the 1990s was H19. Not long after that discovery, another lncRNA was discovered: the X-inactive-specific transcript (XIST) gene, shown to be critical in X chromosome inactivation. The number of lncRNA genes was found to be higher than the number of protein-coding genes. They are noncoding RNA molecules with heterogeneous structures, usually consisting of 200 nucleotides or more. Because they are transcribed by RNA polymerase II, they have properties similar to mRNA [4,5]. However, they differ from mRNA in terms of their structure as they contain fewer exons, have lower expression levels in different tissues, and contain an open reading frame [6].

Transcribed lncRNAs mature by undergoing certain transcriptional changes. Thus, each lncRNA follows its own unique functional structure. Although they do not code for proteins, most of the intronic and antisense lncRNAs are located in the nucleus and cytoplasm. This shows that transcripts are involved in the regulation of cytoplasmic processes. More than 80% of lncRNAs are found in the nucleus [7]. One of their most well-known functions in the nucleus is to regulate gene and genome activity. LncRNAs are involved in many cellular events such as chromosome rearrangement, histone modifications, modification of genes by alternative splicing, and

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regulation of gene expression. Cytoplasmic noncoding lncRNAs can act as templates for the synthesis of small peptides with microRNA-like behavior. They can perform mRNA degradation or regulate the translation process [8]. LncRNAs cause genomic changes in many different cancer types and are used for diagnosis and therapeutic treatment in cancer [9].

In this review, the aim is to summarize the expression patterns, biological functions, and molecular mechanisms of lncRNAs that play roles in pancreatic cancer (PC) progression and the potential clinical utility of lncRNAs in PC.

2. Pancreatic cancer

The incidence of PC is increasing day by day around the world. This insidious cancer has a 5-year survival rate ranging from 2% to 9%. The mortality rate increases with age and the disease has particularly poor prognosis in men. The formation mechanisms of PC have not been sufficiently elucidated yet. Tobacco use, chronic pancreatitis, diabetes, and genetic factors are known to be important factors for cancer growth [10]. In recent years, scientific studies have focused on the link between chronic pancreatitis and the development of PC. It is thought that the progression to PC can be clarified by deciphering the molecular codes of chronic pancreatitis [11,12].

Unfortunately, PC has limited treatment options. Therefore, elucidating molecular tumor mechanisms in a detailed manner will have indispensable effects in terms of follow-up and treatment. Although genetic mutations such as *ATM*, *BRCA1/2*, and *PALB2* are effective in PC initiation and progression, epigenetic factors also play pivotal roles [13]. The most common genetic mutations in PC include p53 [8], *CDKN2A* [9], *SMAD4* [10], and *KRAS* mutations [14]. In this hereditary cancer, mutations in the *BRCA2*, *STK11*, *ATM*, *PALB1*, *MLH1*, *BRCA1*, *TP53*, *MSH2*, and *CDKN2A* genes also significantly affect the familial PC history [15]. Surgery, chemotherapy, and radiotherapy strategies are at the forefront considering current treatment methods. The elucidation of the molecular features of cancer increases the success of targeted personalized therapy. Systemic chemotherapy combinations containing 5-fluorouracil, folinic acid (leucovorin), irinotecan, and oxaliplatin (FOLFIRINOX) and gemcitabine plus nab-paclitaxel are frequently used as treatment regimens for patients with advanced PC. Conventional chemotherapy agents are used in a large number of PC cases [16]. However, clinical applications are limited due to low selectivity and numerous systemic side effects. In fact, the ability of chemotherapy to induce cancer cell death is due to its strong cytotoxicity, inhibiting the process of cell division and mitosis [17]. Biomarker-based research is ongoing to develop potential drug targets for PC therapy. The impact of genetic markers for microRNAs (miRNAs) or lncRNAs interacting with protein-coding genes is a focus for researchers in studies of pancreatic ductal adenocarcinoma (PDAC) [18]. Studies performed in previous years showed that lncRNAs play a central role in cancer biology. Researchers continue to show that lncRNAs are specifically expressed or deregulated in many cancer types; hence, lncRNAs are used as biomarkers. In addition, it was shown that lncRNAs can be used for the determination of cancer treatment response. In addition, lncRNAs play roles in the regulation of epigenetic modification of the cancer process, alternative splicing, transcription, and translation mechanisms. As lncRNAs have roles in regulating the biological behavior of cancer cells, they also affect events such as epithelial–mesenchymal transition (EMT), migration, proliferation, and chemoresistance [19].

3. LncRNAs in cancer

LncRNAs are involved in the cell cycle, proliferation, differentiation, metabolism, apoptosis, and maintenance of pluripotency. In other words, lncRNAs play active roles in the regulation of many processes [20]. LncRNAs have varying expression levels in different cell types. LncRNAs function as transcriptional factors. It was reported that lncRNAs cause changes in transcription and translational levels, and they also cause tumorigenesis. Abnormal levels of lncRNA expression play a role in cancer development and progression, and lncRNA expression is important in therapeutic treatment as it has the potential to be a biomarker for many diseases. Very few lncRNAs circulate from the cytoplasm and can be isolated from any bodily fluids, tissues, or cells [21]. They generally have oncogenic properties in cancer and little functionality as tumor suppressors. However, lncRNAs were found to function as both oncogenes and tumor suppressors. Overexpression of PCA3, one of the lncRNAs, was the first widely used biomarker in prostate cancer. In urine samples, PCA3 was reported to have specificity of 59%–76% and sensitivity of 58%–82% [22,23].

It was postulated that the overexpression of HOX antisense intergenic RNA (HOTAIR) is important for many types of cancers. HOTAIR is overexpressed in solid tumors in particular, acting as both an oncogene and a tumor suppressor. It plays an inevitable role in the shaping of cancer events such as tumor growth, invasion, and metastasis, and it is linked to poor prognosis [24]. It was reported that HOTAIR is deregulated in hepatocellular and colorectal carcinomas, pancreatic tumors, and tumors with poor prognosis such as ovarian cancer. In esophageal cancer, increased expression of HOTAIR facilitates EMT and promotes metastasis and invasion. Moreover, it was shown that increased HOTAIR expression in bladder

transitional cell carcinoma causes poor prognosis [25]. A study of tissues from 300 patients with gastric cancer showed that increased HOTAIR expression was associated with peritoneal cancer diffusion [26].

Metastasis-related lung adenocarcinoma transcript 1 (MALAT1), located on chromosome 11q13.1, is involved in gene regulation at the transcriptional and posttranscriptional levels. MALAT1 modulates the activity of the spliceosome complex, which is necessary for the correct addition and activity of B related to the transcriptional factor Myp (B-Myp) during the transition to the G2/M mitotic phase. Increased upregulation of MALAT1 was observed in lung and bladder cancers, esophageal squamous cell carcinoma, and glioma [27]. MALAT1 was suggested for use as a biomarker in the early diagnosis of prostate cancer. Patent applications were filed by some researchers for the use of HOTAIR and MALAT1 (CN105586399A) as adjunctive biomarkers in gastric cancer. In a study of gastric cancer, it was found that high expression of MALAT1 resulted in lower survival rates compared to the normal group. It was also shown that MALAT1 might be a biomarker for the recurrence potential of hepatocellular carcinoma after liver transplantation. MALAT1 was reported to increase invasion and metastasis in breast cancer cells [13,28].

It was shown that the expression level of NEAT1, a type of lncRNA transcribed from the multiple endocrine neoplasia locus, is increased in solid tumors. However, it has decreased expression levels in cases of leukemia and multiple myeloma. NEAT1 expression varies according to the cell in which it is located, and it has potential as a biomarker and can be targeted therapeutically. Expression changes in tumor tissues provide information about the prognosis of cancer [29]. Some tumor-suppressor lncRNAs, such as MEG3, GAS5, neuroblastoma-associated transcript-1 (NBAT-1), and long intergenic noncoding RNA/p53-induced transcript (LINC-PINT), have decreased expression levels in cancer cells [30]. Among them, MEG3 expression is epigenetically altered. It was determined that the expression level of MEG3 is considerably reduced in brain, lung, colon, and liver cancers and leukemia. MEG3 works together with different miRNAs to induce apoptosis in tumors. It regulates the TGF-beta genes that affect invasion and the immune system in cancer. In addition, it activates an important target, p53 protein [31]. H19 has high specificity and high sensitivity for expression in the cell in cancer. Plasma H19 expression levels have higher sensitivity than conventionally used biomarkers in breast cancer patients. Working with many miRNAs, H19/miR-675 activates EGFR and c-Met [32]. The expressions of some lncRNAs that vary according to tissues show high specificity, sensitivity, and accuracy when these lncRNAs are evaluated together with helper biomarkers. Examples of the use of lncRNAs for both diagnosis and prognosis in the early diagnosis and treatment of various types of cancer were reported [33,34]. LncRNAs that play roles in diagnosis and prognosis in different tissues are given in Figure 1.

4. LncRNAs in pancreas cancer

4.1. Oncogenic and tumor-suppressor roles of lncRNAs in PC

LncRNAs affect various behaviors of pancreatic malignant cells such as the proliferation, differentiation, or migration of tumor cells. LncRNAs are a focus for molecular research due to their effects on cancer-related processes such as cell proliferation and migration [35].

There is increasing interest in the effects of lncRNAs in PC tissues. The lncRNA most highly expressed in PC was identified as MACC1-AS1 and it is particularly expressed in patients with low survival. MACC1-AS1 increases the expression of the PAX8 protein, which plays a role in aerobic glycolysis, and promotes the proliferation and metastasis of PC cells by activating NOTCH1 signaling. The MACC1-AS1/PAX8/NOTCH1 signaling axis was proposed as a therapeutic target for the treatment of PC in the literature [36].

It was reported that HOTAIR functions as an oncogenic lncRNA in PC. HOTAIR, a HOX antisense intergenic RNA, combines with PRC2 (polycomb repressive complex 2) to transcriptionally silence the HOXD locus. With the increased regulation of HOTAIR, the cell cycle progresses, cell proliferation is ensured, and apoptosis of cancer cells is inhibited. In vitro experiments suggested that HOTAIR influences cell proliferation and regulates apoptosis [37], which are required for cancer growth.

Another lncRNA associated with the HOX gene is HOXA transcript at the distal tip (HOTTIP). HOTTIP binds to the WDR5 protein and activates HOXA transcription, causing H3K4 methylation. Among the genes targeted by HOTTIP, aurora kinase A (AURKA) was reported to inhibit apoptosis, regulate cell growth, and induce cell migration independently of WDR5 [38]. The lncRNA FGD5 antisense RNA 1 (FGD5 AS1) was found to be highly expressed in PC and plays a role in cell proliferation, migration, and invasion. In the same study, it was shown that FGD5-AS1 activates the Wnt/β-catenin signaling pathway by suppressing miR-577, a tumor suppressor in PC. It was reported that the expression of NUTF2P3-001, another lncRNA that increases in cases of hypoxia, plays a positive role in the regulation of KRAS expression and supports cell proliferation in PC [39].

It was shown that NR2F1-AS1 plays a role as a carcinogenic factor in various cancer types and is associated with poor prognosis. In PC, NR2F1-AS1 is associated with cell proliferation, cell migration, and

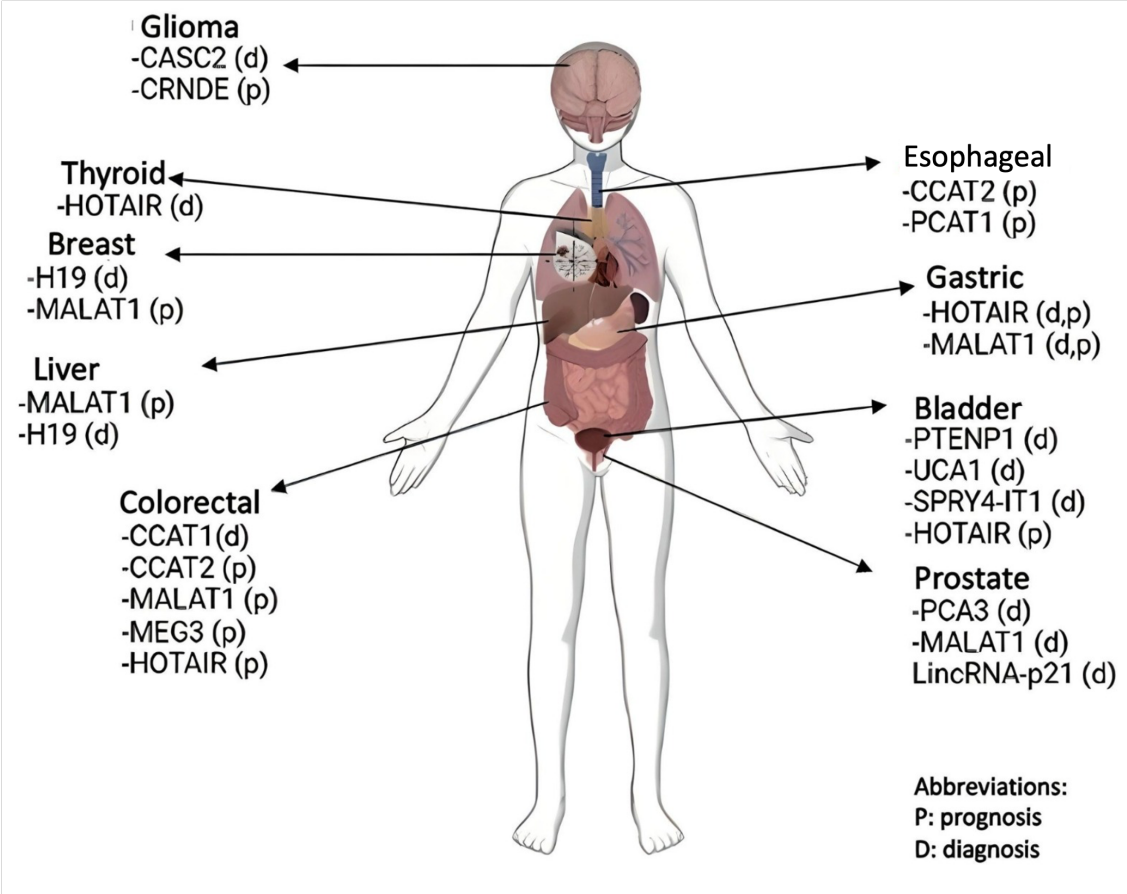

Figure 1. LncRNAs that play roles in diagnosis and prognosis in different tissues.

metastasis, and these effects are manifested by hypoxia-inducible factor-1α (HIF-1a). Therefore, NR2F1-AS1 was found to be a hypoxia-inducible lncRNA. The AKT/mTOR signaling pathway is activated by increased regulation of NR2F1-AS1 in hypoxic environments. The active AKT/mTOR pathway promotes PC cell proliferation, migration, and invasion. Moreover, it was suggested that NR2F1-AS1 may be a potential prognostic biomarker and therapeutic target for PC [40].

The lncRNA LINC00941 was reported to play an oncogenic role in proliferation and metastasis in PC. The increase in ROCK1 expression initiates LIMK1/cofilin-1 signaling, which promotes tumorigenic activities. These results demonstrate the potential for LINC00941 to be a diagnostic biomarker in PC [41].

CERS6-AS1 activates the ERK signaling pathway by binding to miR-217 to regulate YWHAG, which is involved in the phosphorylation of RAF1. miR-217 suppresses cell proliferation and metastasis by directly targeting YWHAG. The binding of CERS6-AS1 to miR-217 activates the ERK signaling pathway, thus promoting cell proliferation, cell migration, and metastasis [42]. Hence, the CERS6-AS1/miR-217/YWHAG/RAF1 signaling axis has the potential to be a therapeutic target for PC [43].

A recent study found that the expression of the lncRNA BM466146.1 was significantly reduced in PC tissues compared to normal pancreatic tissues. Because BM466146.1 regulates transcription as a transcription inhibitor of its neighboring gene, zinc finger protein 24 (ZNF24), it was named ZNF24 transcription regulator (ZNFTR). ZNFTR was found to play a role in inhibiting the proliferative, metastatic, and proangiogenic properties of PC cells. In addition, it was shown that low expression rates of ZNFTR, which functions as an inhibitor, are associated with low survival rates. Another lncRNA, LINC00337, acts as an E2F1 coactivator in PC, increasing the expression of target proteins and promoting cell proliferation [44].

The lncRNA GAS5 has antiproliferative effects in PC cells. The expression level of GAS5, which is decreased in PC, increases PC cell proliferation by negatively regulating the expression of cyclin-dependent kinase 6 (CDK6). Methylation-mediated LINC00261 suppresses c-Myc

transcription. Thus, it inhibits cell proliferation, migration, and metastasis in PC [45].

Knockdown of the lncRNAs LINC01559 and UNC5B-AS1 was found to cause decreased glucose uptake and lactate production in PC cells. Thus, they play a role in suppressing tumor growth by reducing the glycolytic capacity of PC cells [46].

LINC00976 expression was found to be increased in PC, and it was associated with poor prognosis. It was reported that when LINC00976 is silenced, cell proliferation and invasion are also suppressed. LINC00976 targets OTUD7B, which deubiquitinates EGFR, thereby activating the MAPK signal [47].

LncRNAs have tumor-suppressive properties as well as oncogenic and therapeutic potential. With these properties, lncRNAs play an important role in the formation and development of human cancers [48].

In a recent study, overexpression of LINC01963 inhibited proliferation and invasion in PC cells and also induced apoptosis [49]. Another lncRNA, MEG3, was shown to suppress PC progression by regulating the activity of apoptotic signal sequences. At the same time, it was determined that patients with low MEG3 expression rates had poor prognosis in survival analyses [50].

LINC00261 was found to be downregulated in PC tissues and stem cells. Likewise, ITIH5 was shown to be downregulated in PC cells. In the presence of LINC00261, the expression of ITIH5 is increased, thus increasing the sensitivity of PC stem cells to gemcitabine while reducing tumorigenic properties such as cell proliferation and invasion [51].

FLVCR1-AS1 is an important regulator involved in cancer progression. Lin et al. reported that FLVCR1-AS1 is downregulated in PC and is associated with poor prognosis. FLVCR1-AS1 overexpression was shown to suppress cell proliferation, cell cycle, and migration by activating PTEN/AKT signaling. It was reported that LINC01111 can suppress the metastatic ability of neoplastic cells in PC while lncRNA GAS5 suppresses PC metastasis by regulating the miR-32-5p/PTEN axis [52]. LncRNAs related to PC are given in the Table.

4.2. LncRNAs that play important roles in invasion and metastasis in PC

In PC, lncRNAs regulate important biological events such as the proliferation, invasion, and metastasis of cells [53]. Overexpression of LINC01232 in PC causes increased upregulation of HNRNPA2B1. HNRNPA2B1 promotes

Table. Summary of lncRNAs related to pancreatic cancer.

LncRNA	Genomic location	Function	Expression	Mechanism of action
MACC1-AS1	7p21.1	Oncogenic	↑	MACC1-AS1 → PAX8 → NOTCH1 → Proliferation, metastasis
HOTAIR	12q13.13	Oncogenic	↑	HOTAIR/ PRC2 ⇢ HOXD → Proliferation, invasion, apoptosis inhibition
HOTTIP	7p15.2	Oncogenic	↑	HOTTIP/ WDR5 → H3K4me3 at HOXA9 → Proliferation, migration, apoptosis inhibition HOTTIP → HOXA13 → EMT
FGD5-AS1	3p25.1	Oncogenic	↑	FGD5-AS1 ⇢ miR-577 → Wnt/ β Katenin → Proliferation, migration, invasion
NUTF2P3-001	9q21.2	Oncogenic	↑	NUTF2P3-001→ KRAS → ProliferationHIF-I*a* → NUTF2P3-001 → Invasion
NR2F1-AS1	5q15	Oncogenic	↑	NR2F1-AS1 → NR2F1→ AKT/mTOR → Proliferation, migration, invasion
LINC00941	12p11.21	Oncogenic	↑	LINC00941 ⇢ miR-335-5p →ROCK1 → LIMK1/ Cofilin-1 → Proliferation, metastasis
CERS6-AS1	2q24.3	Oncogenic	↑	CERS6-AS1 ⇢ miR-217 → YWHAG → ERK→ Proliferation, migration, metastasisCERS6-AS1 ⇢ miR-195-5p → WIPI2 → reduced proliferation, inhibit apoptosis
BM466146.1 (ZNFTR)	18:35,446,176–35,446,941	Oncogenic	↓	BM466146.1 → Poor survival time, poor prognosis
BM466146.1 (ZNFTR)	18:35,446,176–35,446,941	Tumor supressive	↑	BM466146.1 (ZNFTR) ⇢ ATF3 → ZNF24 ⇢ VEGFA → inhibit proliferative, metastatic, pro-angiogenic capacities

Table. (Continued).

NEAT1	11q13.1	Oncogenic	↑	NEAT1 ⇢ miR-506-3p → Proliferation
LINC00337	1p36.31	Oncogenic	↑	LINC00337 → E2F1 → Proliferation, regulate cell cycle
LINC00261	20p11.21	Tumor supressive	↑	LINC00261 → p300/CBP ⇢ c-Myc → Inhibit proliferation, migration, metastasisLINC00261 → ITIH5/ GATA6 → Reduced proliferation, invasion and increased sensitivity of gemsitabine
GAS5	1q25.1	Tumor supressive	↑	GAS5 ⇢ miR-32-5p → PTEN → supresses metastasis
GAS5	1q25.1	Oncogenic	↓	GAS5 ⇢ CDK6 → Poliferation
LINC01559	12p13.1	Tumor supressive	↓	LINC01559 → inhibit aerobic glycolysis
UNC5B-AS1	10q22.1	Tumor supressive	↓	UNC5B-AS1 → inhibit aerobic glycolysis
LINC00976	8q24.21	Oncogenic	↑	LINC00976 → OTUD7B/EGFR → MAPK → Proliferation, invasion
LINC01963	2q35	Tumor supressive	↑	LINC01963 → Inhibit proliferation, invasion, induced apoptosis
MEG3	14q32.2	Tumor supressive	↑	MEG3 → PI3K/AKT/Bcl-2/Bax/siklin D1/P53 → Suppresses tumor progressionMEG3 → PI3K/AKT/ MMP-2/MMP-9 → Suppresses tumor progression
FLVCR1-AS1	1q32.3	Tumor supressive	↑	FLVCR1-AS1 → PTEN/AKT → Suppresses proliferation, migration
LINC01111	8q21.13	Tumor supressive	↑	LINC01111 → suppresses the metastatic ability of neoplastic cells
DGCR5	22q11.21	Tumor supressive	↑	DGCR5 ⇢ miR-27a-3p → BNIP3 → p38 MAPK → apoptosis
LINC01232	13q32.3	Oncogenic	↑	LINC01232 → HNRNPA2B/ A-Raf → MAPK → metastasis
LOC389641	8p21.3	Oncogenic	↑	LOC389641→ Vimentin/ Snail ⇢ E-cadherin → EMT
ENST00000480739	12q13.3	Tumor supressive	↓	ENST00000480739 → OS-9 → HIF-1/ HIF-1*a* → suppresses invasion, metastasis
H19	11p15.5	Oncogenic	↑	H19 → Invasion, metastasis
ANRIL	9p21.3	Oncogenic	↑	ANRIL ⇢ miR-181a → Proliferation, invasion, migration and increases gemsitabine resistance
BX111	10p11.22	Oncogenic	↑	BX111→ metastasis, angiogenesis
AC009974.1		Oncogenic	↓	AC009974.1 → EMT
LINC00462	13q14.2	Oncogenic	↑	LINC00462 → EMT, invasion, metastasis
LINC00958	11p15.3	Oncogenic	↑	LINC00958 → EMT
SNHG12	1p35.3	Oncogenic	↑	SNHG12 → EMT
OIP5-AS1	15q15.1	Oncogenic	↑	OIP5-AS1 → EMT
CASC9	8q21.13	Oncogenic	↑	CASC9 → Glycolysis metabolism ↑ → EMT
MALAT-1	11q13.1	Oncogenic	↑	MALAT-1 → Vimentin/ E-cadherin → EMT
ROR	18q21.31	Oncogenic	↑	ROR ⇢ p53/ ZEB1 → EMT
GATA3-AS1	10p14	Oncogenic	↑	GATA3-AS1 ⇢ miR-30b-5p → Tex10 → Wnt/β- catenin → Proliferation, invasion, apoptosis inhibition
CTD-3252C9.4	19p13.12	Tumor suppressive	↑	CTD-3252C9.4 ⇢ IFI6 → reduced proliferation, migration, invasion and increased apoptosis
LINC00460	13q33.2	Tumor suppressive	↓	LINC00460 → miR-320b → suppresses proliferation, migration, invasion and support apoptosis

PC metastasis by playing a role in the alternative splicing of A-Raf, the protein kinase in the MAPK signaling pathway. Therefore, LINC01232 plays an active role in the metastasis of PC [54]. It was reported that overexpression of HOTAIR may increase cell invasion in PC cell lines. When HOTTIP, another lncRNA, was silenced in PC, it was observed that migration in PC cells decreased [55].

In a recent study, LncRNA LOC389641 expression was significantly increased in PDAC tissues. It was stated that LOC389641 contributes to EMT by increasing Vimentin and Snail expression and suppressing E-cadherin expression [56].

Sun et al. reported that decreased lncRNA ENST00000480739 expression levels in PC tissues are effective in cancer metastasis. In in vitro experiments, increased expression of ENST00000480739 directly targeted osteosarcoma amplified-9 (OS-9) and led to its upregulation. OS-9 is effective in suppressing invasion and metastasis by interacting with HIF-1 and HIF-1a. Overexpression of HIF-1 and HIF-1a in PC was suggested to play a critical role in invasion and metastasis. Therefore, the production of drugs targeting the lncRNA ENST00000480739/OS-9/HIF-1 signaling pathway may be promising for the treatment of PC [57]. In patients with PDAC, patients with lymph node metastases were found to have lower expression levels of ENST00000480739 than patients without metastasis. Thus, ENST00000480739 was shown to have the potential to be a new biomarker to evaluate metastasis status [57]. LncRNA H19 is an important maternally inherited oncogenic factor. It is effective in the malignancy of tumors by affecting specific miRNAs in many cancer types, such as PDAC [58–60]. H19 expression is significantly increased in metastatic PDAC. It was found that invasion and metastasis were inhibited when H19 was silenced in PDAC cells [61].

In a study by Wang et al., miR-181a was downregulated and ANRIL was upregulated in PC tissues. Downregulated miR-181a was also found to increase HMGB1 expression by targeting HMGB1, which is involved in the activation of cell autophagy. In summary, ANRIL activates HMGB1-induced cell autophagy by targeting miR-181a. Overexpression of ANRIL promotes cell proliferation, invasion, and migration in PC cells and increases their resistance to gemcitabine. Likewise, with the degradation of ANRIL, cell proliferation, migration, invasion, and resistance to gemcitabine are suppressed. As a result of this study, it was suggested that ANRIL and miR-181a may be potential targets for PC therapy [41].

LncRNA BX111, which is overexpressed in PC tissues, plays a role in lymphatic vessel invasion and distant metastasis, leading to a decrease in patient survival rates [62]. There is a correlation between high expression levels of HOTTIP in PC and survival rates [63].

5-Methylcytosine (m5C) methylation is a posttranscriptional modification that plays an important role in RNA metabolism. It was shown that m5C methyltransferases play a role in cell proliferation in many cancers. While m5C regions are known to be abundant in lncRNAs, their exact functions are not known. In PC, AC009974.1 was found to be effective in the EMT process [64].

Increased expression of LINC00462 contributes to the invasion and metastasis processes of PC by accelerating the EMT process. On the other hand, LINC00462, LINC00958, SNHG12, and OIP5-AS1 are important lncRNAs involved in the progression of EMT in PC [65].

It was shown that CASC9 promotes PC progression and invasion by interacting with miR-497-5p and also affect Cyclin D1 [66].

MALAT-1 is overexpressed in PC stem cells and plays a role in angiogenesis and proliferation. It is also effective in increasing resistance to drugs during the treatment of PC. The expression of MALAT-1 is also effective during the EMT process in PC cell lines. With the suppression of MALAT-1 expression, it was observed that the expression levels of N-cadherin and Vimentin were decreased and the expression of E-cadherin was increased [67]. In PC, MALAT-1 also decreased the expression of Sox2. It was reported that MALAT-1 can accelerate the proliferation and metastasis of PC cells by stimulating autophagy [68]. Another lncRNA, ROR, contributes to EMT in PC by causing inhibition of p53 and ZEB1 expression [69].

4.3. LncRNAs in the apoptosis of pancreatic cancer cells

It was observed that PC cells undergo apoptosis with the degradation of HOTAIR and HOTTIP. Silencing of HOTAIR in Panc1 cells reduced the interaction of the histone-lysine N-methyltransferase enzyme, EZH2, with the promoter region of proapoptotic gene GDF15. The suppression of GDF15 also supports the apoptosis of tumor cells [70]. AF339813, a lncRNA upregulated in PC, was also reported to induce apoptosis via mitochondria and caspase-dependent pathways [71].

A recent study reported that GATA3 AS1 knockdown reduces the cell proliferation and invasion capabilities of PANC 1 or AsPC 1 cell lines while increasing cell apoptosis. GATA3-AS1 was reported to modulate the Wnt/β-catenin pathway in association with miR-30b-5p/Tex10 and it regulates cell proliferation, invasion, and apoptosis processes. As a result of this study, it was suggested that the GATA3-AS1/miR-30b-5p/Tex10 signaling axis could be used in the diagnosis and treatment of PC [72].

CERS6-AS1 was found to be highly upregulated in PC cells in a recent study. When CERS6-AS1 is silenced, it suppresses the proliferation of PC cells and increases cell apoptosis. CERS6-AS1 interacts with miR-195-5p, increasing the expression of WD repeat domain

phosphoinositide interacting 2 (WIPI2-WD repeat domain phosphoinositide interacting 2). Upregulation of WIPI2 inhibits apoptosis and increases cell proliferation [73].

CTD-3252C9.4 was reported to be downregulated in PC cells and tissues. Overexpression of CTD-3252C9.4 suppressed cell proliferation, migration, and invasion while increasing apoptosis. The antiproliferative and proapoptotic effects of CTD-3252C9.4 are mediated by downregulation of IFI6. Overexpression of IFI6 has tumorigenic effects. IFI6 is targeted and downregulated by CTD-3252C9.4. IRF1 is blocked by CTD-3252C9.4 to inhibit IFI6 transcription [74].

A recent study found that LINC00460 knockdown inhibits cell proliferation, migration, and invasion and promotes apoptosis. LINC00460 was able to directly target miR-320b, and downregulation of LINC00460 significantly increased the miR-320b level. Previous studies showed that miR-320 has a suppressive effect on increased migration and invasion in proliferation, while, on the contrary, downregulation of miR-320b contributes to invasion and EMT. This recent study revealed the effect of miR-320, which is increased by LINC00460 degradation, on proliferation, migration, and apoptosis in PC [75]. LncRNAs that are effective in cancer progression are summarized in Figure 2.

4.4. LncRNAs in drug resistance

Oncogenic lncRNAs such as LINC00346, linc-ROR, TUG1, and AB209630 are associated with gemcitabine resistance in PC. For example, knockdown of linc-ROR can reduce gemcitabine resistance by targeting HOXA13 [76]. Unlike others, overexpression of lncRNA AB209630 was reported to suppress gemcitabine resistance. The overexpression of AB209630 inhibits the PI3K/AKT signaling pathway and suppresses drug resistance. Another tumor suppressor in PC, MEG3, was also reported to suppress gemcitabine resistance [77].

Yin et al. reported that HOTTIP plays a role in cisplatin resistance by suppressing miR-137 expression [78]. In a recent study, HIF1a antisense RNA1 (HIF1A-AS1) expression levels were significantly increased in gemcitabine-resistant PC cells. As a result of that experiment, increased HIF1A-AS1 expression was shown to upregulate HIF1a to support glycolysis. Thus,

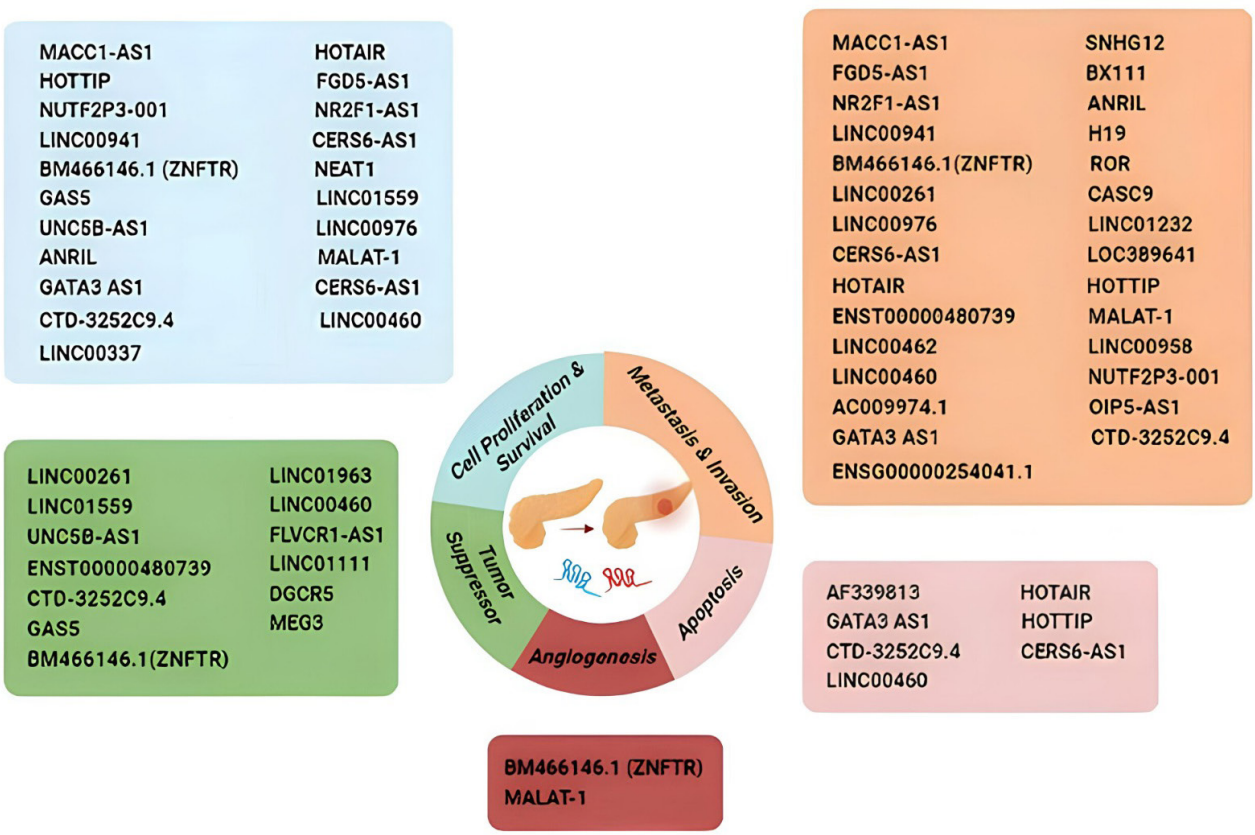

Figure 2. LncRNAs that are effective in cancer progression.

overexpression of HIF1A-AS1 was found to increase gemcitabine resistance in PC and cause a decrease in survival [79].

UPK1A-AS1 induced by IL8/NF-kappa B signaling was found to be a lncRNA involved in drug resistance in PC. The blockade of UPK1A-AS1 expression increased the oxaliplatin sensitivity of tumor cells. UPK1A-AS1 is induced by IL-8/NF-kappa B signaling. UPK1A-AS1 enables DNA double-strand break repair by reinforcing the interaction between Ku70 and Ku80 in nonhomologous end-joining (NHEJ) repair. UPK1A-AS1 expression appeared to be associated with poorer chemotherapeutic response and shorter survival time in PDAC patients. As a result of this study, it was concluded that UPK1A-AS can be used as a biomarker to observe the response to platinum-based chemotherapy in patients with PDAC [80].

4.5. LncRNAs as biomarkers in pancreatic cancer

Studies have shown that lncRNAs have extensive functions in mediating PC progression and may therefore serve as prognostic markers or therapeutic targets [13,19,20]. In a recent study, it was suggested that the expression levels of PVT1 and HIF-1a could be used as biomarkers for survival in PC patients [46].

Overexpression of LINC00675 was associated with progression of lymph node metastasis and perineural invasion in PC. It was reported that LINC00675 can be used as a marker for the prediction of disease recurrence after surgical resection in PDAC [81].

It was also suggested that highly regulated C9orf139 could be a biomarker for determining PC staging [82]. Overexpression of RUNX1-IT1 was identified to be a factor that increases mortality, and it was reported to be a biomarker showing poor survival. Increased expression of LINC01963 and LINC00261 was shown to be significantly associated with higher survival rates in PC patients. Increased expression levels of MACC1-AS1, LINC00462, LINC01559, and UCA1 were associated with shorter survival rates [65]. It was also suggested that lncRNAs such as UFC1, RP11-263F15.1, ABHD11-AS1, and HULC can be used as diagnostic markers in PC [65]. The HOTAIR-miR-613-Notch3 signaling axis is a promising therapeutic target for PC [83]. It is important to identify the expression profiles of lncRNAs in order to discover biomarkers that will enable the diagnosis and treatment of PC in the early stages with noninvasive methods.

5. Conclusion

LncRNAs can be used as biomarkers in cancer cases as well as to predict prognosis. These molecules also play leading roles in the regulation of the genes they target by interacting with various cell signaling pathways, but, as a challenge, they are affected by various factors such as age, sex, nutrition, and hormones [84,85]. On the other hand, the aberrant expressions and single nucleotide polymorphisms of some lncRNAs that play roles as suppressors of protooncogenes and tumors are associated with tumorigenesis and metastasis. Therefore, lncRNAs hold strong promise for cancer diagnosis and treatment. However, there are still controversial gray areas and limitations in this regard. First of all, many lncRNAs have been discovered, but their use in clinical practice will not be easy without demonstrating their clear links to particular cancer types or subtypes. Secondly, lncRNAs are a relatively new topic in cancer research, and since the structural and functional information of most lncRNAs cannot be characterized in detail, it is difficult to link lncRNAs with cancer processes [86]. Moreover, without a detailed explanation of the structure and functions of lncRNAs, efforts to develop lncRNA-based therapies seem to be overly optimistic. On the other hand, in order to fully reveal the potential of lncRNAs in cancer diagnosis and targeted therapy, it is necessary to describe each lncRNA in detail and to elucidate its cellular functions and roles in diseases [87].

Finally, chromosome rearrangement, histone modifications, modification of genes by alternative splicing, and regulation of gene expression are all different activities of lncRNAs. Moreover, they can perform mRNA degradation or regulate the translation process. All of these mechanisms are extremely important in the pathophysiology of cancer growth. In other words, lncRNAs can be used for the diagnosis of many types of cancer including PC [88]. In conclusion, lncRNAs can be used as biomarkers and may be applied in therapeutic interventions in cases of PC.

Conflict of interest

The authors declare no conflicts of interest.

Funding

No funding was received to assist with the preparation of this manuscript.

References

1. Hombach S, Kretz M. Non-coding RNAs: classification, biology and functioning. Advances in Experimental Medicine and Biology 2016; 937: 3-17. https://doi.org/10.1007/978-3-319-42059-2_1
2. St Laurent G, Wahlestedt C, Kapranov P. The landscape of long noncoding RNA classification. Trends in Genetics 2015; 31 (5): 239-251. https://doi.org/10.1016/j.tig.2015.03.007
3. Mercer TR, Munro T, Mattick JS. The potential of long noncoding RNA therapies. Trends in Pharmacological Sciences 2022; 43 (4): 269-280. https://doi.org/10.1016/j.tips.2022.01.008
4. Brown CJ, Ballabio A, Rupert JL, Lafreniere RG, Grompe M et al. A gene from the region of the human X inactivation centre is expressed exclusively from the inactive X chromosome. Nature 1991; 349 (6304): 38-44. https://doi.org/10.1038/349038a0
5. Brannan CI, Dees EC, Ingram RS, Tilghman SM. The product of the *H19* gene may function as an RNA. Molecular and Cellular Biology 1990; 10 (1): 28-36. https://doi.org/doi:10.1128/mcb.10.1.28-36.1990
6. Gibb EA, Brown CJ, Lam WL. The functional role of long non-coding RNA in human carcinomas. Molecular Cancer 2011; 10: 38. https://doi.org/10.1186/1476-4598-10-38
7. Ayupe AC, Tahira AC, Camargo L, Beckedorff FC, Verjovski-Almeida S et al. Global analysis of biogenesis, stability and sub-cellular localization of lncRNAs mapping to intragenic regions of the human genome. RNA Biology 2015; 12 (8): 877-892. https://doi.org/10.1080/15476286.2015.1062960
8. Schmitz SU, Grote P, Herrmann BG. Mechanisms of long noncoding RNA function in development and disease. Cellular and Molecular Life Sciences 2016; 73 (13): 2491-2509. https://doi.org/10.1007/s00018-016-2174-5
9. Pierouli K, Papakonstantinou E, Papageorgiou L, Diakou I, Mitsis T et al. Long non-coding RNAs and microRNAs as regulators of stress in cancer (Review). Molecular Medicine Reports 2022; 26 (6): 361. https://doi.org/10.3892/mmr.2022.12878
10. GBD 2017 Pancreatic Cancer Collaborators. The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterology & Hepatology 2019; 4 (12): 934-947. https://doi.org/10.1016/S2468-1253(19)30347-4
11. Tanoglu EG. Differential expressions of miR-223, miR-424, miR-145, miR-200c, miR-139 in experimental rat chronic pancreatitis model and their relationship between oxidative stress, endoplasmic reticulum stress, and apoptosis. Iranian Journal of Basic Medical Sciences 2021; 24 (9): 1301-1306. https://doi.org/10.22038/ijbms.2021.57664.12823
12. Güzel Tanoğlu E, Tanoğlu A, Aydın Meriçöz MÇ, Esen MF. Melatonin has favorable preventive effects on experimental chronic pancreatitis rat model. Turkish Journal of Medical Sciences 2021; 51 (5): 2734-2740. https://doi.org/10.3906/sag-2103-2134
13. Ramya Devi KT, Karthik D, Mahendran T, Jaganathan MK, Hemdev SP. Long noncoding RNAs: role and contribution in pancreatic cancer. Transcription 2021; 12 (1): 12-27. https://doi.org/10.1080/21541264.2021.1922071
14. Khan AA, Liu X, Yan X, Tahir M, Ali S et al. An overview of genetic mutations and epigenetic signatures in the course of pancreatic cancer progression. Cancer and Metastasis Reviews 2021; 40 (1): 245-272. https://doi.org/10.1007/s10555-020-09952-0
15. Zhen DB, Rabe KG, Gallinger S, Syngal S, Schwartz AG et al. *BRCA1*, *BRCA2*, *PALB2*, and *CDKN2A* mutations in familial pancreatic cancer: a PACGENE study. Genetics in Medicine 2015; 17 (7): 569-577. https://doi.org/10.1038/gim.2014.153
16. Mahmood J, Shukla HD, Soman S, Samanta S, Singh P et al. Immunotherapy, radiotherapy, and hyperthermia: a combined therapeutic approach in pancreatic cancer treatment. Cancers (Basel) 2018; 10 (12): 469. https://doi.org/10.3390/cancers10120469
17. Mizrahi JD, Surana R, Valle JW, Shroff RT. Pancreatic cancer. Lancet 2020; 395 (10242): 2008-2020. https://doi.org/10.1016/S0140-6736(20)30974-0
18. Uddin MH, Mohammad RM, Philip PA, Azmi AS, Muqbil I. Role of non-coding RNAs in pancreatic ductal adenocarcinoma associated cachexia. American Journal of Physiology-Cell Physiology 2022; 323 (6): C1624-C1632. https://doi.org/10.1152/ajpcell.00424.2022
19. Chandra Gupta S, Nandan Tripathi Y. Potential of long non-coding RNAs in cancer patients: from biomarkers to therapeutic targets. International Journal of Cancer 2017; 140 (9): 1955-1967. https://doi.org/10.1002/ijc.30546
20. Qian Y, Shi L, Luo Z. Long non-coding RNAs in cancer: implications for diagnosis, prognosis, and therapy. Frontiers of Medicine 2020; 7: 612393. https://doi.org/10.3389/fmed.2020.612393
21. Schmitt AM, Chang HY. Long noncoding RNAs in cancer pathways. Cancer Cell 2016; 29 (4): 452-463. https://doi.org/10.1016/j.ccell.2016.03.010
22. Hessels D, Klein Gunnewiek JM, van Oort I, Karthaus HF, van Leenders GJ et al. $DD3^{PCA3}$-based molecular urine analysis for the diagnosis of prostate cancer. European Urology 2003; 44 (1): 8-15. https://doi.org/10.1016/s0302-2838(03)00201-x
23. Lemos AE, Ferreira LB, Batoreu NM, de Freitas PP, Bonamino MH et al. PCA3 long noncoding RNA modulates the expression of key cancer-related genes in LNCaP prostate cancer cells. Tumour Biology 2016; 37 (8): 11339-11348. https://doi.org/10.1007/s13277-016-5012-3
24. Hajjari M, Salavaty A. HOTAIR: An oncogenic long non-coding RNA in different cancers. Cancer Biology & Medicine 2015; 12 (1): 1-9. https://doi.org/10.7497/j.issn.2095-3941.2015.0006
25. Sun X, Du P, Yuan W, Du Z, Yu M et al. Long non-coding RNA HOTAIR regulates cyclin J via inhibition of microRNA-205 expression in bladder cancer. Cell Death and Disease 2015; 6: e1907. https://doi.org/10.1038/cddis.2015.269

26. Okugawa Y, Toiyama Y, Hur K, Toden S, Saigusa S et al. Metastasis-associated long non-coding RNA drives gastric cancer development and promotes peritoneal metastasis. Carcinogenesis 2014; 35 (12): 2731-2739. https://doi.org/10.1093/carcin/bgu200

27. Tripathi V, Shen Z, Chakraborty A, Giri S, Freier SM et al. Long noncoding RNA MALAT1 controls cell cycle progression by regulating the expression of oncogenic transcription factor B-MYB. PLoS Genetics 2013; 9 (3): e1003368. https://doi.org/10.1371/journal.pgen.1003368

28. Fu S, Wang Y, Li H, Chen L, Liu Q. Regulatory networks of LncRNA MALAT-1 in cancer. Cancer Management and Research 2020; 12: 10181-10198. https://doi.org/10.2147/CMAR.S276022

29. Ghafouri-Fard S, Taheri M. Nuclear enriched abundant transcript 1 (NEAT1): a long non-coding RNA with diverse functions in tumorigenesis. Biomedicine & Pharmacotherapy 2019; 111: 51-59. https://doi.org/10.1016/j.biopha.2018.12.070

30. Wu Z, He Y, Li D, Fang X, Shang T et al. Long noncoding RNA MEG3 suppressed endothelial cell proliferation and migration through regulating miR-21. American Journal of Translational Research 2017; 9 (7): 3326-3335.

31. Mondal T, Subhash S, Vaid R, Enroth S, Uday S et al. MEG3 long noncoding RNA regulates the TGF-β pathway genes through formation of RNA-DNA triplex structures. Nature Communications 2015; 6: 7743. https://doi.org/10.1038/ncomms8743

32. Ghafouri-Fard S, Esmaeili M, Taheri M. H19 lncRNA: roles in tumorigenesis. Biomedicine & Pharmacotherapy 2020; 123: 109774. https://doi.org/10.1016/j.biopha.2019.109774

33. Wang Z, Ran R, Zhang S, Zhou W, Lv J et al. The role of long non-coding RNA HCG18 in cancer. Clinical and Translational Oncology 2023; 25 (3): 611-619. https://doi.org/10.1007/s12094-022-02992-8

34. Ashrafizadeh M, Rabiee N, Kumar AP, Sethi G, Zarrabi A et al. Long noncoding RNAs (lncRNAs) in pancreatic cancer progression. Drug Discovery Today 2022; 27 (8): 2181-2198. https://doi.org/10.1016/j.drudis.2022.05.012

35. Xie W, Chu M, Song G, Zuo Z, Han Z et al. Emerging roles of long noncoding RNAs in chemoresistance of pancreatic cancer. Seminars in Cancer Biology 2022; 83: 303-318. https://doi.org/10.1016/j.semcancer.2020.11.004

36. Qi C, Xiaofeng C, Dongen L, Liang Y, Liping X et al. Long non-coding RNA MACC1-AS1 promoted pancreatic carcinoma progression through activation of PAX8/NOTCH1 signaling pathway. Journal of Experimental & Clinical Cancer Research 2019; 38 (1): 344. https://doi.org/10.1186/s13046-019-1332-7

37. Chiyomaru T, Fukuhara S, Saini S, Majid S, Deng G et al. Long non-coding RNA HOTAIR is targeted and regulated by miR-141 in human cancer cells. Journal of Biological Chemistry 2014; 289 (18): 12550-12565. https://doi.org/10.1074/jbc.M113.488593

38. Cheng Y, Jutooru I, Chadalapaka G, Corton JC, Safe S. The long non-coding RNA HOTTIP enhances pancreatic cancer cell proliferation, survival and migration. Oncotarget 2015; 6 (13): 10840-10852. https://doi.org/10.18632/oncotarget.3450

39. Zhang WT, Zhang JJ, Shao Q, Wang YK, Jia JP et al. FGD5-AS1 is an oncogenic lncRNA in pancreatic cancer and regulates the Wnt/β-catenin signaling pathway via miR-577. Oncology Reports 2022; 47 (1): 21. https://doi.org/10.3892/or.2021.8232

40. Liu Y, Chen S, Cai K, Zheng D, Zhu C et al. Hypoxia-induced long noncoding RNA NR2F1-AS1 maintains pancreatic cancer proliferation, migration, and invasion by activating the NR2F1/AKT/mTOR axis. Cell Death and Disease 2022; 13 (3): 232. https://doi.org/10.1038/s41419-022-04669-0

41. Wang L, Bi R, Li L, Zhou K, Yin H. lncRNA ANRIL aggravates the chemoresistance of pancreatic cancer cells to gemcitabine by targeting inhibition of miR-181a and targeting HMGB1-induced autophagy. Aging (Albany NY) 2021; 13 (15): 19272-19281. https://doi.org/10.18632/aging.203251

42. Liu SL, Wu XS, Li FN, Yao WY, Wu ZY et al. ERRα promotes pancreatic cancer progression by enhancing the transcription of PAI1 and activating the MEK/ERK pathway. American Journal of Cancer Research 2020; 10 (11): 3622-3643. https://doi.org/10.1016/j.hpb.2022.05.545

43. Xu J, Wang J, He Z, Chen P, Jiang X et al. LncRNA CERS6-AS1 promotes proliferation and metastasis through the upregulation of YWHAG and activation of ERK signaling in pancreatic cancer. Cell Death and Disease 2021; 12 (7): 648. https://doi.org/10.1038/s41419-021-03921-3

44. Li W, Han S, Hu P, Chen D, Zeng Z et al. LncRNA ZNFTR functions as an inhibitor in pancreatic cancer by modulating ATF3/ZNF24/VEGFA pathway. Cell Death and Disease 2021; 12 (9): 830. https://doi.org/10.1038/s41419-021-04119-3

45. Lu X, Fang Y, Wang Z, Xie J, Zhan Q et al. Downregulation of gas5 increases pancreatic cancer cell proliferation by regulating CDK6. Cell and Tissue Research 2013; 354 (3): 891-896. https://doi.org/10.1007/s00441-013-1711-x

46. Zhu Y, Wu F, Gui W, Zhang N, Matro E et al. A positive feedback regulatory loop involving the lncRNA PVT1 and HIF-1α in pancreatic cancer. Journal of Molecular Cell Biology 2021; 13 (9): 676-689. https://doi.org/10.1093/jmcb/mjab042

47. Lei S, He Z, Chen T, Guo X, Zeng Z et al. Long noncoding RNA 00976 promotes pancreatic cancer progression through OTUD7B by sponging miR-137 involving EGFR/MAPK pathway. Journal of Experimental & Clinical Cancer Research 2019; 38 (1): 470. https://doi.org/10.1186/s13046-019-1388-4

48. Guzel E, Okyay TM, Yalcinkaya B, Karacaoglu S, Gocmen M et al. Tumor suppressor and oncogenic role of long non-coding RNAs in cancer. Northern Clinics of Istanbul 2020; 7 (1): 81-86. https://doi.org/10.14744/nci.2019.46873

49. Li K, Han H, Gu W, Cao C, Zheng P. Long non-coding RNA LINC01963 inhibits progression of pancreatic carcinoma by targeting miR-641/TMEFF2. Biomedicine & Pharmacotherapy 2020; 129: 110346. https://doi.org/10.1016/j.biopha.2020.110346

50. Gu L, Zhang J, Shi M, Zhan Q, Shen B et al. lncRNA MEG3 had anti-cancer effects to suppress pancreatic cancer activity. Biomedicine & Pharmacotherapy 2017; 89: 1269-1276. https://doi.org/10.1016/j.biopha.2017.02.041

51. Zou L, He H, Li Z, Chen O, Jia X et al. Long noncoding RNA LINC00261 upregulates ITIH5 to impair tumorigenic ability of pancreatic cancer stem cells. Cell Death Discovery 2021; 7 (1): 220. https://doi.org/10.1038/s41420-021-00575-0

52. Lin J, Zhai S, Zou S, Xu Z, Zhang J et al. Positive feedback between lncRNA FLVCR1-AS1 and KLF10 may inhibit pancreatic cancer progression via the PTEN/AKT pathway. Journal of Experimental & Clinical Cancer Research 2021; 40 (1): 316. https://doi.org/10.1186/s13046-021-02097-0

53. Li Y, Yang X, Kang X, Liu S. The regulatory roles of long noncoding RNAs in the biological behavior of pancreatic cancer. Saudi Journal of Gastroenterology 2019; 25 (3): 145-151. https://doi.org/10.4103/sjg.SJG_465_18

54. Meng LD, Shi GD, Ge WL, Huang XM, Chen Q et al. Linc01232 promotes the metastasis of pancreatic cancer by suppressing the ubiquitin-mediated degradation of HNRNPA2B1 and activating the A-Raf-induced MAPK/ERK signaling pathway. Cancer Letters 2020; 494: 107-120. https://doi.org/10.1016/j.canlet.2020.08.001

55. Li Z, Zhao X, Zhou Y, Liu Y, Zhou Q et al. The long non-coding RNA HOTTIP promotes progression and gemcitabine resistance by regulating HOXA13 in pancreatic cancer. Journal of Translational Medicine 2015; 13: 84. https://doi.org/10.1186/s12967-015-0442-z

56. Zheng S, Chen H, Wang Y, Gao W, Fu Z et al. Long non-coding RNA LOC389641 promotes progression of pancreatic ductal adenocarcinoma and increases cell invasion by regulating E-cadherin in a TNFRSF10A-related manner. Cancer Letters 2016; 371 (2): 354-365. https://doi.org/10.1016/j.canlet.2015.12.010

57. Sun YW, Chen YF, Li J, Huo YM, Liu DJ et al. A novel long non-coding RNA ENST00000480739 suppresses tumour cell invasion by regulating OS-9 and HIF-1α in pancreatic ductal adenocarcinoma. British Journal of Cancer 2014; 111 (11): 2131-2141. https://doi.org/10.1038/bjc.2014.520

58. Yalçınkaya B, Güzel Tanoğlu E, Taştekin D, Pençe S. Role of mir-33a, mir-203b, mir-361-3p, and mir-424 in hepatocellular carcinoma. Turkish Journal of Medical Sciences 2021; 51 (2): 638-643. https://doi.org/10.3906/sag-2004-214

59. Guzel E, Karatas OF, Semercioz A, Ekici S, Aykan S et al. Identification of microRNAs differentially expressed in prostatic secretions of patients with prostate cancer. International Journal Cancer 2015; 136 (4): 875-879. https://doi.org/10.1002/ijc.29054

60. Guzel Tanoglu E, Arıkan Y, Kabukcuoglu YS, Kabukcuoglu F, Tanoglu A et al. Mir-129-2-3p has tumor suppressor role in Ewing sarcoma cell lines and cancer tissue samples. Brazilian Archives of Biology and Technology 2021; 64: e21210306. https://doi.org/10.1590/1678-4324-2021210306

61. Sasaki N, Toyoda M, Yoshimura H, Matsuda Y, Arai T et al. H19 long non-coding RNA contributes to sphere formation and invasion through regulation of CD24 and integrin expression in pancreatic cancer cells. Oncotarget 2018; 9 (78): 34719-34734. https://doi.org/10.18632/oncotarget.26176

62. Deng SJ, Chen HY, Ye Z, Deng SC, Zhu S et al. Hypoxia-induced LncRNA-BX111 promotes metastasis and progression of pancreatic cancer through regulating ZEB1 transcription. Oncogene 2018; 37 (44): 5811-5828. https://doi.org/10.1038/s41388-018-0382-1

63. Fu Z, Chen C, Zhou Q, Wang Y, Zhao Y et al. LncRNA HOTTIP modulates cancer stem cell properties in human pancreatic cancer by regulating HOXA9. Cancer Letters 2017; 410: 68-81. https://doi.org/10.1016/j.canlet.2017.09.019

64. Gao Y, Liu J, Cai B, Chen Q, Wang G et al. Development of epithelial-mesenchymal transition-related lncRNA signature for predicting survival and immune microenvironment in pancreatic cancer with experiment validation. Bioengineered 2021; 12 (2): 10553-10567. https://doi.org/10.1080/21655979.2021.2000197

65. Ghafouri-Fard S, Fathi M, Zhai T, Taheri M, Dong P. LncRNAs: Novel biomarkers for pancreatic cancer. Biomolecules 2021; 11 (11): 1665. https://doi.org/10.3390/biom11111665

66. Zhou J, Song G, Su M, Zhang H, Yang T et al. Long noncoding RNA CASC9 promotes pancreatic cancer progression by acting as a ceRNA of miR-497-5p to upregulate expression of CCND1. Environ Toxicol 2023;38(6):1251-1264. https://doi: 10.1002/tox.23761

67. Jiao F, Hu H, Han T, Yuan C, Wang L et al. Long noncoding RNA MALAT-1 enhances stem cell-like phenotypes in pancreatic cancer cells. International Journal of Molecular Sciences 2015; 16 (4): 6677-6693. https://doi.org/10.3390/ijms16046677

68. Li L, Chen H, Gao Y, Wang YW, Zhang GQ et al. Long noncoding RNA MALAT1 promotes aggressive pancreatic cancer proliferation and metastasis via the stimulation of autophagy. Molecular Cancer Therapeutics 2016; 15 (9): 2232-2243. https://doi.org/10.1158/1535-7163.MCT-16-0008

69. Duguang L, Jin H, Xiaowei Q, Peng X, Xiaodong W et al. The involvement of lncRNAs in the development and progression of pancreatic cancer. Cancer Biology & Therapy 2017; 18 (12): 927-936. https://doi.org/10.1080/15384047.2017.1385682

70. Kim K, Jutooru I, Chadalapaka G, Johnson G, Frank J et al. HOTAIR is a negative prognostic factor and exhibits pro-oncogenic activity in pancreatic cancer. Oncogene 2013; 32 (13): 1616-1625. https://doi.org/10.1038/onc.2012.193

71. Hu P, Shangguan J, Zhang L. Downregulation of NUF2 inhibits tumor growth and induces apoptosis by regulating lncRNA AF339813. International Journal of Clinical and Experimental Pathology 2015; 8 (3): 2638-2648.

72. Liu Y, Xu G, Li L. LncRNA GATA3-AS1-miR-30b-5p-Tex10 axis modulates tumorigenesis in pancreatic cancer. Oncology Reports 2021; 45 (5): 59. https://doi.org/10.3892/or.2021.8010

73. Gao KF, Zhao YF, Liao WJ, Xu GL, Zhang JD. CERS6-AS1 promotes cell proliferation and represses cell apoptosis in pancreatic cancer via miR-195-5p/WIPI2 axis. Kaohsiung Journal of Medical Sciences 2022; 38 (6): 542-553. https://doi.org/10.1002/kjm2.12522

74. Yin X, Yang J, Chen J, Ni R, Zhou Y et al. LncRNA CTD-3252C9.4 modulates pancreatic cancer cell survival and apoptosis through regulating IFI6 transcription. Cancer Cell International 2021; 21 (1): 433. https://doi.org/10.1186/s12935-021-02142-0

75. Cheng J, Lou Y, Jiang K. Downregulation of long non-coding RNA LINC00460 inhibits the proliferation, migration and invasion, and promotes apoptosis of pancreatic cancer cells via modulation of the miR-320b/ARF1 axis. Bioengineered 2021; 12 (1): 96-107. https://doi.org/10.1080/21655979.2020.1863035

76. Lin Z, Lu S, Xie X, Yi X, Huang H. Noncoding RNAs in drug-resistant pancreatic cancer: a review. Biomedicine Pharmacotherapy 2020; 131: 110768. https://doi.org/10.1016/j.biopha.2020.110768

77. Ma L, Wang F, Du C, Zhang Z, Guo H et al. Long non-coding RNA MEG3 functions as a tumour suppressor and has prognostic predictive value in human pancreatic cancer. Oncology Reports 2018; 39 (3): 1132-1140. https://doi.org/10.3892/or.2018.6178

78. Yin F, Zhang Q, Dong Z, Hu J, Ma Z. LncRNA HOTTIP participates in cisplatin resistance of tumor cells by regulating miR-137 expression in pancreatic cancer. OncoTargets and Therapy 2020; 13: 2689-2699. https://doi.org/10.2147/OTT.S234924

79. Xu F, Huang M, Chen Q, Niu Y, Hu Y et al. LncRNA HIF1A-AS1 promotes gemcitabine resistance of pancreatic cancer by enhancing glycolysis through modulating the AKT/YB1/HIF1α pathway. Cancer Research 2021; 81 (22): 5678-5691. https://doi.org/10.1158/0008-5472.CAN-21-0281.

80. Zhang X, Zheng S, Hu C, Li G, Lin H et al. Cancer-associated fibroblast-induced lncRNA UPK1A-AS1 confers platinum resistance in pancreatic cancer via efficient double-strand break repair. Oncogene 2022; 41 (16): 2372-2389. https://doi.org/10.1038/s41388-022-02253-6

81. Li DD, Fu ZQ, Lin Q, Zhou Y, Zhou QB et al. Linc00675 is a novel marker of short survival and recurrence in patients with pancreatic ductal adenocarcinoma. World Journal of Gastroenterology 2015; 21 (31): 9348-9357. https://doi.org/10.3748/wjg.v21.i31.9348

82. Ge JN, Yan D, Ge CL, Wei MJ. LncRNA C9orf139 can regulate the growth of pancreatic cancer by mediating the miR-663a/Sox12 axis. World Journal of Gastrointestinal Oncology 2020; 12 (11): 1272. https://doi.org/10.4251/wjgo.v12.i11.1272

83. Cai H, Yao J, An Y, Chen X, Chen W et al. LncRNA HOTAIR acts a competing endogenous RNA to control the expression of notch3 via sponging miR-613 in pancreatic cancer. Oncotarget 2017; 8 (20): 32905-32917. https://doi.org/10.18632/oncotarget.16462

84. Yilmaz SS, Guzel E, Karatas OF, Yilmaz M, Creighton CJ et al. Mir-221 as a pre- and postoperative plasma biomarker for larynx cancer patients. Laryngoscope 2015; 125: E377-E381. https://doi.org/10.1002/lary.25332

85. Knoll M, Lodish HF, Sun L. Long non-coding RNAs as regulators of the endocrine system. Nature Reviews Endocrinology 2015; 11: 151-160. https://doi.org/10.1038/nrendo.2014.229

86. Freedman JE, Miano JM; National Heart, Lung, and Blood Institute Workshop Participants. Challenges and opportunities in linking long noncoding RNAs to cardiovascular, lung, and blood diseases. Arteriosclerosis, Thrombosis, and Vascular Biology 2017; 37: 21-25. https://doi.org/10.1161/ATVBAHA.116.308513

87. Zhao Y, Teng H, Yao F, Yap S, Sun Y et al. Challenges and strategies in ascribing functions to long noncoding RNAs. Cancers (Basel) 2020; 12 (6): 1458. https://doi.org/10.3390/cancers12061458.

88. Mattick JS, Amaral PP, Carninci P, Carpenter S, Chang HY et al. Long non-coding RNAs: definitions, functions, challenges and recommendations. Nature Reviews Molecular Cell Biology 2023; 24: 430-447. https://doi.org/10.1038/s41580-022-00566-8