

Role of non-coding RNA in pancreatic cancer (Review)

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Abstract. Pancreatic cancer is a malignant disease that develops rapidly and carries a poor prognosis. Currently, surgery is the only radical treatment. Non-coding RNAs (ncRNAs) are protein-free RNAs produced by genome transcription; they play important roles in regulating gene expression, participating in epigenetic modification, cell proliferation, differentiation and reproduction. ncRNAs also play key roles in the development of cancer; microRNA (miRNA) and long non-coding RNA (lncRNA) may lead the way to new treatments for pancreatic cancer. miRNAs are short-chain ncRNAs (19-24 nt) that inhibit the degradation of protein translation or their target gene mRNAs to regulate gene expression. lncRNAs contain >200 nt of ncRNA and play important regulatory roles in a number of malignant tumors, in terms of tumor cell proliferation, apoptosis, invasion and distant metastasis. lncRNAs can be exploited for the diagnosis and treatment of pancreatic cancer and have substantial prospects for clinical application. Nevertheless, the molecular mechanism of their regulation and function, as well as the significance of other ncRNAs, such as piwi-interacting RNA, in the pathogenesis of pancreatic cancer, are largely unknown. In this review, the structures of ncRNAs with various classifications, as well as the functions and important roles of ncRNAs in the diagnosis and treatment of pancreatic cancer are reviewed.

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1. Introduction

Non-coding RNAs (ncRNAs) are protein-free RNAs produced by genome transcription. There are 20,000-25,000 genes encoded in the human genome, of which 40-90% are estimated to be regulated by miRNA (1). A variety of RNAs, including microRNAs (miRNAs/miRs) and long non-coding RNAs (lncRNAs), regulate gene expression at the transcription, post-transcription and epigenetic levels. Research has shown that ncRNA inhibits the translation activity of mRNA, regulates the expression of specific target genes, and ultimately regulates biological signaling pathways and manipulates cell fates (2,3). In recent years, substantial progress has been made in basic research regarding the underlying disease mechanisms, using model organisms and new experimental systems. For example, mir-21 was shown to promote cell migration and invasion, and play a key role in cancer cell infiltration and remote metastasis. These studies have provided evidence that ncRNAs play important roles in the development and progression of pancreatic cancer (1,4).

Pancreatic cancer ranks 4th in the world among all malignant tumors, with high invasiveness, early metastasis, lack of specific symptoms and high mortality. The median survival time is only 3-6 months, with a 5-year survival rate of <5%. In China, the incidence of pancreatic cancer has increased 6-fold in the past 20 years (5). In 2012, the incidence of pancreatic cancer was 4.8/100,000, ranking 7th among all malignant tumors. Even when early diagnosed, small pancreatic cancer (<2 cm in diameter) can easily metastasize and lead quickly to the death of the patient. Surgical resection remains the only treatment for radical treatment. Nevertheless, only 15-20% of pancreatic cancer patients are suitable for surgical treatment (1,6,7). Even with multidisciplinary comprehensive treatment, the median survival time of patients with advanced pancreatic cancer is only ~6 months. Furthermore, early postoperative recurrence and occult metastasis also reduce the efficacy of surgical treatment. Even after systemic therapy, liver metastasis occurs in 50% of patients. However, the main reasons for the high mortality rates of pancreatic cancer are the failure of an early diagnosis, before it moves to other organs, and the resistance of the cancer to existing therapies (8).

In recent years, with the development of molecular biology, especially gene sequencing technology, the mechanism

of action of lncRNAs in various types of cancer has been gradually revealed, and the study of ncRNAs has been significantly augmented for various types of cancer. In the case of pancreatic cancer, various lncRNAs are involved in the biological behavior and signal pathways of metastatic pancreatic cancer, including the cell cycle, apoptosis, autophagy, epithelial-mesenchymal transition (EMT) and cancer stem cells (CSCs) (6,9). The present review focuses on the characteristics and biological roles of several ncRNAs, with particular emphasis on their role in pancreatic cancer (Table I).

2. miRNA

miRNA is the most characteristic ncRNA; it is a short sequence of RNA with a length of ~22 nt. miRNA expression is related to the type of tumor, as well as its occurrence and development (10). Therefore, miRNA, as a potential tumor marker, has been the focus of clinical research. As miRNA binds mRNA through incomplete pairing, thereby inhibiting translation, the same miRNA can simultaneously regulate several target genes and signaling pathways (11). Furthermore, miRNAs are also conservative, testable and can exist stably outside cells. Therefore, they have become diagnostic markers and therapeutic targets of tumors (8).

miRNAs are usually produced as primary transcripts for RNA polymerase 2 transcription, known as pri-miRNAs. Recent studies have shown that miRNAs can act as intermediates, regulating a large part of human gene transcription (12). At present, feedback loops are widely known to exist between miRNAs and basic transcription factors (TFs). Although there are numerous differences between them, TFs positively or negatively regulate the expression of miRNA, while miRNAs inhibit the translation of TF-miRNA (13). Studies have shown that, after transfection of let-7 into pancreatic cancer cells, the proliferation capacity of the transfected cells is significantly inhibited, presumably related to the effect of miRNA on the expression of the k-ras gene and the activation of mitogen-activated protein kinase (8,14).

There are various ways in which miRNAs alter the levels of gene expression. In particular, they typically bind to the mRNA 3'UTR. Genomic DNA is transcribed into mRNA, and mRNA has 5'UTR and 3'UTR structures. miRNA binds to the mRNA 3'UTR, and then alters the translation process after mRNA, thereby affecting the expression results of the particular gene (Fig. 1) (15-18).

Generation of model organisms and their use in miRNA functional studies. Despite the fact that *Caenorhabditis elegans* do not develop cancer, they have been widely used as model organisms to identify molecular functions and to describe pathways involved in normal cellular processes that are severely impaired in cancer, including cell proliferation, differentiation, metabolism and death (19). Full sequencing of *C. elegans* genomes showed that ~60% of miRNAs have a human homologous gene. As the number of conserved miRNAs in the miRNA family of *C. elegans* decreased, the study of miRNA function in *C. elegans* eliminated redundancy as a barrier to be overcome. Moreover, *C. elegans* are self-fertilized hermaphrodites that can produce large numbers of genetically identical offspring (19,20). The visual tracking

of *C. elegans*, with a well-organized transparent body, makes for an excellent model system. Phenotypic and genetic screening, the application of molecular techniques, and the development of transgenic *C. elegans* have identified a number of key miRNAs, and have elucidated their mechanisms of action. Research on *C. elegans* has also contributed to the understanding of the molecular basis of the miRNA biological genome. For example, Dicer *C. elegans* ortholog gene, dcr-1, involved in RNA-mediated silencing, has been identified as a key component necessary for the processing of mature let-7 from its precursor molecule (19,21).

The zebrafish is a model system that plays an important role in elucidating the functional role of miRNA in both normal and cancer cells. Since let-7 was identified during *in silico* prediction as a cross-species conserved miRNA, the other miRNAs, initially found in zebrafish, have considerable homology with the miRNAs encoded by humans and other vertebrates, in terms of composition and function (20,21). Thanks to a complete angiogenesis and immune system, as well as a developed organ system, human cancer cells were successfully transplanted into zebrafish embryos, enabling the tumor to grow in the host microenvironment. Therefore, the zebrafish was also shown to be a successful model system for assessing tumor response to anticancer therapy *in vivo*. In summary, despite the fact that the zebrafish is a simple model system, the striking properties of *D. rerio* permit the use of this organism to better understand the effects of aberrant changes in endogenous levels of certain miRNAs (21,22). The zebrafish has been proven to be a successful model system, leading to the recognition of several miRNAs through basic biochemical and molecular studies, and has great potential as a model to identify clinically relevant miRNAs.

Previous studies used mir-520d-5p to confirm its possible therapeutic effect on cancer cells (23,24). The size and signal intensity of green fluorescent protein (GFP)-expressing tumors was measured in mice weekly, for 4 weeks after subcutaneous inoculation. It was found that, compared with the control group, 520d treatment, which consisted of introducing exogenous gene 520d into mice, inhibited tumor growth by >80% per week, resulting in the disappearance of ~30% of the tumors. In mice with tumor disappearance, the presence of human genomic material at the injection site was quantitatively detected by alu-PCR, confirming the coexistence of the two cell sources. GFP was expressed in connective tissue at each site where the immune-deficient mouse tumors disappeared, and ~0.1% of the extracted DNA contained human genomic material.

miRNAs can be divided into two forms, namely those with high and low expression in pancreatic cancer cells, similar to proto-oncogenes and tumor suppressor genes. These two factors have wide influence on biological pathways, and their abnormal regulation is an important factor leading to the development of pancreatic cancer (25).

Oncogenic miRNAs. Researchers detected 95 miRNAs with abnormal expression in pancreatic cancer using RT-PCR. Among these, mir-196a, mir-190, mir-186, mir-221, mir-222, mir-200b, mir-15b and mir-95 were significantly upregulated, while let-7, mir-96, mir-15 and mir-132 were significantly downregulated (2). Studies reported that mir-217

Table I. Specific types and functions of different ncRNAs and their association with pancreatic cancer.

First author (year)	Type of RNAs	Length, nt	Function	(Refs.)
Fu (2017), Gao (2018) Gao (2018)	Small nucleolar RNAs	70-200	Involved in maturation of other ncRNAs	(6,7,59)
Fu (2017), Gao (2018)	Small nuclear RNAs	100-215	Binding to proteins to form splicers that control selective splicing	(6,59)
Gu (2017)	Small interfering RNAs	21-22	Silencing specific genes in a sequence-specific manner	(60)
Gao (2018), Gu (2017)	Small ncRNAs	<200	Carrying amino acids that bind to the ribosome	(59,60)
Peng (2016)	lncRNAs	>200	Component of ribosomes	(61)
Peng (2016), Peng (2016)	Ribosomal 28S and 18SRNA	200-5,050	Component of ribosomes	(2,61)
Vorvis (2016), Wang (2017)	Piwi-interacting RNA	25-34	Controlling retro transposition and regulating methylation	(3,71)
Xiong (2017), Zhang (2017)	Promoter-associated short RNAs	<200	Regulating gene expression through interaction with gene promoter sites	(11,63)
Zhou (2017)	Long intergenic ncRNAs or long intronic ncRNAs	>200	Various	(68)
Zhou (2017)	Antisense RNA	>200	Binding and blocking of mRNA target genes	(68)
Zhou (2017), Zhang (2017)	Promoter-associated short RNAs	>200	Regulating gene expression through interaction with gene promoter sites	(31,85)
Zhang (2017)	Telomere-associated ncRNAs	100 bp >9 kb	Negative telomere regulators	(79)
Zhang (2017), Zhang (2017)	Transcribed ultra-conserved regions	200-799	Long-range enhancer-like activity, maintenance of splicing factor expression levels and transcription regulation	(79,85)

ncRNAs, non-coding RNAs; lncRNAs, long ncRNAs.

and mir-148a/b were downregulated in pancreatic cancer cells, mir-155 and mir-21 were found to be highly expressed in breast cancer and they may also be used as landmarks of pancreatic cancer (10,18). Previous studies analyzed tumors, including those of the lung, stomach, prostate, rectum and pancreas, and found that mir-17-5p, mir-20a, mir-21, mir-92, mir-106a and mir-155 were all highly expressed in tumor cells (10,18). Of these, mir-20a was highly sensitive and specific, and could be used as a marker for differentiating various stages of pancreatic cancer from paracarcinoma tissue and chronic pancreatitis. Previous studies compared the plasma levels of 50 pancreatic cancer patients and 10 healthy patients, and found that 37 types of miRNA were decreased and 54 types of miRNA were increased (2,26,27). Among these miRNAs, mir-21 is an oncogene. Therefore, it is thought that the high expression of mir-21 can be used as an indicator of poor survival in pancreatic cancer patients, as well as a prognostic marker. Additionally, the miRNA expression profile, including mir-99, mir-100 and mir-100-1/2, varied in pancreatic cancer tissues, adjacent and chronic pancreatitis tissues (CP) (27,28). mir-199a-1 and mir-199a-2 were relatively highly expressed in pancreatic cancer and CP, possibly indicating that they stimulate the growth of neoplasms. This could be caused by the

interference of inflammatory factors. The study also found that mir-196a-2 was significantly correlated with patient survival. Other studies found that miRNA precursors with increased expression were mir-22-1, -424, -301, -100, -376a, -125b-1, -021, -016-1, -181a, c, -092-1, -092-1, -212, -107, -024-1, 2, let-7f-1, let-7d, mir-345, -142-p, -139 (14,29). These results were similar to those of Volinia (30). Volinia (30) and Zhou *et al* (31) used endpoint immuno PCR to detect the expression of mir-196a in normal pancreatic cells, pancreatic duct epithelial neoplasms (PanIN, precancerous) cells and pancreatic cancer cells. It was found that, in normal pancreatic cells, mir-196a expression was not present; however, PanIN and all tumor cells showed positive expression of miR-196a, suggesting that mir-196a might indicate the carcinogenic transformation process of pancreatic cells. Volinia (30) and Yu *et al* (29) compared the differences in expression of miRNAs in the peripheral blood of ovarian cancer patients and normal individuals, and found that mir-21, -92, -93, -126 and -29a were highly expressed in ovarian cancer. Xiong *et al* (11) and Yan *et al* (32) found that mir-184 was highly expressed in the peripheral blood of tongue squamous cell carcinoma. Yan *et al* (33) found that mir-92 was highly expressed in the peripheral blood of rectal cancer patients.

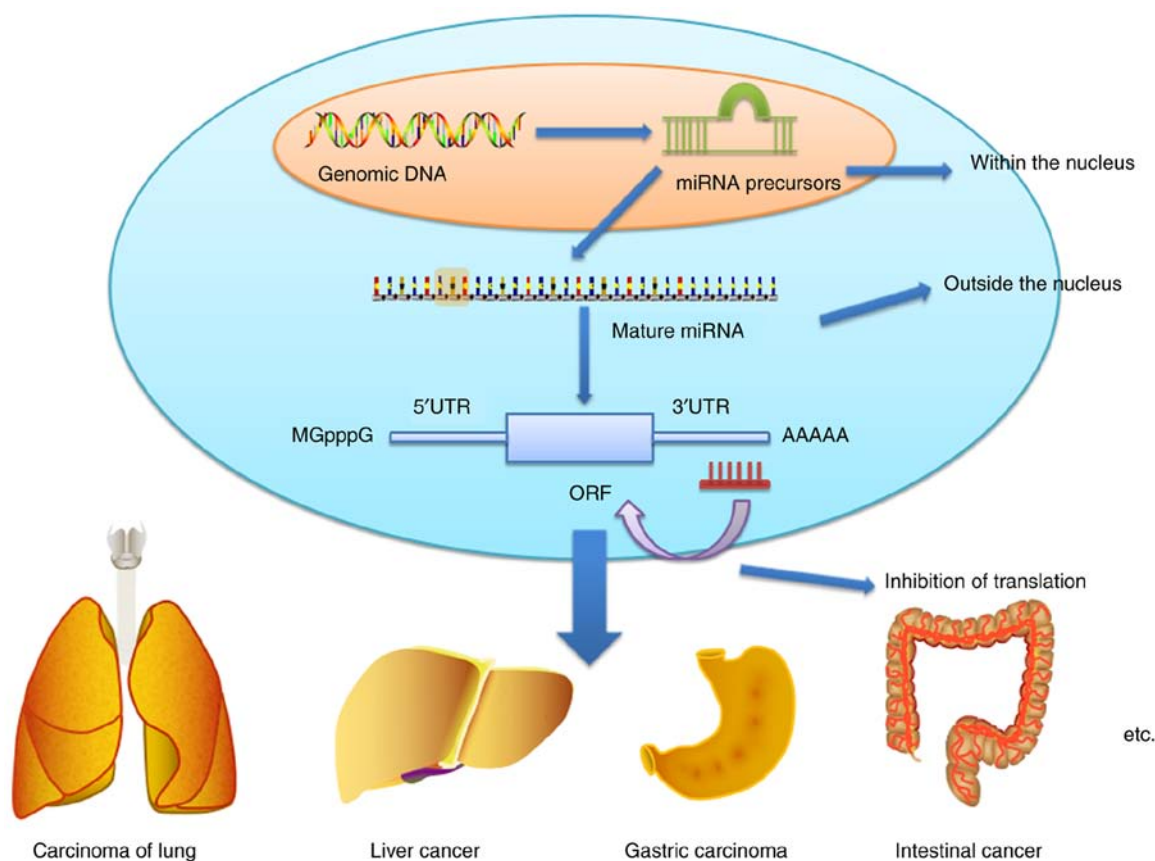


Figure 1. Mechanism by which miRNA alters gene expression, via inhibition of translation of mRNA by binding the 3'UTR. miRNA, microRNA.

Tumor suppressor gene-related miRNAs. As opposed to proto-oncogenes, some miRNAs are less well expressed in pancreatic tissue than in normal pancreatic tissue; they inhibit the development of pancreatic cancer by negatively regulating the cell cycle and proliferation. The decreased levels of mature miRNAs may be caused by defects in any step of miRNA biosynthesis, eventually leading to the expression of inappropriate miRNA target proteins. Wang *et al* (34) found that the expression of two miRNAs, mir-15a and mir-16a, was downregulated or missing in most patients with chronic lymphocytic leukemia (CLL). Sun *et al* (27) and Vassaux *et al* (35) found that the expression of mir-127 in some human primary tumors was downregulated or missing, while it was normal in normal cells; therefore, mir-127 was hypothesized to be a potential tumor suppressor gene. Recently, a study reported that mir-615-5p was significantly downregulated in pancreatic cancer compared with its expression in normal adjacent tissues, and that it inhibited proliferation, migration and invasion of pancreatic cancer cells by targeting AKT2 (36). The let-7 family miRNAs are also well known among all types of miRNA. mir-1181 was found to have low expression in the middle of pancreatic cancer, and it was shown to directly inhibit the expression of sox2 and stat3 (37). mir193-b is a tumor suppressor gene that demonstrates interaction inhibition with MillHG (38,39). mir-193b negatively regulates mir31HG by directly targeting two miRNA binding sites in the MillHG sequence and inhibits proliferation of pancreatic cancer cells, while mir31HG can be used as an endogenous 'sponge' to reduce its anticancer effect (10,40).

Studies on miRNAs in the treatment of pancreatic cancer have been ongoing. The Panpane-1, LPc111 and LPc006 cell lines of pancreatic cancer showed increased tolerance to gemcitabine when they were transfected with precursor mir-21; apoptosis levels decreased or proliferation levels increased. By contrast, mir-21 expression in the suit-2 pancreatic cancer cell line was inhibited; apoptosis levels increased and proliferation activity decreased (41). Li *et al* (42) and Hancock and Skalsky (43) showed that mir-21 can be used as an indicator of resistance of pancreatic cancer cells in the Hengtian region. Pancreatic cancer cell lines with low expression of mir-21 are highly sensitive to fluorouracil. Li *et al* (18) and Hancock and Skalsky (43) screened and verified pancreatic cancer tissues and two types of pancreatic cancer cell lines that were resistant to gemcitabine using miRNA microarray. It was found that cells with high expression of mir-142-5p and mir-204 had significantly increased tolerance to gemcitabine. It was proposed that the expression levels of mir-142-5p can be thought of as indicators of resistance of pancreatic cancer cells to gemcitabine.

DNA methylation is a form of DNA chemical modification that alters the genetic expression without changing the DNA sequence, causing changes in chromatin structure, DNA conformation, DNA stability and the way DNA interacts with proteins, thereby controlling gene expression. DNA methylation has a definite effect on cell carcinogenesis in various ways. A methyl group attaches to the DNA region near the tumor suppressor gene, inhibits the activity of the gene, and effectively 'silences' the gene. Recently, researchers focused

on a class of ncRNAs that specifically affect CCAAT enhancer binding protein α (CEBPA), a tumor suppressor gene (44,45). CEBPA silencing is associated with acute myeloid leukemia, lung and pancreatic cancer, as well as other types of cancer. ncRNA binds DNA methyltransferase 1 to prevent methylation of CEBPA. This principle, which is likely to be applied to thousands of other genes, holds promise for 'reactivating' downregulated cancer suppressors. Researchers (46) found that the newly-discovered ncRNA specifically inhibits DNA methylation, and the introduction of RNA selectively demethylates certain genes, thereby initiating the expression of tumor suppressors. This mechanism is expected to be exploited in the treatment of a variety of diseases, including cancer (Fig. 2) (1,8,46).

miRNA-301. mir-301 is highly expressed only in pancreatic cancer, suggesting that mir-301 may be a molecular marker of specificity in pancreatic cancer. Studies have shown that mir-301 is highly expressed in genes related to the invasion and metastasis of pancreatic cancer, including cox-2 and mmp-2. mir-301 is closely related to the invasion and metastasis of pancreatic cancer (47). mir-301 inhibitors effectively suppress the expression of the invasion- and metastasis-related genes cox-2 and mmp-2, and significantly inhibit the invasion and metastasis of pancreatic cancer cells, suggesting that mir-301 is effective (10,12). mir-301 may be a new molecular target for the therapy of pancreatic cancer. The establishment of effective detection methods and targeted treatment strategies for mir-301 will provide important theoretical and experimental bases for the early diagnosis, treatment option selection, efficacy evaluation and prognosis in pancreatic cancer (47).

miRNA-20a. miRNA-20a was shown to be expressed at low levels in pancreatic tissue and cell lines. The expression of the miRNA inhibits the growth and invasion of pancreatic cancer cell lines, and its role in pancreatic cancer is achieved through the negative regulation of oncogenes Stat3 and cyclin D1 (48). Studies have reported that miRNA-20a directly inhibits E2F TF1 (E2F1) and regulates the cell cycle. The miRNA also plays the role of an oncogene as it is overexpressed in a number of malignant tumors, including lung cancer and B-cell lymphoma. The mechanism involved may be the downregulation of Stat3 and cyclin D1 expression by miRNA-20a (16,49).

mir-200 family. Peng *et al* (2) and Qian *et al* (38) found that the expression of the mir-200 family is downregulated or is missing in the course of EMT. The results were related to EMT, and it was reported that EMT is closely related to the relatively low survival rate after surgical resection of pancreatic duct cell carcinoma. Studies found that the gemcitabine resistance of pancreatic cancer cells was associated with the lower expression of mir-200 and let-7 in these cells. The epithelial phenotype was restored by transfection of mir-200 with generate gemcitabine resistant cells; therefore, the epithelial marker E-calcium mucins was increased, and the leaf-cutting marker E-box zinc-finger protein was combined with vimentin to inhibit EMT and invasion of tumor cells (27,50).

Therapeutic application of miRNAs. miRNA can be involved in treatment in two ways, namely the reduction and replacement

of miRNA. Downregulation of miRNA is targeted at the acquisition of functions, and oncogenic miRNA can be inhibited in the following ways: i) Small molecule inhibitors act on the regulation of miRNA expression at the transcriptional level; ii) antisense oligonucleotides bind to complementary miRNAs, inducing duplex formation or miRNA degradation; iii) miRNA masking uses molecules complementary to the 3'UTR of the target miRNA to competitively inhibit downstream target effects; and iv) miRNA sponge, constructed by oligonucleotide with multiple complementary miRNA binding sites, binds to target miRNA (51,52). The second strategy, miRNA substitution, is targeted at functional loss, including the restoration of functional loss by introducing systemic miRNA (miRNA mimics) or inserting miRNA-coding genes into viral construction, and reintroducing tumor suppressor miRNA (51,53). Despite the promise of both approaches, two major problems have, thus far, hampered the development and effectiveness of miRNA-based therapies. The first is that it is necessary to obtain tissue-specific delivery and develop more efficient cellular uptake of synthetic oligonucleotides to achieve constant target inhibition. The second important problem is the relatively low efficiency of miRNAs in body fluids or tissues, seeking to restore lost function or block tumor-enhanced miRNAs, which have been partially overcome by the construction of locked nucleic acids (LNA). The most successful use of the so-called 'LNA anti-miRs' resulted in the first miRNA-based clinical trial for the treatment of hepatitis C virus infection, which used lna-anti-mir to target mir-122 (54,55).

Chemotherapy is an important treatment strategy for most pancreatic cancer patients. Chen Q and Hong L reported the results of a phase III clinical trial that directly compared gemcitabine with 5-FU and showed that gemcitabine significantly improved the median survival time. Soon thereafter, gemcitabine became the first-line and gold-standard chemotherapy for pancreatic cancer (51,54). Nevertheless, drug resistance to gemcitabine and other drugs may lead to treatment failure. Despite the fact that research in drug resistance has been ongoing, the mechanism of its occurrence has not been fully explained. The three most common reasons for acquiring drug resistance are the expression of energy-demanding transporters, insensitivity to drug-induced apoptosis and drug detoxification-induced mechanisms (53,55). In one study, oncogenic mir-155 levels were shown to increase after gemcitabine was used for the treatment of pancreatic cancer cells. mir-200a, mir-200b and mir-200c were downregulated in gemcitabine-resistant pancreatic cancer cells (55). A recent report showed that mir-34 was involved in the self-renewal of pancreatic CSCs, and the deletion of mir-34 in pancreatic cancer was related to the enrichment of CSCs, which are not sensitive to chemotherapy (52,56). There is also evidence that miRNAs may regulate EMT by regulating cadherin-1 and other molecules, mediating various cell resistance mechanisms (54,56). When studying the expression levels of mir-200 and let-7 in gemcitabine-resistant pancreatic cancer cells with the EMT phenotype, the downregulated expression of mir-200 family upregulated cadherin-1 and downregulated ZeB1 and vimentin (EMT inducer). Downregulation of ZeB1 in mesenchymal Panc1 cells led to upregulation of mir-200c (56).

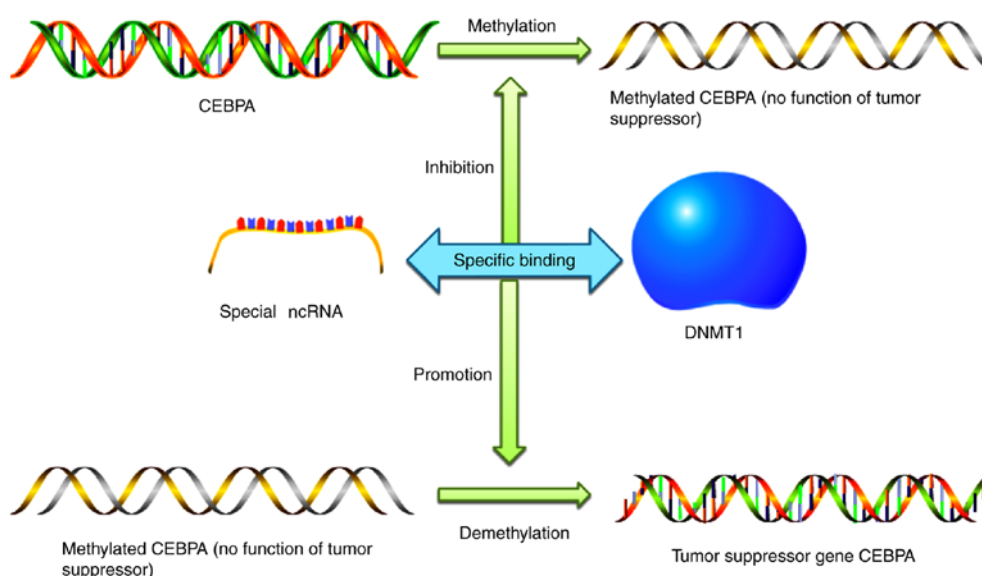


Figure 2. ncRNA influences the methylation of DNA by binding DNMT1, thereby inhibiting the inactivation of tumor suppressor gene CEBPA. ncRNA, non-coding RNA; DNMT1, DNA methyltransferase 1; CEBPA, CCAAT enhancer binding protein α .

Therefore, by targeting CSCs or EMT phenotype cells that lead to tumor recurrence and metastasis, the re-expression of specific miRNAs can be used as a new strategy for the treatment of pancreatic cancer.

3. piRNA

piRNA research began more recently. piRNAs are ncRNAs of 24-30 nt in length. piRNAs rely on the piwi protein group that inhibits the expression of transposable elements in two ways by forming a complex with piwi. At present, there are two proposed pathways for generating piRNAs, namely a primary processing pathway and a 'ping-pong' amplification loop. Similar to miRNA, the 5'-end also has a strong uracil bias (57,58). A previous study has shown that piRNA exists in mammalian germ cells, and regulates the gene silencing pathway by binding with the piwi subfamily proteins to form piRNA complexes (2). The discovery of piRNA opens a new field for the study of non-coding small molecular RNAs. To date, piRNA research has achieved interim results. However, it is too early to predict their use in biomedicine (2,58). At present, piRNA regulates mRNA primarily via two mechanisms: Degradation and shear. CAF1 mRNA in miRNA regulation has a very important role in degradation. Studies in mouse CAF1 by Andersen *et al* (57) demonstrated its combination with piRNA/piwi complexes. This complex process recognizes the target mRNA after removal of adenosine piRNA, eventually causing mRNA degradation. Repoila *et al* (47) reported the piRNA/piwi-mediated shear mechanism of mRNA. There remain numerous problems that require further discussion (44,58). For example, the homologous conservation of piRNA sequences in various species is not easy to analyze. In piRNA panspermia, it remains unknown how the division mechanisms of the 3'-end and the piRNA amplification cycle are regulated. piRNA research not only enriches the research content of small molecular RNA, but also helps further the understanding of molecular regulation and mechanisms of

biological gametes with substantial theoretical value (57). There are three members of the piwi subfamily, namely MIWI, MILI and MIWI2, which are specific proteins in germ cells and closely related to the occurrence of sperm. Knockout of MIWI, MILI or MIWI2 resulted in sperm production disorders in male mice (58). MILI was expressed during early spermatogenesis, from mitosis of spermatocytes to the pachytene stage of spermatocytes, and the MILI deficient mice stopped at pachytene stage. MIWI is expressed later, from pachytene to spermatogenesis. Knockout of MIWI causes spermatogenesis to stop at spermatogenesis. However, mice with knockout MIWI2 had defects in meiosis progression at early meiosis stage and significant loss of germ cells with age (57).

piRNA forms a complex with piwi protein that is involved in the regulation of target sequences. Piwi is also detected in cancer cells. There are four piwi proteins in humans: PIWIL1/HIWI, PIWIL2/HILI, PIWIL3 and PIWIL4/HIWI2, and there are specific types of piwi proteins in various cancers (57). Piwi proteins play four major roles in cancer cells: The promotion of cell proliferation, the inhibition of apoptosis, the enhancement cell migration and the maintenance of genomic stability. Cancer cells have unlimited ability to proliferate and migrate, and they also have the ability to escape apoptosis and divide continuously (57,58). In order to maintain this ability, the relative stability of their genome structure must be ensured. Although piwi protein was found in cancer cells, piRNA that binds to piwi protein was not found, suggesting that a number of unknown functions of the piwi and piRNA complex remain undiscovered.

4. lncRNA

lncRNA is a long-chain ncRNA of >200 nt. Studies have shown that abnormal expression of lncRNA is closely related to the development of various tumors and can show the function of oncogenes and tumor suppressor genes (59,60).

According to the currently known lncRNAs, the following functions can be summarized as follows: i) Some lncRNAs bind epigenetic-related proteins after transcription, modifying specific sequences, activating or inhibiting the activity of chromatin-related regions, and regulating cell activities, such as X-chromosome inactivation; ii) lncRNAs inhibit or promote gene transcription via base pairing and recruitment of TFs; iii) lncRNA are precursors to the formation of miRNAs and regulate the network regulation of miRNA by mediating the generation of miRNAs; and iv) lncRNAs participate in the formation of nuclear sub-structures by regulating related genes (5,9). Furthermore, lncRNAs can be involved in gene network regulation in three ways: i) In the transcriptional level: When lncRNA itself is transcribed, wherein it interferes with the transcription of adjacent genes, and where it can be used as an endogenous competitive RNA to control myoblast differentiation; ii) in the post-transcriptional level: By interacting with miRNA, lncRNA affects post-transcriptional translation of related mRNA, thereby promoting the malignant transformation and proliferation of cells; and iii) in the epigenetic level: lncRNA regulates histone modification to silence expression of adjacent genes, also affecting chromosome reconstruction to promote tumor invasion and metastasis (42). Nevertheless, the mechanism of action of lncRNA on tumorigenesis and development remains in its infancy. Further research and elaboration of the mechanism of action of lncRNA will provide new approaches to tumor diagnosis, treatment and prognosis.

In terms of structure, lncRNAs usually have the same structure as mRNAs, including 5'-caps and 3'-polyadenylated tails, and they are spliced to form the final product. Despite the fact that lncRNAs are poorly sequentially conserved, some studies suggest that their functions may be relatively conserved (3,61). Furthermore, genes are usually located very close to lncRNA in the genome, and according to the proximity of their protein-coding genes, lncRNA can be divided into five categories: i) Antisense lncRNA; ii) intronic transcript lncRNA; iii) large intergenic lncRNA; iv) promoter-associated lncRNA; and v) UTR-associated lncRNA (42,61). Similar to miRNA, lncRNA plays both carcinogenic and anti-oncogene roles in terms of occurrence, development and metastasis of various tumors. While similarities between lncRNA and miRNA exist, they are usually highly diverse in structure and function. HOTAIR was the first lncRNA shown to regulate gene expression in the form of reverse transcription, as identified by Vorvis *et al* (3) lncRNA HOTAIR showed higher expression in pancreatic cancer with peripheral tissue infiltration and lymph node metastasis (29,62). Survival analysis of pancreatic cancer patients showed that patients with low expression of lncRNA HOTAIR had a significantly longer survival time than those with high expression, which is of great significance in predicting prognosis (62).

Oncogenic lncRNA. To date, a partial oncogenic lncRNA has been identified. Zhang *et al* (63) used gene chip technology and found that ZEB1 antisense RNA 1 (zebl-as1) was upregulated in liver cancer tissues, especially in metastatic tumor tissues. zebl-as1 overexpression was associated with abnormal DNA methylation. Yan *et al* (33) and Volinia *et al* (64) found that colorectal cancer-associated lncRNA showed high expression in colorectal cancer tissues. A recent study showed that

repulsive guidance molecule B as1 (rgmb-as1), upregulated in non-small cell lung cancer, was associated with the degree of tumor differentiation, lymph node metastasis and clinical stage, and was negatively correlated with RGMB (25). As a pro-apoptotic factor, GDF15 inhibits the proliferation of cancer cells, and HOTAIR binding with the GDF15 gene region weakens its anticancer effect in pancreatic cancer tissues.

Tumor suppressor gene-related lncRNA. In contrast to oncogenic lncRNA, some lncRNAs have been shown to act as tumor suppressors. Ferreira and Esteller (16) and He *et al* (36) found that the expression of cell adhesion molecule as1 (cadm1-as1) was downregulated in renal clear cell carcinoma, and that interfering with the expression of cadm1-as1 promoted the growth and migration of tumor cells, and reduced the apoptosis rate. Some researchers found that the low expression of taurine upregulated gene 1 (TUG1) was related to high-level TNM stage, large tumor size and lower overall survival in patients with non-small cell lung cancer. The inhibition of TUG1 expression significantly promoted the proliferation of tumor cells and tissues (40,65). One study found that overexpression of tscl1-as1 induced upregulation of TSLC1 and inhibited proliferation, migration and invasion of tumor cells. The expression of tscl1-as1 was positively correlated with other tumor suppressor genes, including neurofibromatosis type 1, von Hippel-Lindau tumor suppressor and phosphoinositide-3-kinase regulatory subunit 1, while it was negatively correlated with the oncogene B-Raf proto-oncogene serine/threonine kinase. In an *in vitro* study, Li *et al* (42) and Yu *et al* (29) found that the overexpression of growth arrest-specific 5 (GAS5) significantly inhibited the proliferation and invasion of PANC1 and bxp-3 cell lines. After inhibition of GAS5 expression by RNA interference, GAS5 was arrested in the G₀/G₁ stage. The proportion of cells in the stage decreased, and more cells were in the S stage, suggesting that GAS5 regulates the cell cycle of pancreatic cancer cells and inhibits the invasion of cancer cells (66,67).

Bc-819 is a plasmid vector capable of expressing diphtheria toxin A chain under the regulation of H19, which has antitumor effects. Bc-819 was initially used in the treatment of bladder cancer. In human trials, after ingestion, it expresses a large amount of diphtheria toxin in cells, causing tumor volume reduction. With the extensive development of clinical trials, the effective concentration and dose of bc-819 have been further determined (33,64). On this basis, Zhang *et al* (63) and Zhou *et al* (68) used gemcitabine, a first-line chemotherapy drug for pancreatic cancer, in combination with bc-819 in an animal model of pancreatic cancer, and achieved good efficacy. Pvt1 oncogene (PVT1) is directly related to the sensitivity of pancreatic cancer to gemcitabine. In the human pancreatic cancer aspc-1 cell line, decreased PVT1 activity improved the sensitivity to gemcitabine. When Kim *et al* (69) conducted high-throughput sequencing for pancreatic cancer, it was found that homeobox A distal transcript antisense RNA (HOTTIP) increased the expression in pancreatic cancer and was involved in the development of resistance to gemcitabine through HOXA13. Tseng *et al* (50) found that PVT1 in the aspc-1 cell line regulated the sensitivity of cells to gemcitabine, and showed that the overexpression of full-length PVT1 positive-sense cDNA increased the sensitivity of cells to

gemcitabine. Meller *et al* (40) confirmed that malat-1 reduces the sensitivity of aspc-1 and cfpac-1 cell lines to gemcitabine chemotherapy.

lncRNA mir31HG. lncRNA mir31HG is one of the lncRNA molecules with the most significant differential expression, primarily located in the cytoplasm. Recent studies have shown that mir-31 is located in the intron region of mir31HG, and the transcription of mir-31 is regulated by mir31HG. Both miR-31 and mir31HG were found to be significantly positively correlated in pancreatic cancer tissues, while the expression of mir31HG was not changed with the decrease of mir-31 level, suggesting that both may exert their respective roles independently (33,64). mir-31 expression did not change at low concentrations of mir31HG, and the inhibition or expression of mir-31 did not affect the expression of mir31HG. At the transcriptional level, mir31HG and mir-31 did not regulate the expression of each other, and their biological functions were independent. The pancreatic cancer gene function of mir31HG acted by promoting the proliferation, migration and invasion of pancreatic cancer cells (34,64). Another study suggested that the low expression of mir-193b in pancreatic cancer has a significant negative correlation with the expression of mir31HG (70). mir-193b was found to negatively regulate the expression and function of mir31HG by directly targeting mir31HG.

Maternally expressed 3 (MEG3). MEG3 is an imprinted gene expressed by the mother, located in the positive q32 region of chromosome 14, and its transcription product MEG3 is a 1,595-bp long RNA molecule. Another study found that tumor protein p53 and growth differentiation factor 15 play important roles in the regulation of MEG3 (71). There are two differentially methylated regions (DMRs) upstream of the MEG3 gene: IG-DMR and meg3-dmr. Previous studies found that these two DMRs may be the control centers of gene expression for the entire dlk1-meg3 unit (61,71). Zhang *et al* (63) found that the meg3-dmr was fully methylated in a neuroblastoma cell line. The ultimate effect was an increase in the methylation level of the MEG3 gene promoter, which was also the direct cause of MEG3 inactivation. Zhang *et al* (63) and Peng and Jiang (61) found that the expression of MEG3 in pancreatic cancer was negatively correlated with the clinicopathological features of the tumor. MEG3 overexpression inhibited pancreatic cancer activity by regulating the PI3K/AKT/bcl-2/BAX/cyclin D1/p53 and PI3K/AKT/mmp-2/mmp-9 signaling pathways. AKT, bcl-2 cell cycle protein and D1 are found in normal tissues and inhibit pyruvate dehydrogenase kinase during cell division to promote the expression of p53 and BAX. They inhibit the invasion and migration of the pancreatic cancer PANC1 cell line by inhibiting the expression of mmp-2 and mmp-9 (39,72).

H19 imprinted maternally expressed transcript (H19). H19 plays an oncogenic role by antagonizing hmga2-mediated EMT through antagonizing the anti-oncogene let-7, which is primarily located in the cytoplasm and has a high expression level during embryonic development, while it is strongly suppressed after birth (70). As the first exon of H19 transcription, mir-675 is negatively correlated with the expression level of H19. As a key TF, E2F-1 is positively correlated with the

expression levels of H19, and E2F-1 is a direct target of miR675. mir-675 reduces H19 activation by affecting the expression of E2F-1 protein by binding to the 3'UTR on E2F-1 mRNA (73). Furthermore, some studies have shown that H19 has the dual function of oncogene and tumor suppressor. H19 was the earliest lncRNA used for pancreatic cancer treatment. DNA treatment controlled by the H19 gene sequence, whether used alone or combined with gemcitabine, significantly improves the therapeutic effect in pancreatic cancer (36,74,75).

PVT1. PVT1 has the potential to cause cancer in numerous malignant tumors. However, only recently, studies revealed the role of PVT1 in pancreatic cancer. Tseng *et al* (50) found that the expression levels of PVT1 were positively correlated with clinical stage and total survival time in pancreatic cancer. PVT1 is a regulator of the sensitivity of pancreatic cancer cells to gemcitabine. Other studies showed that curcumin inhibited the prc2-pvt1-c-myc axis by inhibiting the prc2-subunit enhancer of zeste 2 polycomb repressive complex 2 subunit, targeting CSCs and enhancing the sensitivity of cancer cells to chemical therapeutic agents (2,42). Tutar (39) and Tseng *et al* (50) found that PVT1 promoted the proliferation and metastasis of pancreatic cancer cells by acting as a 'molecular sponge' to inhibit mir-448 activation, thus inhibiting the effect of SERPINE1 mRNA binding protein 1 on target cells. Nevertheless, studies on the detailed mechanism of PVT1 in pancreatic cancer and other tumor types are rare. Furthermore, other genes play a crucial role in pancreatic cancer, and they are located at various sites (11) (Table II).

Drug resistance and sensitivity in drug application. The clinical efficacy of some pancreatic cancer-targeted drugs, such as gemcitabine, remains controversial. To date, some lncRNAs have been found to be associated with pancreatic cancer therapy. Sethi *et al* (76) and Taucher *et al* (25) used a high-throughput microarray to measure the expression profiles of lncRNAs in pancreatic cancer tissue and found that quantitative PCR upregulated the expression of HOTTIP in pancreatic cancer. Moreover, the study also reported that HOTTIP promoted gemcitabine resistance through HOXA13, suggesting that HOTTIP and HOXA13 may be new therapeutic targets for pancreatic cancer. Unfortunately, the study failed to identify the downstream signaling pathways that HOTTIP regulates (77). Tang *et al* (78) found that the PVT1 gene regulated the sensitivity of gemcitabine in the human aspc-1 pancreatic cancer cell line. It was found that the sensitivity of gemcitabine increased when the full-length PVT1 cDNA was overexpressed from the antisense strand, and decreased when the full-length PVT1 cDNA was overexpressed from the positive-sense strand. Nevertheless, the underlying mechanism by which PVT1 regulates gemcitabine in pancreatic tumorigenesis remains unknown. Xiong *et al* (11) found that malat-1 reduced the chemical sensitivity of gemcitabine in aspc-1 and cfpac-1 cells.

5. circRNA

Circular RNAs (circRNAs) are a class of ncRNAs involved in the regulation of transcription and post-transcriptional gene expression; they are also a class of covalently bonded

Table II. Function and location of typical genes involved in pancreatic cancer.

First author (year)	Gene name	Genomic localization	Involvement in pancreatic cancer	(Refs.)
Wang (2017), Liu (2016)	H19	11p15.5	Cell proliferation, invasion, targeted therapy	(70,73)
Martens-Uzunova (2014)	PVT 1	8q24.21	Drug resistance	(65)
Vallot (2017), Xie (2017)	HULC	6p24.3	Cell proliferation	(66,67)
Meller (2015)	AF 339813	13q31.3	Cell proliferation and apoptosis	(40)
Pang (2015)	Gas5	1q25.1	Cell proliferation, the cell cycle	(72)
Kim (2013)	HOTAIR	12q12.13	Proliferation, apoptosis, drug resistance, chemotherapy sensitivity	(69)
Fuschi (2019)	UCA1	19p11.12	Proliferation, migration, invasion	(75)
He (2018), Martens-Uzunova (2014)	ROR	1p31.3	Proliferation, migration, invasion, drug resistance (autophagy)	(36,65)
Li (2017)	TUG1	22q12.2	Proliferation, migration (EMT)	(42)
Meller (2015), Hancock (2018)	ENST00000480739	12q13	Unspecified	(40,43)

single-stranded ncRNAs. circRNA has the following biological characteristics: i) As opposed to linear RNA, circRNA forms a closed covalently circular structure that it is more stable than linear RNA; ii) compared with linear mRNA, the species of circRNA are more abundant and varied; iii) non-circRNA is primarily derived from exons, and a large number of circRNAs exist in the cytoplasm of eukaryotic cells; nevertheless, a small number of circRNAs, derived from introns or intron fragments, exist in the nucleus with spatiotemporal specificity of expression in various tissues at various stages of development; iv) most circRNAs are ncRNAs that are evolutionarily conserved; and v) most circRNAs are regulated at the transcriptional or post-transcriptional level (79,80). Knupp (81) and Li *et al* (82) compared microarray expression profiles of circRNA in pancreatic ductal adenocarcinoma and normal first-line tissues, and found that the expression of circRNA was different in two different tissues, and the most typical of which were ci-7 and ci-sirt7. circRNA alters the occurrence of pancreatic cancer, and is expressed in normal and tumor tissues with specificity, being more stable than linear RNA, and at higher concentration in serum. These characteristics make circRNA an ideal biomarker of pancreatic cancer and a substantial potential therapeutic target (83-85). Nevertheless, research on the correlation between circRNA and pancreatic cancer remains in the preliminary stage, and the study of the association between circRNA and pancreatic cancer is a hotspot in the current field of pancreatic cancer research.

6. Conclusions

ncRNAs have become hotspots of modern medical research; they promote the proliferation and metastasis of pancreatic cancer through EMT, competitive endogenous RNA (ceRNA), the cell cycle, apoptosis and other pathways. These various aspects are isolated; nevertheless, they are interwoven with one another. Several lncRNAs have been identified as oncogenes or tumor suppressors involved in tumorigenesis. Despite

the fact that protein biomarkers are widely used in cancer detection and in follow-up studies of diseases, lncRNAs have their own advantages. lncRNA itself is an effector molecule that reflects the actual level of a tumor. The correlation between lncRNA levels and specific types of tumors makes it an accurate tool for tumor diagnosis and classification (2,85). The expression of lncRNA is related to tumor therapeutic response and can be used as an indicator of therapeutic effect. Combined with other prognostic methods, lncRNAs can be used as new tumor markers, facilitating the identification of patients with poor prognosis and prolonging their survival. Furthermore, lncRNA has extensive application prospects in terms of tumor treatment (37,85). Currently, lncRNA has been used in the treatment of various tumors. However, most of the current studies on lncRNA focus on the differences in the expression levels, and relatively few studies have identified molecular functions. The discovery and understanding of carcinogenic effects in pancreatic cancer are also incomplete, and the details of these mechanisms remain to be elucidated. With the continuous innovation and development of research methods, lncRNAs may become potential biomarkers and therapeutic targets for pancreatic cancer (2,35).

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

YL and SH contributed to the design, as well as the writing of the review. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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