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**Noncoding RNAs and pancreatic cancer**

Peng JF *et al*. NcRNAs and pancreatic cancer

Juan-Fei Peng, Yan-Yan Zhuang, Feng-Ting Huang, Shi-Neng Zhang

**Juan-Fei Peng, Yan-Yan Zhuang, Feng-Ting Huang, Shi-Neng Zhang,** Department of Gastroenterology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou 510120, Guangdong Province, China

**Author contributions:** Peng JF, Zhuang YY and Huang FT performed the literature search, wrote the first draft of the manuscript and approved the final version; Zhang SN reviewed the literature and revised this paper critically.

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**Correspondence to: Dr. Shi-Neng Zhang, PhD,** Department of Gastroenterology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, 107 Yangjiang Rd, Guangzhou 510120, Guangdong Province, China. shinengz@163.net

**Telephone:** +86-20-81332598

**Fax:** +86-20-81332244

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**Abstract**

Noncoding RNAs (ncRNAs) represent a class of RNA molecules that typically do not code for proteins. Emerging data suggest that ncRNAs play an important role in several physiological and pathological conditions such as cancer. The best-characterized ncRNAs are the miRNAs, which are short, approximately 22-nucleotide sequences of RNA of approximately 22-nucleotide in length that regulate gene expression at the posttranscriptional level, through transcript degradation or translational repression. MicroRNAs (miRNAs) can function as master gene regulators, impacting a variety of cellular pathways important to normal cellular functions as well as cancer development and progression. Apart from miRNAs, recently long ncRNAs, which are transcripts longer than 200 nucleotides, have emerged as novel drivers of tumorigenesis. However, the molecular mechanisms of their regulation and function, and the significance of other ncRNAs such as piwi-interacting RNAs in pancreas carcinogenesis are largely unknown. This review summarizes the growing body of evidence supporting the vital roles of ncRNAs in pancreatic cancer, focusing on their dysregulation through both genetic and epigenetic mechanisms, and highlighting the promises of ncRNAs in diagnostic and therapeutic applications of pancreatic cancer.

**Key words:** Noncoding RNAs; Pancreatic cancer; Diagnosis; Therapy; Prognosis

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**Core tip:** Emerging data suggest that noncoding RNAs (ncRNAs) play a vital role in pancreatic cancer. They make contributions to pancreatic cancer through regulation of gene expression at chromatin, transcriptional, or posttranscriptional level. However, their function and mechanism in pancreatic cancer development have not been fully understood. This review focuses on the area of ncRNAs dysregulation in pancreatic cancer through both genetic and epigenetic mechanisms, and impact of this dysregulation on pancreatic cancer risk. We highlight the potential role of the most promising ncRNAs in diagnostic and therapeutic application.

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**INTRODUCTION**

The incidence of pancreatic cancer ranges from 1/100000 to 10/100000, and is generally higher in developed countries and among men. It has remained stable for the past 30 years, in contrast to that of other common solid tumors. It is the eighth leading cause of cancer death in men and the ninth in women throughout the world[1]. In China, the incidence rate of pancreatic cancer increased from 3.24/100000 in 2003 to 3.59/100000 in 2011 with an annual percentage change of 1.44. The mortality rate was 5.40/100000 (male 5.88/100000, female 4.89/100000), ranking 6th among all cancers[2]. In the United States, pancreatic cancer is expected to affect 46000 people, and 40000 people are expected to die from it. The American Cancer Society reported 43920 new cases of pancreatic cancer in the US in 2012[3,4]. The overall 5-year survival rate of patients with pancreatic cancer is less than 6% and this dismal prognosis has not improved in recent years, resulting in an increasing number of deaths. The high fatality of pancreatic cancer is attributed to failure to diagnose the disease early before it has metastasized to other organs and resistance of the cancer cells to current therapies[5].

Genetic analysis has established a model of pancreatic cancer progression. Key shared genetic alterations associated with pancreatic cancer progression include earliest genetic events such as mutations in *K-RAS* and overexpression of HER-2/neu. At later stages, inactivation of the p16 tumor suppressor gene often occurs, followed by loss of p53, disturbance of SMAD4, and BRCA2 signaling pathways and other genomic-transcriptomic alterations that facilitate deregulation of cell-cycle control and survival, invasion and metastasis[6]. Findings from genetically engineered mouse models are consistent with this model of genetic progression[7]. Since these are alterations of tumor suppressor genes, they have not yet led to solutions for therapeutic interventions. Beyond these mutational events, the pancreatic cancer genome is characterized by diverse, large scale chromosomal changes with frequent amplifications, deletions, and rearrangements[8]. Recently, basic research on potential disease mechanisms has benefited greatly from studies using model organisms and/or novel experimental systems. Insights from such studies are providing mounting evidence that noncoding RNAs (ncRNAs) and ncRNA-regulatory processes are important players in the tumorigenesis of pancreas. In this review, we will focus on the characteristics and biological roles of several ncRNAs, with particular emphasis on their roles in pancreatic cancer. Potential therapeutic applications of the ncRNAs will also be discussed.

**FUNCTIONAL CLASSIFICATION OF MAJOR HUMAN NCRNAS**

Early biochemistry studies identified three families of RNA that function cooperatively in the process of protein synthesis: messenger, transfer, and ribosomal RNA. Messenger RNAs (mRNA) carry genetic information copied from DNA that specifies a particular amino acid, dictating the polypeptide sequence. Transfer RNAs (tRNA) bind a complementary amino acid and carry it to the growing end of a polypeptide chain. Ribosomal RNAs (rRNA) bind to protein complexes, which physically move along mRNAs and catalyze the assembly of amino acids into the nascent polypeptide chain[9]. The technological advances applied to functional genomics during the last decade have opened new frontiers in the field of RNA biology. To date, approximately 35% of the human genes identified by the ENCODE project (about 57000; GENCODE version17) encode for proteins[10,11]. The vast majority of the remaining genes (about 65%) are transcribed into RNAs but do not encode proteins, which are generally known as "noncoding" RNAs (ncRNAs). NcRNAs comprise several classes of RNAs, classified in different groups according to their length, function, cellular localization, orientation or other criteria (these classifications are continuously being adjusted as new data are being acquired). Generally, ncRNAs less than 200 nucleotides (nt) in length are classified as short, while all larger transcripts are regarded as long ncRNAs (lncRNAs). There are several subtypes of long and short ncRNAs species, many of which are involved in regulation of gene expression. These can be further grouped according to their genomic origins and biogenic processes (Table 1).

The majority of the non-protein-coding transcripts belong to the group of lncRNAs. The number of genes encoding for lncRNAs identified so far is approximately 13000 (GENCODE version 17), representing more than 20% of human genome. To date, a small number of these have been studied in detail, shedding light on their functions and mechanisms of action in regulating cellular processes such as cell growth and apoptosis, development, and cell pluripotency and differentiation)[12-14]. Unlike miRNAs and piRNAs, lncRNAs are highly diverse in structure and function. LncRNAs typically have the same structures as mRNAs such as the 5' cap, polyadenylated 3' tail and undergo splicing to give rise to the final product. They are localized both in the nucleus and cytoplasm, but the signals that drive their localization are not known. One important consideration is that, while sequence conservation of lncRNAs is reportedly poor, transcripts with corresponding positions and directions in reference to protein coding genes are more common, indicating that their functions may well be conserved. It is observed that genes are usually located very proximal to the lncRNA on the genome[15]. Based on their proximity to protein coding genes, LncRNAs can be further classified into five categories: sense, antisense, bidirectional, intronic, and intergenic[16]. Although lncRNAs constitute the majority of the transcriptome, we certainly understand less of their biologic functions than those of their lesser counterparts. They are attributed with an ever-increasing number of functional activities including genomic imprinting and transcriptional regulation, including both cis- and trans-acting effect. This is achieved *via* a variety of mechanisms such as antisense inhibition, transcriptional interference, recruitment of chromatin remodeling complexes, and promoter inactivation by binding to basal transcriptional factors (TFs)[17]. Recently, it has been shown that several lncRNAs maybe spliced at their 5' and 3' ends to form circular RNAs. However, the functional importance of circularization, presumably for increased stability, has not been confirmed[18].

In contrast to lncRNAs, short ncRNAs have been extensively classified based on their genomic origins and precise mechanisms of action. The miRNAs are the most well-characterized family of ncRNA to date. Mature, functional miRNAs sequences are 20-23 nt in length, and are usually produced as RNA polymeraseⅡ-transcribed primary transcript, namely pri-miRNA. The biogenesis of pri-miRNA transcript occurs either through the canonical pathway involving Drosha and Dicer or through various noncanonical pathways that are Drosha- and even Dicer-independent[19-21]. Likewise, recent data show that miRNAs could be produced from snoRNA, tRNA, or Y-RNA, as intermediate products[22]. The human genome encodes thousands of miRNAs, which regulate a large fraction of the human transcriptome. An increasing number of TFs and miRNAs are known to form feedback loops (FBLs) of interactions where a TF positively or negatively regulates the expression of a miRNA, and the miRNA suppresses the translation of the TF messenger RNA. FBLs are potential sources of instability in a gene regulatory network. Positive FBLs can give rise to switching behaviors while negative FBLs can generate periodic oscillations. MiRNAs and TFs can modulate the expression of multiple targets, alter cell fate and are often engaged in mutually reinforcing functions. However, miRNAs differ from TFs in many critical ways. Firstly, almost all the known miRNAs are repressors while TFs are either repressors or activators and in some rare cases can act as both depending on the target and interacting partners. Secondly, miRNAs usually bring about down-regulation of their targets by a post-transcriptional mechanism, by degrading the target RNA or blocking its translation. TF interaction with target DNA is largely mediated through structural elements while miRNA interaction with targets is largely governed by the rules of nucleic acid complementarity and are therefore more easily predicted. When a particular gene is targeted by a TF, there is usually a single or at most a few tandemly repeated sites present at that locus. However, a typical miRNA-target interaction is characterized by miRNA molecules binding to several messenger RNA molecules. Lastly, TFs are usually not consumed in the TF-DNA interactions and may indeed engage in multiple rounds of regulation. The fate of the miRNA engaged in a miRNA-target complexe is not understood with similar clarity[23-27]. MiRNAs have been shown to be associated with many of the classical hallmarks of cancer, including proliferation, apoptosis, differentiation, and angiogenesis. With their widespread range of influence on biological pathways and implications as either oncogenes or tumor suppressor genes, their dysregulation is naturally an important factor in tumorigenesis leading to pancreatic cancer.

The piwi-interacting RNAs (piRNAs) are 25-33 nt in length, which depend on the PIWI protein group they bind to, and they lack sequence conservation between organisms. PiRNAs were first discovered in *Drosophila* as repeat-associated siRNAs, which show complementarily to a variety of transposable and repetitive elements. Unlike Drosophila piRNAs, more than 90% of mammalian piRNAs can be mapped uniquely in the genome and they cluster to a small number of loci. PiRNA clusters are transcribed in the sense or antisense direction, and the long single-stranded RNA serves as the basis for piRNA production. Recent research highlighted the complexity of piRNA biogenesis pathways, which just begin to be elucidated[28]. PiRNAs are distinct from miRNA in that there is no evidence for a double-stranded RNA precursor and their biogenesis is independent of Dicer. There are two proposed pathways for generating piRNAs: a primary processing pathway and a "ping-pong" amplification loop, as recently reviewed[29,30].

**LONG NCRNAS IN PANCREATIC CANCER**

As showed above, lncRNAs, including several newly found lncRNAs: enhancer RNA (eRNA)[31], competing endogenous RNA (ceRNA)[32], circular RNA (circRNA)[33], and antisense long non-coding RNA[34], are a class of transcripts longer than 200 nt, which is functional, rather than “transcriptional noise” (non-functional RNA) as believed all along. Although only a small part of lncRNAs has been well-characterized so far, the significance of lncRNAs dysregulation has been investigated in diverse human diseases, especially in malignant tumor[35-41]. Here, we systematically summarize the dysregulated lncRNAs in pancreatic cancer (Table 2).

***H19***

As the first lncRNA to be identified in human disease, H19 is a maternally imprinted gene on chromosome 11p15.5, and contains five exons and four introns. The gene is mainly localized in cytoplasm, and is highly expressed during embryo development and strongly repressed after birth. However, multiple studies showed that H19 was re-expressed in many types of cancers, such as esophagus, colon, liver, and bladder cancers. What’s more, studies indicated that H19 posses both tumor promoter and suppressor functions[42-44]. In pancreatic cancer, H19 was not only markedly overexpressed in tumor tissues and cell lines, its expression also positively correlated with invasion and migration of the tumor. H19 plays its role by partially antagonizing let-7’s targeting of HMGA2-mediated EMT (epithelial-mesenchymal transition)[45]. In addition, studies demonstrated that DNA-based therapy controlled by H19 gene sequences either alone or in combination with gemcitabine could improve the effectiveness of pancreatic cancer treatment[46,47].

***HOTAIR***

HOTAIR (HOX transcript antisense intergenic RNA) is a 2158nt transcript located on chromosome 12q12.13, which regulates the nearby HOX genes[48,49]. Previous studies reported that HOTAIR acted as oncogene in many cancers, including breast cancer, hepatocellular carcinoma, non-small cell lung cancer and colon cancer. Artificially up-regulating HOTAIR in cancer cells caused strongly increased cell proliferation, and invasive and metastatic abilities. Whereas knockdown of HOTAIR in cancer cells that overexpressed HOTAIR impaired their invasion and metastasis[48,50-52]. Several studies demonstrated that this could be attributed to its 5'- and 3'- domain selectively binding PRC2 (polycomb repressive complex 2) and LSD1/coREST/REST protein complexes respectively. Once binding PRC2 and LSD1/coREST/REST protein complexes, HOTAIR could recruit these complexes to HOXD locus on chromosome 2. This is followed by further recruitment of zeste12 suppressed and zeste homolog2 enhanced, leading to H3K27 trimethylation and H3K4 demethylation, finally resulting in repression of genes involved in cell proliferation and metastasis. In fact, further analysis of gene expression indicated that there were also a great number of genes up regulated except for down regulated genes when HOTAIR was overexpressed, While depleting PRC2 in cancer cells over expressing HOTAIR resulted in gene expression profile changing into that of cancer cells without HOTAIR overexpression[48,50-52].

HOTAIR also has higher expression level in pancreatic cancer tissues compared to adjacent non-cancerous pancreatic tissues[53]. RNAi-mediated knockdown of HOTAIR resulted in: ⑴decrease of cell proliferation, changes in cell cycle progression, and induction of apoptosis ; ⑵ blockage of cell invasiveness and metastatic ability both *in vitro* and *in vivo* ; ⑶ Significant changes in gene expression profile. Interestingly, analyzing some of these changed genes, researchers found the changes involve both PRC2-dependent and -independent mechanisms. Since HOTAIR was located both in nucleus and cytoplasm, it was very likely, besides functioning through PRC2, HOTAIR may play roles through different mechanisms[53].

***HOTTIP***

HOTTIP (HOXA transcript at the distal tip) is another HOX-associated lncRNA transcribed from the 5’ tip of the HOXA locus, which directly controls the expression of multiple 5’ HOXA locus gene *via* interaction with PRC2 and WDR5/MLL1 chromatin modifying complexes[54]. While HOTTIP was found significantly expressed and functioned in anatomically distal human fibroblasts[55], its up-regulation and coordination with HOXA13 have been recently studied in hepatocellular carcinomas[56]. In hepatocellular carcinomas, HOTTIP serves as a negative prognostic factor, and HOTTIP expression was associated with increased cell proliferation and enhanced metastasis. In addition, HOTTIP is linked to deletion of vitamin D receptor in keratinocytes, which contribute to the formation of skin cancer[57]. As for pancreatic cancer, it was found that HOTTIP was significantly up-regulated in pancreatic cancer tissues and in pancreatic cancer cell lines compared with non-cancerous pancreatic tissues and non-tumor pancreatic cell line HPDE6. In the same study, it was further documented that HOTTIP inhibition resulted in proliferation arrest, impaired cell invasion by inhibiting epithelial-mesenchymal transition, and potentiated antitumor effects of gemcitabine both *in* *vitro and in vivo.* All of these function was fulfilled partially through coordinating the activation of HOXA13[58]. Another research group showed that HOTTIP regulates pancreatic cancer cell proliferation, apoptosis and migration *via* its regulation of several other HOX genes including HOXA10, HOXB2, HOXA11, HOXA9, and HOXA1 rather than HOXA13[59], thus further studies are needed to elucidate the mechanism of HOTTIP function.

***MALAT-1***

MALAT-1 (metastasis-associated lung adenocarcinoma transcript 1), also named NEAT1 (nuclear-enriched abundant transcript 2) is another extensively investigated lncRNA. It is more than 8,000 nt in length, expressed from chromosome 11q13 and localizes to nuclear speckles after being spliced. The gene was first found in non-small cell lung cancer and could serve as predictive marker of metastasis and therapeutic target in non-small cell lung cancer, so came the name[60]. Thereafter, an increasing number of studies reported that MALAT-1 was also overexpressed in many other cancer types, and was associated with cancer metastatic potential, shorter survival, and poor prognosis in patients with these cancers as well as non-small cell lung cancer. Moreover, the mechanisms of MALAT-1 functioning in cancer occurrence and development were also widely explored. For example, the mechanism that MALAT-1 could interact and bind unmethylated PC2 (polycomb 2 protein) which controls the relocalization of growth-related genes between polycomb bodies and interchromatin granules (ICGs) has been reported in detail[61], and a study on colorectal cancer demonstrated that the 3' end of MALAT-1 has an vital biological motif in colorectal cancer cells invasiveness and metastasis[62].

MALAT-1 was also up-regulated in pancreatic cancer tissues and cell lines[63,64]. Further studies demonstrated that high MALAT-1 expression was correlated with advanced tumor clinical stages, positive lymph node and distant metastasis, and poor survival. Knockdown of MALAT-1 resulted in declining cell proliferation, migration, and invasion *in vitro*, and blocking cell metastasis *in vivo*[65]. All these findings indicated that MALAT-1 may act as a cancer promoting factor in pancreatic cancer, and suggested a potential therapeutic role of MALAT-1 targeted therapy in pancreatic cancer.

***PVT1***

PVT1 was identified in 1986[66]. Previous studies showed that PVT1 possessed oncogenic potential in many malignant tumors. While it was not until recently that studies investigating PVT1 gene in pancreatic cancer have emerged[66], including the study of negative regulation of PVT1 on pancreatic cancer cell sensitivity to gemcitabine, the finding of a susceptibility allele rs1561927 in PVT1[67], and a study on PVT1 expression level in pancreatic tissues[68]. In this study, researchers used qRT-PCR to measure PVT1 expression level in pancreatic tissues and analyzed its association with clinical-pathological parameters and patient overall survival, and found that PVT1 had much higher expression in pancreatic cancer tissues than non-cancerous tissues, and was positively correlated to poor survival of patients. However, studies on the detailed mechanisms of PVT1 in pancreatic cancer as well as in other cancer types are very scarce.

***Other newly found overexpressed lncRNA***

HULC (highly up-regulated in liver cancer) is a cancer-related lncRNA, residing on chromosome 6p24.3. It mainly functions in cytoplasm. HULC was found overexpressed in a group of metastatic and advanced clinical stage pancreatic tumors and could promote cell proliferation *in vitro*[69]. Recently, lncRNA AF339813 was found to be overexpressed and positively regulated by NUF2 (Ndc80 kinetochore complex component) in pancreatic cancer cells[70].

***Down-regulated lncRNAs***

Besides the above lncRNAs up-regulated in pancreatic cancer, there are also some lncRNAs down-regulated in pancreatic cancer. LncRNA Gas5 (growth arrest-specific 5) was markedly down-regulated in pancreatic cancer tissues and cancer cell lines, and involved in cell proliferation and cell cycle regulation. The mechanism may be partially explained by its negative regulation of CDK6 expression[71]. A novel lncRNA called ENST00000480739 was significantly downregulated in pancreatic cancerous tissues compared to adjacent non-cancerous tissues, and the ENST00000480739 expression level was negatively correlated with tumor TNM stages and poor overall survival of patient with pancreatic cancer[72].

**MiRNAS IN PANCREATIC CANCER**

Mounting evidence has shown the involvement of deregulation and aberrant expression of miRNAs in carcinogenesis of various organs, including the pancreas. Although the understanding of miRNAs expression profile in pancreatic cancer has been improving significantly, the role of these miRNAs in pancreatic cancer tumorigenesis and progression is only fractionally documented[73-77]. MiRNAs dysregulated in pancreatic cancer can be classified into oncogenic miRNAs and tumor suppressor miRNAs in relation to their function in carcinogenic processes. In Table 3, we have listed a number of important miRNA candidates that might be clinically relevant in the management of pancreatic cancer.

***Oncogenic miRNAs***

Several studies revealed that distinct cell- and tissue-specific miRNA expression in pancreatic cancer specimens compared with normal cells and tissues[78-81]. Hong *et al*[82]analyzed the miRNA profile in pancreatic cancer tissues and cell lines in comparison with normal tissues and cells, and found 8 aberrantly overexpressed miRNAs (miR-196a, miR-190, miR-186, miR-221, miR-222, miR-200b, miR-15b and miR-95). Interestingly, it has been found that miR-196a play a vital role in pancreatic cancer. High expression of miR-196a had good potential to predict poor survival of patients with pancreatic cancer [median, 14.3 mo (95%CI: 12.4-16.2 mo) *vs* 26.5 mo (95%CI: 23.4-29.6 mo)][83]. miR-196a may have promoted pancreatic cancer proliferation and migration by targeting nuclear factor kappa-B-inhibitor alpha (NFKBIA), which is a metastasis-related protein itself[84]. Several studies have reported that miR-221 may have functioned as a proto-oncogene. Up-regulation of miR-221 is known to contribute to the proliferation, invasion, inhibition of apoptosis and chemoresistance of pancreatic cancer. Its target genes include MMP 2 and MMP 9, which were closely related to cell migration and invasion, and were regarded as markers of cancer invasion and metastasis[85]. Another target gene of miR-221 was PTEN, a tumor suppressor that negatively regulates cell proliferation and survival through antagonizing the phosphatidylinositol 3-kinase (PI3K) signaling[86].

As mentioned above, tissue miRNAs play an important role in pancreatic cancer initiation and development. In addition, circulating miRNAs may also contribute to pancreatic cancer progression. For example, circulating miR-200a/b were elevated and could be potential markers for early diagnosis and treatment monitoring of pancreatic cancer. One of its downstream targets was SIP1, whose protein product suppressed E-cadherin expression and contributed to EMT[87]. One study reported that combinations of 7 miRNA (miR-20a, miR-21, miR-24, miR-25, miR-99a, miR-185, and miR-191) served as great biomarkers and showed high sensitivity and specificity for distinguishing various stages of pancreatic cancer from cancer-free controls and also from chronic pancreatitis[88]. Among the 7 miRNAs, miR-21 levels in serum were significantly associated with overall pancreatic cancer survival[88,89]. Furthermore, Overexpression of miR-21 contributed to gemcitabine chemoresistance and enhanced malignancy of pancreatic cancer cells *via* p85α, the phosphoinositide 3-kinase (PI3K) regulatory subunit[90]. MiR-21 is also known to be involved in other cancers[91-94]. It played an oncogenic role by targeting FOXO1 and activating the PI3K/AKT pathway in diffuse large B-cell lymphoma[95]. In addition, miR-21 may promote intrahepatic cholangiocarcinoma proliferation *in vitro* and *in vivo*, probably by targeting PTPN14 and PTEN[96].

What’s more, miRNA have an important role in cancer stem cells (CSCs) function[97-99]. MiR-34 was down-regulated in pancreatic cancer, and miR-34 restoration led to a significant reduction of CD44+/CD133+ cells and inhibition of tumor sphere growth in pancreatic cancer, implying that miR-34 may be involved in pancreatic cancer stem cell self-renewal[100]. Moreover, MiR-34 may be involved in cancer stem cell activity *via* direct modulation of downstream targets Bcl-2 and Notch[101]. MiR-200a was significantly down-regulated in pancreatic cancer stem cells (PCSCs) compared with their counterpart control, PANC-1 cells. Artificial overexpression of miR-200a in the PCSCs resulted in up-regulation of epithelial marker E-cadherin and down-regulation of mesenchymal markers ZEB1, N-cadherin and Vimentin, suggesting that the loss of miR-200a was critical for the acquisition of EMT characteristics and that the overexpression of miR-200a could reverse the EMT phenotype of PCSCs[102]. The miR-17-92 family can negatively regulate and control PCSCs features by targeting genes involved in activated Nodal/Activin/TGF-β signaling pathway or by targeting ALK4, p21 and transcription factor T-box 3[103] Taken together, miRNAs play an crucial role in PCSCs biological function.

***Tumor suppressor miRNAs***

Contrary to described above, there are also tumor suppressor miRNAs, which were often deregulated in pancreatic cancer. They inhibit the initiation and progression of pancreatic cancer though negatively regulating cell cycle and proliferation (miR-124[103], miR-203[104], miR-143[105], miR-126[106], and let-7[107]), or facilitating apoptosis and DNA repair (miR-34a[108-110], miR-203[104], miR-150 and miR-630[111]), or decreasing the capacity of tumor invasion and metastasis (miR-200a/b/c[112,113], miR-141[114], miR-429[115], miR-203[116], miR-143[105], and miR-146[117]). Recently, a study reported that miR-615-5p was significantly down regulated in pancreatic cancer than in adjacent normal tissues, and could inhibit proliferation, and migration and invasion of pancreatic cancer cell lines by targeting AKT2[118]. Another well-known tumor suppressor miRNA is let-7 family. Let-7 was found downregulated in a number of pancreatic cancer cell lines. Reexpression of let-7 (including let-7a and let-7f) retarded the migratory potential of pancreatic cancer, and decreased expression of Vimentin and Fibronectin. Furthermore, STAT3 phosphorylation and STAT3-activated gene expression were inhibited with upregulation of let-7[119]. Similarly, miR-1181 was also found underexpressed in pancreatic cancer. Clinically, decreased expression of miR-1181 was found associated with poorer overall survival and disease-free survival. Experimentally, miR-1181 contributed to CSC-like phenotypes by gain-of-function and loss-of-function assay, and it was demonstrated that SOX2 and STAT3 expression were inhibited directly by miR-1181[120].

**NCRNAS AS DIAGNOSTICS AND PROGNOSTICS FOR PANCREATIC CANCER**

Development of diagnostic and prognostic pancreatic cancer biomarkers has the potential to detect disease at an early stage, improve disease management, and reduce mortality from this disease. CA19-9 is widely used for the diagnosis and prognosis of pancreatic cancer, although its limitations are well understood. The expression level of miR-16, miR-21, miR-210, miR-155, miR-20a, miR-25 and miR-196a in plasma of patients with pancreatic cancer were higher than that of the normal controls. Of which, miR-21 had the highest diagnostic value when used as a diagnostic marker alone. An additional study confirmed that the diagnostic sensitivity and accuracy could be improved when miR-16, miR-155 and miR-25 were combined with CA19-9, respectively[121,122]. The concentration of miR-18a in plasma/serum was reported to be much higher than that of healthy volunteers[123]. Besides in plasma, miRNA-10b, -30c, -106b, -155, and -212 in bile have also been reported to provide excellent accuracy for distinguishing pancreatic cancer patients from others[124].

Intraductal papillary mucinous neoplasm (IPMN) is a precursor cystic lesion to pancreatic cancer. In a study[125], researchers evaluated 700 miRNAs in PanIN lesions and found 35 miRNAs dysregulated in PanIN-3, including overexpression of let-7f/g, -18a, -15b, -21, -29a/b/c, -31,-93, -95, miR-101, -103, -106b, -146a, -155, -182, -190, -193b, -194, -196b, -200a/b, -203,-222, -338-3p, -429, and 486-3p, but no or weak expression of miR-107, -139-3p/5p,-216a/b, -217, -218 and -483-5p in PanIN-3. Among which, miR-196b emerges as the most useful biomarker in discriminating PanIN-3 lesions. In addition, miR-138, miR-195, miR-204, miR-216a, miR-217, miR-218, miR-802, miR-155, miR-214, miR-26a, miR-30b, miR-31, and miR-125 were enriched in the cyst fluids derived from invasive carcinomas. Cyst fluid miRNomes may develop as informative early detection biomarkers of pancreatic cancer developing from pancreatic cystic lesions[126].

Besides the implication of miRNAs for diagnosis, some specific miRNAs can predict outcome of pancreatic cancer. It was demonstrated that low expression of miR-200c in tumor tissue and high expression of miR-200c in serum were associated with worse survival in pancreatic cancer[127]. In addition, miR-221 and miR-222 were known to target the tumor suppressor gene coding for cyclin-dependent kinase inhibitor p27Kip1, and their role was established in pancreatic cancer as key inhibitors of cell cycle arrest, apoptosis, and sensitization of cells to gemcitabine. Up-regulation of these two miRNAs is often related with poor patient survival rate[128]. However, these studies of miRNAs as diagnostic and prognostic factors involved small sample sets; thus, validation in larger, independent cohorts is required prior to application of miRNA assays in a clinical setting[129].

**NCRNAS AS PANCREATIC CANCER THERAPEUTICS**

One of the major drawbacks and obstacles toward pancreatic cancer therapy is chemoresistance, which largely attributed to genetic mutations, epigenetic modifications and complex alterations within the tumor microenvironment. Over the past years, it has emerged that therapeutic resistance is, at least in part, mediated by CSCs and EMT, some miRNAs are promising targets to tackle chemoresistance in pancreatic cancer[130]. Nucleic acid-based therapeutic strategies are those in which a chemically modified nucleic acid is used to restore the normal activity of miRNAs. Here, nucleic acid-based strategies are classified into two main categories: (1) miRNA replacement therapy; and (2) anti-miRNA therapy.

***MiRNA replacement therapy***

MiRNA replacement therapy is one of nucleic acid-based therapeutic strategies. MiRNA replacement studies have been conducted in some animal models of cancer. However, this strategy has not yet been performed in pancreatic cancer cells. A replacement strategy seems to be a promising methodology for developing tools to replace malfunctioning tumor suppressor miRNAs and overcoming pancreatic cancer. MiRNA mimic delivery is best tolerated by non-tumorigenic cells because the pathways they activate or suppress have already been activated or suppressed by endogenous miRNAs, and normal cells can regulate the pathway while cancer cells can not[131]. Let-7 was the first miRNA in humans to be discovered and is regularly expressed in normal pancreatic cells, and its down-regulation plays a critical role in renewal and metastasis of pancreatic cancer cells. Restoration of lost let-7 expression in gemcitabine-resistant pancreatic cancer cells inhibits cellular proliferation, restores epithelial phenotype, and renders the tumor cells sensitive to gemcitabine[132]. Furthermore, down-regulated miRNAs miR-143, miR-148b, and miR-141 can be restored through miRNA replacement therapy[133,134].

***Anti-miRNA therapy***

Anti-miRNA therapy is another strategy of nucleic acid-based therapeutics. There are three ways to remove overexpressed oncomiRNAs: (1) genetic knockout (not discussed in this review); (2) antisense oligonucleotides (antagomiRs); and (3) miRNAs sponges. AntagomiRs are miRNA antagonists that affect miRNA-related pathways by binding and blocking oncogenic miRNAs. These nucleic acid antagonists are one of the known approaches to inhibit oncogenic miRNAs, and therefore they may be an effective way to treat cancer[135]. AntagomiRs are chemically modified antisense oligonucleotides containing 2'-O-methylation of ribose residues, 3'-conjugated cholesterol residues, and partial replacement of phosphodiester bonds through phosphorothioate linkages, wherein one of the non-bridging oxygens is replaced by sulfur[136]. In the case of antagomiR therapy, miR-21 and miR-221 are well-known oncogenic miRNAs overexpressed in pancreatic cancer that can be knocked-down using antisense oligonucleotides (ASO). ASOs for miR-21 and miR-221 increase the expression levels of their targets (PTEN, RECK, and CDKN1B), reduce proliferation, and increase apoptosis of pancreatic cancer cells. ASOs also sensitize pancreatic cancer cells to gemcitabine and generate synergistic antitumor effects[137,138]. Recently, developing human serum albumin-1-palmitoyl-2-oleoyl-snglycero-3-ethylphosphocholine:cholesterol/antimiRNA oligonucleotides (+/-) (4/1) nanosystem exhibited the ability to efficiently deliver anti-miRNA oligonucleotides targeting the overexpressed miRNAs including miR-21, miR-221, miR-222, and miR-10 in pancreatic cancer cells, promoting an almost complete abolishment of expression of these miRNAs. Silencing of these miRNAs resulted in a significant increase in the levels of their targets (PTEN and p27Kip1).

Sponge RNA contains complementary binding sites to miRNAs of interest. MiRNA sponges are comprised of transgenic cells and block all other miRNAs from the same family. Sponges bind to seed sequences of certain miRNAs that contain 2-7 specific sequential nucleotides. MiRNA sponges have multiple binding sites (usually 4-16). Both RNA polymerase II and III promoters have been used to transcribe miRNA sponges. However, transcripts of RNA polymerase II promoters are more stable due to their 5' caps and 3' polyadenylated tails[139]. MiR-103a-3p is a notable miRNA in that it is evolutionarily conserved and involved in regulating multiple cellular processes such as cell division, cellular metabolism, and angiogenesis[140,141]. MiR-103a-3p's dysregulation has been associated with many human diseases including several cancers, Alzheimer's disease, and diabetes. It has been shown that more than 50% of miR-103a-3p activity is reduced by miR-103a-3p sponges[142]. However, RNA sponges contain several seed sequences that may bind to other noncoding RNAs as well as mRNAs. Therefore, the safety of miRNA therapy needs to be fully elucidated to ensure that other important metabolic pathways are not affected.

***Small-molecule drugs***

In contrast to nucleic acid-based strategies, the expression of miRNAs can also be modulated by drugs. A number of agents, including isoflavone and 3,3-diindolylmethane, have been shown to alter expression of miR-200, and let-7 family in gemcitabine-resistant cancer cells[143]. Curcumin, one of polyphenols isolated from plants such as Curcuma longa, has been shown to induce miR-7. This induction inhibits cell growth, migration, and invasion. The apoptotic effects of curcumin appear to be mediated by down-regulating SET8 *via* miR-7 upregulation[144]. As a potent anti-cancer natural product, curcumin also down-regulates miR-21 and up-regulates miR-200, thereby improving gemcitabine sensitivity *via* the induction of PTEN[145]. Flavonoids are another group of polyphenolic compounds reported to have anti-oxidant and anti-cancer effects. Genisteins are flavonoids affecting the ER (anti-estrogenic effects) and can be found in soybeans. It has been reported that genistein treatment in pancreatic cancer cells upregulates miR-34a[146] and downregulates miR-27, and miR-223[147,148].

**CONCLUSION**

NcRNAs have undoubtedly become one of the ‘hot’ spots in modern biological and biomedical research. As ncRNAs can be efficiently targeted by stable ASO, this approach may be explored to target specific regulatory ncRNAs to understand their biological functions and action mechanisms and to develop novel strategies for disease intervention. Differential expression of ncRNAs is now a recognized trait of pancreatic carcinogenesis. However, the functional role of many of these molecules unearthed during profiling studies remains undetermined. Relatively speaking, biomarker studies into pancreatic cancer ncRNAs are in their infancy. Further work is needed to establish the role of distinguishing between free-circulating ncRNAs, those bound to Argonaute proteins and circulating microvesicle-encapsulated ncRNAs. The therapeutic applications of ncRNAs in pancreatic cancer are still in a formative stage and require extensive investigation *in vitro* and in animal models before their true potential can be realized.

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**Table 1 Main classes and function of human noncoding RNAs**

|  |  |  |
| --- | --- | --- |
| **RNA types** | **Length (nt)** | **Function** |
| **Small non-coding RNAs (< 200 nt)** | | |
| Protein synthesis RNAs | | |
| Transfer RNAs  (tRNA) | ~80 | Carrying aminoacids to connect with mRNA |
| Ribosomal 5S and 5.8S RNAs  (rRNA) | 121-200 | Component of ribosomes |
| Small nuceolar RNAs  (snoRNA) | 70-200 | Involving in maturation of other nocoding RNAs |
| Small nuclear RNAs  (snRNA) | ~150 | Joining with proteins to form spliceosomes controling alternative splicing |
| Regulatary RNAs | | |
| MicroRNAs  (miRNA) | 20-23 | Negtively regulating gene expression by joining an enzyme and blocking mRNA, or speeding its breakdown |
| Small interfering RNAs  (siRNA) | 21-22 | Silencing specific genes in sequence-specific manners. |
| PIWI-interacting RNAs  (piRNA) | ~25-33 | Controlling retrotransposition and regulating methylation. |
| Promoter-associated short RNAs  (PASRs) | < 200 | Regulating gene expression through interaction with gene promoter sites |
| **Long non-coding RNAs (> 200 nt)** |  |  |
| Ribosomal 28S and 18S RNAs  (rRNA) | 200-5070 | Component of ribosomes |
| Long intergenic non-coding RNAs (lincRNA)  or  long intronic non-coding RNAs  (lincRNA) | > 200 | Virious |
| Telomere-associated ncRNAs  (TERRAs) | 100 bp.> 9 kb | Negative regulators of telomere |
| Antisense RNAs |  | Binding and blocking the translation of mRNA target |
| Promoter-associated short  RNAs(PASRs) | > 200 | Regulating gene expression through interaction with gene promoter sites |
| Transcribed-ultraconserved regions  (T-UCRs) | 200-799 | Long-range enhancer-like activity, maintenance of splicing factor expression levels and transcription regulation |

**Table 2 Long** **noncoding RNAs dysregulated in pancreatic cancer**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Names of**  **lncRNAs** | **Genomic**  **Location** | **Expression** | **Roles in pancreatic cancer** | **Reference** |
| H19 | 11p15.5 | Upregulated | Cell proliferation, migration, invasion, target therapy | [42-47] |
| HOTAIR | 12q12.13 | Upregulated | Cell proliferation, cell cycle, apoptosis, migration, invasion | [48-52] |
| HOTTIP | 7p15.2 | Upregulated | Cell proliferation, cell cycle, migration, invasion, drug resistance | [58,59] |
| MALAT-1 | 11q13 | Upregulated | Cell proliferation, migration, invasion | [60-65] |
| PVT1 | 8q24.21 | Upregulated | Drug resistance | [66-69] |
| HULC | 6p24.3 | Upregulated | Cell proliferation | [70] |
| AF339813 | 13q31.3 | Upregulated | Cell proliferation, apoptosis | [71] |
| Gas5 | 1q25.1 | Downregulated | Cell proliferation, cell cycle | [72] |
| ENST00000480739 | 12q13 | Downregulated | N | [73] |

N: Not mentioned.

**Table 3 Some selected microRNAs in pancreatic cancer**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **MiRNA** | **Expression** | **Role** | **Target genes** | **Biological significance** | **Clinical significance** |
| miR-21 | Up | O | PTEN, EGFR, HER2/neu, PDCD4, Bcl2, TIMP2, TIMP3 | Proliferation  and cell division | Gem chemosesitivity, Biomarker, Prognosis, potential target for treatment |
| miR-221/222 | Up | O | CDKN1B, PUMA, PTEN, Bim | Cell cycle progression | Gem chemosesitivity, Biomarker for diagnosis, Prognosis, potential target for treatment |
| miR-192 | Up | O | SIP1, cell cycle regulatory genes | Cell proliferation and migration, reduced apoptosis and cell cycle progression | Biomarker for diagnosis (serum) |
| miR-424-5p | Up | O | SOCS6 | Cell proliferation and migration | Prognosis |
| miR-208 | Up | O | CDH1 | EMT | N |
| miR-155 | Up | O | TP53INP1 | Apoptosis | Biomarker for diagnosis, Prognosis |
| miR-10a/b | Up | O | HOXB8, HOXA1 | Invasivity and metastasis | Gem chemosesitivity, Prognosis |
| miR-196a-2/196 | Up | O | HOXB8, ANXA1, HMGA2 | N | Biomarker for diagnosis, Prognosis |
| miR-375 | Up | O | PDK1, 14-3-3zeta | Cell proliferation and apoptosis | Biomarker for diagnosis, Potential target for treatment |
| miR-210 | Up | O | HOXA1, FGFRL1, HOXA9, COX10, E2F3, RAD52, ACVR1B, MNT | Regulating the interaction between pancreatic cancer cells and stellate cells | Biomarker for diagnosis, Prognosis |
| miR-301a | Up | O | Bim, NKRF | Proliferation and metastasis | Prognosis |
| miR-421 | Up | O | DPANCREATIC CANCER4/Smad | Cell proliferation and colony formation | Potential target for treatment |
| miR-15/16 | Up | O | Anti-apoptotic genes: bcl2l1, naip5, fgfr2 and mybl2 | Apoptosis and tumor angiogenesis | Potential target for treatment |
| miR-124 | Down | TS | RAC1 | Cell proliferation, invasion and metastasis | N |
| miR-203 | Down | TS | BIRC5, CAV1 | Cell cycle progression, apoptosis, EMT | Indicator of the metastatic potential, potential target for treatment |
| miR-143 | Down | TS | GET1, GET2, KRAS | Cell proliferation, invasion and metastasis | N |
| miR126,let-7 | Down | TS | E2F2, c-Myc, KRAS, MAPK, STAT3 | Cell proliferation | Chemosesitivity, potential target for treatment |
| miR-34a/b | Down | TS | TP53, Bcl-2 | Apoptosis,DNA repair,cell cycle progression and angiogenesis | Prognosis, Chemosesitivity |
| miR-200 family | Down | TS | EP300, ZEB1, SIPI1 | EMT | Prognosis, Chemosesitivity |
| miR-146a | Down | TS | IRAK-1, EGFR | Invasivity | Potential target for treatment |
| miR-96 | Down | TS | KRAS, AKT | Tumor growth and invasion | Potential target for treatment |

Up: Upregulated; Down: Downregulated; O: Oncogeneic; TS: Tumor suppressive; N: Not mentioned.