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TOPIC HIGHLIGHT

2016 Pancreatic Cancer: Global view

Noncoding RNAs and pancreatic cancer

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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 microRNAs (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. 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. In addition to miRNAs, long ncRNAs, which are transcripts longer than 200 nucleotides, have recently 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 promise of ncRNAs in diagnostic and therapeutic applications of pancreatic cancer.

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

Core tip: Emerging data suggest that noncoding RNAs (ncRNAs) play a vital role in pancreatic cancer. They contribute to pancreatic cancer through regulation of gene expression at the chromatin, transcriptional, or posttranscriptional level. However, their function and mechanism in pancreatic cancer development are

not fully understood. This review focuses on ncRNAs dysregulation in pancreatic cancer through both genetic and epigenetic mechanisms, and the impact of this dysregulation on pancreatic cancer risk. We highlight the potential role of the most promising ncRNAs in diagnostic and therapeutic applications.

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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 United States 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 due to 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 tumorigenesis of the 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 (rRNA). 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. 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 version 17) 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 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 the 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

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	About 80	Carrying amino acids to connect with mRNA
Ribosomal 5S and 5.8S RNAs	121-200	Component of ribosomes
Small nucleolar RNAs	70-200	Involved in maturation of other non-coding RNAs
Small nuclear RNAs	About 150	Joining with proteins to form spliceosomes controlling alternative splicing
Regulatory RNAs		
MicroRNAs	20-23	Negatively regulating gene expression by joining an enzyme and blocking mRNA, or speeding its breakdown
Small interfering RNAs	21-22	Silencing specific genes in a sequence-specific manner.
PIWI-interacting RNAs	About 25-33	Controlling retrotransposition and regulating methylation.
Promoter-associated short RNAs	< 200	Regulating gene expression through interaction with gene promoter sites
Long non-coding RNAs (> 200 nt)		
Ribosomal 28S and 18S RNAs	200-5070	Component of ribosomes
Long intergenic non-coding RNAs or long intronic non-coding RNAs	> 200	Various
Telomere-associated ncRNAs	100 bp > 9 kb	Negative regulators of telomere
Antisense RNAs		Binding and blocking the translation of mRNA target
Promoter-associated short RNAs	> 200	Regulating gene expression through interaction with gene promoter sites
Transcribed-ultraconserved regions	200-799	Long-range enhancer-like activity, maintenance of splicing factor expression levels and transcription regulation

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 was 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 may be spliced at their 5′ and 3′ ends to form circular RNAs (circRNA). 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 best-characterized family of ncRNAs to date. Mature, functional miRNAs sequences are 20-23 nt in length, and are usually produced as RNA polymerase Ⅱ-transcribed primary transcripts, namely pri-miRNA. The biogenesis of a 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]. Similarly, recent data show that miRNAs can 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 mRNA. 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 interactions with targets are 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 mRNA molecules. Lastly, TFs are usually not

Table 2 Long noncoding RNAs dysregulated in pancreatic cancer

Names of lncRNAs	Genomic location	Expression	Roles in pancreatic cancer	Ref.
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	Not mentioned	[73]

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 complex 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 have just begun 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 shown above, lncRNAs, including several newly found lncRNAs: enhancer RNA[31], competing endogenous RNA[32], circRNA[33], and antisense long noncoding RNA[34], are a class of transcripts longer than 200 nt, which is functional, rather than "transcriptional noise" (non-functional RNA) as previously believed. Although only a small part of lncRNAs has been well-characterized to date, 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 have shown that H19 was re-expressed in many types of cancers, such as esophagus, colon, liver, and bladder cancers. Furthermore, studies have indicated that H19 possesses 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 have 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].

HOX transcript antisense intergenic RNA

HOX transcript antisense intergenic RNA (HOTAIR) is a 2158 nt transcript located on chromosome 12q12.13, which regulates the nearby HOX genes[48,49]. Previous studies reported that HOTAIR acted as an oncogene in many cancers, including breast cancer, hepatocellular carcinoma, non-small cell lung cancer and colon cancer. Artificially up-regulating HOTAIR in cancer cells strongly increased cell proliferation, and invasive and metastatic abilities. 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. Following binding of PRC2 and LSD1/coREST/REST protein complexes, HOTAIR recruits these complexes to the 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.

Further analysis of gene expression indicated that there were also a great number of genes up regulated when HOTAIR was overexpressed. Depleting PRC2 in cancer cells overexpressing HOTAIR resulted in the 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: (1) decrease in cell proliferation, changes in cell cycle progression, and induction of apoptosis; (2) blockage of cell invasiveness and metastatic ability both *in vitro* and *in vivo*; and (3) significant changes in the gene expression profile. Interestingly, when analyzing some of these changed genes, researchers found the changes involved both PRC2-dependent and -independent mechanisms. As HOTAIR was located both in the nucleus and cytoplasm, it was very likely, besides functioning through PRC2, that HOTAIR may play roles through different mechanisms[53].

HOXA transcript at the distal tip

HOXA transcript at the distal tip (HOTTIP) is another HOX-associated lncRNA transcribed from the 5′ tip of the HOXA locus, which directly controls the expression of multiple 5′ HOXA locus genes *via* interaction with PRC2 and WDR5/MLL1 chromatin modifying complexes[54]. Although HOTTIP was 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 the vitamin D receptor in keratinocytes, which contributes to the formation of skin cancer[57]. With regard to 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 the 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 EMT, and potentiated the antitumor effects of gemcitabine both *in vitro and in vivo.* All of these functions were fulfilled partially by 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.

Metastasis-associated lung adenocarcinoma transcript 1

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT-1), also named nuclear-enriched abundant transcript 2 (NEAT1) is another extensively investigated lncRNA. It is more than 8000 nt in length, expressed on chromosome 11q13 and localizes to nuclear speckles after being spliced. The gene was first found in non-small cell lung cancer and serves as a predictive marker of metastasis and a therapeutic target in non-small cell lung cancer, thus 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 underlying MALAT-1 interacting with and binding unmethylated polycomb 2 protein, which controls the relocalization of growth-related genes between polycomb bodies and interchromatin granules, has been reported in detail[61], and a study on colorectal cancer demonstrated that the 3′ end of MALAT-1 has a vital biological motif in colorectal cancer cell invasiveness and metastasis[62].

MALAT-1 was also shown to be 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 reduced cell proliferation, migration, and invasion *in vitro*, and blocked cell metastasis *in vivo*[65]. All these findings indicate that MALAT-1 may act as a cancer promoting factor in pancreatic cancer, and suggest 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. However, it was not until recently that studies investigating PVT1 gene in pancreatic cancer have emerged[66], including the study on 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 with 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

Highly up-regulated in liver cancer (HULC) is a cancer-related lncRNA, residing on chromosome 6p24.3.

Table 3 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 chemosensitivity, Biomarker, Prognosis, Potential target for treatment
miR-221/222	Up	O	*CDKN1B, PUMA, PTEN, Bim*	Cell cycle progression	Gem chemosensitivity, 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 chemosensitivity, 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	Chemosensitivity, potential target for treatment
miR-34a/b	Down	TS	*TP53, Bcl-2*	Apoptosis, DNA repair, cell cycle progression and angiogenesis	Prognosis, Chemosensitivity
miR-200 family	Down	TS	*EP300, ZEB1, SIPI1*	EMT	Prognosis, Chemosensitivity
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.

It mainly functions in the cytoplasm. HULC was found to be 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-mentioned lncRNAs up-regulated in pancreatic cancer, there are also some lncRNAs which are down-regulated in pancreatic cancer. LncRNA 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 the 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. A number of important miRNA candidates that might be clinically relevant in the management of pancreatic cancer are listed in Table 3.

Oncogenic miRNAs

Several studies revealed that distinct cell- and tissue-specific miRNA expression was found 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 plays a vital role in pancreatic cancer. High expression of miR-196a had good potential in predicting 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[84]. Several studies have reported that miR-221 may function 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 by antagonizing 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 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].

Furthermore, miRNAs 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 CSC self-renewal[100]. Moreover, MiR-34 may be involved in CSC activity *via* direct modulation of downstream targets Bcl-2 and Notch[101]. MiR-200a was significantly down-regulated in pancreatic CSCs (PCSCs) compared with their counterpart control, PANC-1 cells. Artificial overexpression of miR-200a in the PCSCs resulted in up-regulation of the 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 the activated Nodal/Activin/TGF-β signaling pathway or by targeting ALK4, p21 and transcription factor T-box 3[103]. Taken together, these data show that miRNAs play a crucial role in PCSCs biological function.

Tumor suppressor miRNAs

In contrast, there are also tumor suppressor miRNAs, which were often found to be deregulated in pancreatic cancer. They inhibit the initiation and progression of pancreatic cancer by 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 downregulated in pancreatic cancer compared with adjacent normal tissues, and could inhibit proliferation, migration and invasion of pancreatic cancer cell lines by targeting AKT2[118]. Another well-known tumor suppressor miRNA is the 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 the 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 to be 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

The development of diagnostic and prognostic pancreatic cancer biomarkers has the potential to detect disease at an early stage, improve disease management, and reduce mortality due to this disease. CA19-9 is widely used for the diagnosis and prognosis of pancreatic cancer, although its limitations are well understood. The expression levels of miR-16, miR-21, miR-210, miR-155, miR-20a, miR-25 and miR-196a in the plasma of patients with pancreatic cancer were higher than those 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 one 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. Of which, miR-196b emerged 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 the 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 in pancreatic cancer therapy is chemoresistance, which is 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, and 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 (ASO) (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 ASO 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 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, the development of the 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 the almost complete abolition of the 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]. The dysregulation of miR-103a-3p 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 ncRNAs 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 the let-7 family in gemcitabine-resistant cancer cells[143]. Curcumin, one of the 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.

REFERENCES

1 **Ryan DP**, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. *N Engl J Med* 2014; **371**: 1039-1049 [PMID: 25207767 DOI: 10.1056/NEJMra1404198]

2 **He Y**, Zheng R, Li D, Zeng H, Zhang S, Chen W. Pancreatic cancer incidence and mortality patterns in China, 2011. *Chin J Cancer Res* 2015; **27**: 29-37 [PMID: 25717223 DOI: 10.3978/j.issn.1000-9604.2015.02.05]

3 **Siegel R**, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014; **64**: 9-29 [PMID: 24399786 DOI: 10.3322/caac.21208]

4 **Ma J**, Siegel R, Jemal A. Pancreatic cancer death rates by race among US men and women, 1970-2009. *J Natl Cancer Inst* 2013; **105**: 1694-1700 [PMID: 24203988 DOI: 10.1093/jnci/djt292]

5 **Hoos WA**, James PM, Rahib L, Talley AW, Fleshman JM, Matrisian LM. Pancreatic cancer clinical trials and accrual in the United States. *J Clin Oncol* 2013; **31**: 3432-3438 [PMID: 23960185 DOI: 10.1200/JCO.2013.49.4823]

6 **Kanda M**, Matthaei H, Wu J, Hong SM, Yu J, Borges M, Hruban RH, Maitra A, Kinzler K, Vogelstein B, Goggins M. Presence of somatic mutations in most early-stage pancreatic intraepithelial neoplasia. *Gastroenterology* 2012; **142**: 730-733.e9 [PMID: 22226782 DOI: 10.1053/j.gastro.2011.12.042]

7 **Corcoran RB**, Cheng KA, Hata AN, Faber AC, Ebi H, Coffee

EM, Greninger P, Brown RD, Godfrey JT, Cohoon TJ, Song Y, Lifshits E, Hung KE, Shioda T, Dias-Santagata D, Singh A, Settleman J, Benes CH, Mino-Kenudson M, Wong KK, Engelman JA. Synthetic lethal interaction of combined BCL-XL and MEK inhibition promotes tumor regressions in KRAS mutant cancer models. *Cancer Cell* 2013; **23**: 121-128 [PMID: 23245996 DOI: 10.1016/j.ccr.2012.11.007]

8 **Fokas E**, O'Neill E, Gordon-Weeks A, Mukherjee S, McKenna WG, Muschel RJ. Pancreatic ductal adenocarcinoma: From genetics to biology to radiobiology to oncoimmunology and all the way back to the clinic. *Biochim Biophys Acta* 2015; **1855**: 61-82 [PMID: 25489989 DOI: 10.1016/j.bbcan.2014.12.001]

9 **Lodish HF**. Translational control of protein synthesis. *Annu Rev Biochem* 1976; **45**: 39-72 [PMID: 786155 DOI: 10.1146/annurev.bi.45.07176.000351]

10 **ENCODE Project Consortium**. An integrated encyclopedia of DNA elements in the human genome. *Nature* 2012; **489**: 57-74 [PMID: 22955616 DOI: 10.1038/nature11247]

11 **Harrow J**, Frankish A, Gonzalez JM, Tapanari E, Diekhans M, Kokocinski F, Aken BL, Barrell D, Zadissa A, Searle S, Barnes I, Bignell A, Boychenko V, Hunt T, Kay M, Mukherjee G, Rajan J, Despacio-Reyes G, Saunders G, Steward C, Harte R, Lin M, Howald C, Tanzer A, Derrien T, Chrast J, Walters N, Balasubramanian S, Pei B, Tress M, Rodriguez JM, Ezkurdia I, van Baren J, Brent M, Haussler D, Kellis M, Valencia A, Reymond A, Gerstein M, Guigó R, Hubbard TJ. GENCODE: the reference human genome annotation for The ENCODE Project. *Genome Res* 2012; **22**: 1760-1774 [PMID: 22955987 DOI: 10.1101/gr.135350.111]

12 **Marchese FP**, Huarte M. Long non-coding RNAs and chromatin modifiers: their place in the epigenetic code. *Epigenetics* 2014; **9**: 21-26 [PMID: 24335342 DOI: 10.4161/epi.27472]

13 **Lee JT**. Epigenetic regulation by long noncoding RNAs. *Science* 2012; **338**: 1435-1439 [PMID: 23239728 DOI: 10.1126/science.1231776]

14 **Mercer TR**, Mattick JS. Structure and function of long noncoding RNAs in epigenetic regulation. *Nat Struct Mol Biol* 2013; **20**: 300-307 [PMID: 23463315 DOI: 10.1038/nsmb.2480]

15 **Mercer TR**, Dinger ME, Mattick JS. Long non-coding RNAs: insights into functions. *Nat Rev Genet* 2009; **10**: 155-159 [PMID: 19188922 DOI: 10.1038/nrg2521]

16 **Ponting CP**, Oliver PL, Reik W. Evolution and functions of long noncoding RNAs. *Cell* 2009; **136**: 629-641 [PMID: 19239885 DOI: 10.1016/j.cell.2009.02.006]

17 **Modarresi F**, Faghihi MA, Lopez-Toledano MA, Fatemi RP, Magistri M, Brothers SP, van der Brug MP, Wahlestedt C. Inhibition of natural antisense transcripts in vivo results in gene-specific transcriptional upregulation. *Nat Biotechnol* 2012; **30**: 453-459 [PMID: 22446693 DOI: 10.1038/nbt.2158]

18 **Memczak S**, Jens M, Elefsinioti A, Torti F, Krueger J, Rybak A, Maier L, Mackowiak SD, Gregersen LH, Munschauer M, Loewer A, Ziebold U, Landthaler M, Kocks C, le Noble F, Rajewsky N. Circular RNAs are a large class of animal RNAs with regulatory potency. *Nature* 2013; **495**: 333-338 [PMID: 23446348]

19 **Bartel DP**. MicroRNAs: target recognition and regulatory functions. *Cell* 2009; **136**: 215-233 [PMID: 19167326 DOI: 10.1016/j.cell.2009.01.002]

20 **Saxena A**, Tabin CJ. miRNA-processing enzyme Dicer is necessary for cardiac outflow tract alignment and chamber septation. *Proc Natl Acad Sci USA* 2010; **107**: 87-91 [PMID: 20018673 DOI: 10.1073/pnas.0912870107]

21 **Yates LA**, Norbury CJ, Gilbert RJ. The long and short of microRNA. *Cell* 2013; **153**: 516-519 [PMID: 23622238 DOI: 10.1016/j.cell.2013.04.003]

22 **Haussecker D**, Huang Y, Lau A, Parameswaran P, Fire AZ, Kay MA. Human tRNA-derived small RNAs in the global regulation of RNA silencing. *RNA* 2010; **16**: 673-695 [PMID: 20181738 DOI: 10.1261/rna.2000810]

23 **Sabin LR**, Delás MJ, Hannon GJ. Dogma derailed: the many influences of RNA on the genome. *Mol Cell* 2013; **49**: 783-794 [PMID: 23473599 DOI: 10.1016/j.molcel.2013.02.010]

24 **Dritsou V**, Deligianni E, Dialynas E, Allen J, Poulakakis N, Louis C, Lawson D, Topalis P. Non-coding RNA gene families in the genomes of anopheline mosquitoes. *BMC Genomics* 2014; **15**: 1038 [PMID: 25432596 DOI: 10.1186/1471-2164-15-1038]

25 **Peschansky VJ**, Wahlestedt C. Non-coding RNAs as direct and indirect modulators of epigenetic regulation. *Epigenetics* 2014; **9**: 3-12 [PMID: 24739571 DOI: 10.4161/epi.27473]

26 **Cech TR**, Steitz JA. The noncoding RNA revolution-trashing old rules to forge new ones. *Cell* 2014; **157**: 77-94 [PMID: 24679528 DOI: 10.1016/j.cell.2014.03.008]

27 **Zheng GX**, Do BT, Webster DE, Khavari PA, Chang HY. Dicer-microRNA-Myc circuit promotes transcription of hundreds of long noncoding RNAs. *Nat Struct Mol Biol* 2014; **21**: 585-590 [PMID: 24929436 DOI: 10.1038/nsmb.2842]

28 **Ishizu H**, Siomi H, Siomi MC. Biology of PIWI-interacting RNAs: new insights into biogenesis and function inside and outside of germlines. *Genes Dev* 2012; **26**: 2361-2373 [PMID: 23124062 DOI: 10.1101/gad.203786.112]

29 **Watanabe T**, Tomizawa S, Mitsuya K, Totoki Y, Yamamoto Y, Kuramochi-Miyagawa S, Iida N, Hoki Y, Murphy PJ, Toyoda A, Gotoh K, Hiura H, Arima T, Fujiyama A, Sado T, Shibata T, Nakano T, Lin H, Ichiyanagi K, Soloway PD, Sasaki H. Role for piRNAs and noncoding RNA in de novo DNA methylation of the imprinted mouse Rasgrf1 locus. *Science* 2011; **332**: 848-852 [PMID: 21566194 DOI: 10.1126/science.1203919]

30 **Wilson RC**, Doudna JA. Molecular mechanisms of RNA interference. *Annu Rev Biophys* 2013; **42**: 217-239 [PMID: 23654304 DOI: 10.1146/annurev-biophys-083012-130404]

31 **Natoli G**, Andrau JC. Noncoding transcription at enhancers: general principles and functional models. *Annu Rev Genet* 2012; **46**: 1-19 [PMID: 22905871 DOI: 10.1146/annurev-genet-110711-155459]

32 **Salmena L**, Poliseno L, Tay Y, Kats L, Pandolfi PP. A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? *Cell* 2011; **146**: 353-358 [PMID: 21802130]

33 **Hansen TB**, Kjems J, Damgaard CK. Circular RNA and miR-7 in cancer. *Cancer Res* 2013; **73**: 5609-5612 [PMID: 24014594 DOI: 10.1158/0008-5472.CAN-13-15]

34 **Djebali S**, Davis CA, Merkel A, Dobin A, Lassmann T, Mortazavi A, Tanzer A, Lagarde J, Lin W, Schlesinger F, Xue C, Marinov GK, Khatun J, Williams BA, Zaleski C, Rozowsky J, Röder M, Kokocinski F, Abdelhamid RF, Alioto T, Antoshechkin I, Baer MT, Bar NS, Batut P, Bell K, Bell I, Chakrabortty S, Chen X, Chrast J, Curado J, Derrien T, Drenkow J, Dumais E, Dumais J, Duttagupta R, Falconnet E, Fastuca M, Fejes-Toth K, Ferreira P, Foissac S, Fullwood MJ, Gao H, Gonzalez D, Gordon A, Gunawardena H, Howald C, Jha S, Johnson R, Kapranov P, King B, Kingswood C, Luo OJ, Park E, Persaud K, Preall JB, Ribeca P, Risk B, Robyr D, Sammeth M, Schaffer L, See LH, Shahab A, Skancke J, Suzuki AM, Takahashi H, Tilgner H, Trout D, Walters N, Wang H, Wrobel J, Yu Y, Ruan X, Hayashizaki Y, Harrow J, Gerstein M, Hubbard T, Reymond A, Antonarakis SE, Hannon G, Giddings MC, Ruan Y, Wold B, Carninci P, Guigó R, Gingeras TR. Landscape of transcription in human cells. *Nature* 2012; **489**: 101-108 [PMID: 22955620 DOI: 10.1038/nature11233]

35 **Wapinski O**, Chang HY. Long noncoding RNAs and human disease. *Trends Cell Biol* 2011; **21**: 354-361 [PMID: 21550244 DOI: 10.1016/j.tcb.2011.04.001]

36 **Taft RJ**, Pang KC, Mercer TR, Dinger M, Mattick JS. Non-coding RNAs: regulators of disease. *J Pathol* 2010; **220**: 126-139 [PMID: 19882673 DOI: 10.1002/path.2638]

37 **Fatica A**, Bozzoni I. Long non-coding RNAs: new players in cell differentiation and development. *Nat Rev Genet* 2014; **15**: 7-21 [PMID: 24296535 DOI: 10.1038/nrg3606]

38 **Yang L**, Froberg JE, Lee JT. Long noncoding RNAs: fresh perspectives into the RNA world. *Trends Biochem Sci* 2014; **39**: 35-43 [PMID: 24290031 DOI: 10.1016/j.tibs.2013.10.002]

39 **Kung JT**, Colognori D, Lee JT. Long noncoding RNAs: past, present, and future. *Genetics* 2013; **193**: 651-669 [PMID: 23463798 DOI: 10.1534/genetics.112.146704]

40 **Qiu MT**, Hu JW, Yin R, Xu L. Long noncoding RNA: an emerging paradigm of cancer research. *Tumour Biol* 2013; **34**: 613-620 [PMID: 23359273 DOI: 10.1007/s13277-013-0658-6]

41 **Li CH**, Chen Y. Targeting long non-coding RNAs in cancers: progress and prospects. *Int J Biochem Cell Biol* 2013; **45**: 1895-1910 [PMID: 23748105 DOI: 10.1016/j.biocel.2013.05.030]

42 **Matouk IJ**, Raveh E, Abu-lail R, Mezan S, Gilon M, Gershtain E, Birman T, Gallula J, Schneider T, Barkali M, Richler C, Fellig Y, Sorin V, Hubert A, Hochberg A, Czerniak A. Oncofetal H19 RNA promotes tumor metastasis. *Biochim Biophys Acta* 2014; **1843**: 1414-1426 [PMID: 24703882 DOI: 10.1016/j.bbamcr.2014.03.023]

43 **Gabory A**, Jammes H, Dandolo L. The H19 locus: role of an imprinted non-coding RNA in growth and development. *Bioessays* 2010; **32**: 473-480 [PMID: 20486133 DOI: 10.1002/bies.200900170]

44 **Amit D**, Hochberg A. Development of targeted therapy for a broad spectrum of cancers (pancreatic cancer, ovarian cancer, glioblastoma and HCC) mediated by a double promoter plasmid expressing diphtheria toxin under the control of H19 and IGF2-P4 regulatory sequences. *Int J Clin Exp Med* 2012; **5**: 296-305 [PMID: 22993648]

45 **Ma C**, Nong K, Zhu H, Wang W, Huang X, Yuan Z, Ai K. H19 promotes pancreatic cancer metastasis by derepressing let-7' s suppression on its target HMGA2-mediated EMT. *Tumour Biol* 2014; **35**: 9163-9169 [PMID: 24920070 DOI: 10.1007/s13277-014-2185-5]

46 **Sorin V**, Ohana P, Gallula J, Birman T, Matouk I, Hubert A, Gilon M, Hochberg A, Czerniak A. H19-promoter-targeted therapy combined with gemcitabine in the treatment of pancreatic cancer. *ISRN Oncol* 2012; **2012**: 351750 [PMID: 22701803 DOI: 10.5402/2012/351750]

47 **Scaiewicz V**, Sorin V, Fellig Y, Birman T, Mizrahi A, Galula J, Abu-Lail R, Shneider T, Ohana P, Buscail L, Hochberg A, Czerniak A. Use of H19 Gene Regulatory Sequences in DNA-Based Therapy for Pancreatic Cancer. *J Oncol* 2010; **2010**: 178174 [PMID: 21052499 DOI: 10.1155/2010/178174]

48 **Cai B**, Song XQ, Cai JP, Zhang S. HOTAIR: a cancer-related long non-coding RNA. *Neoplasma* 2014; **61**: 379-391 [PMID: 25027739]

49 **Rinn JL**, Kertesz M, Wang JK, Squazzo SL, Xu X, Brugmann SA, Goodnough LH, Helms JA, Farnham PJ, Segal E, Chang HY. Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. *Cell* 2007; **129**: 1311-1323 [PMID: 17604720 DOI: 10.1016/j.cell.2007.05.002]

50 **Zhang J**, Zhang P, Wang L, Piao HL, Ma L. Long non-coding RNA HOTAIR in carcinogenesis and metastasis. *Acta Biochim Biophys Sin* (Shanghai) 2014; **46**: 1-5 [PMID: 24165275 DOI: 10.1093/abbs/gmt117]

51 **Kogo R**, Shimamura T, Mimori K, Kawahara K, Imoto S, Sudo T, Tanaka F, Shibata K, Suzuki A, Komune S, Miyano S, Mori M. Long noncoding RNA HOTAIR regulates polycomb-dependent chromatin modification and is associated with poor prognosis in colorectal cancers. *Cancer Res* 2011; **71**: 6320-6326 [PMID: 21862635 DOI: 10.1158/0008-5472.CAN-11-1021]

52 **Gupta RA**, Shah N, Wang KC, Kim J, Horlings HM, Wong DJ, Tsai MC, Hung T, Argani P, Rinn JL, Wang Y, Brzoska P, Kong B, Li R, West RB, van de Vijver MJ, Sukumar S, Chang HY. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. *Nature* 2010; **464**: 1071-1076 [PMID: 20393566 DOI: 10.1038/nature08975]

53 **Kim K**, Jutooru I, Chadalapaka G, Johnson G, Frank J, Burghardt R, Kim S, Safe S. HOTAIR is a negative prognostic factor and exhibits pro-oncogenic activity in pancreatic cancer. *Oncogene* 2013; **32**: 1616-1625 [PMID: 22614017 DOI: 10.1038/onc.2012.193]

54 **Burgess DJ**. Non-coding RNA: HOTTIP goes the distance. *Nat Rev Genet* 2011; **12**: 300 [PMID: 21483457 DOI: 10.1038/nrg2992]

55 **Mohamadkhani A**. Long Noncoding RNAs in Interaction With RNA Binding Proteins in Hepatocellular Carcinoma. *Hepat Mon* 2014; **14**: e18794 [PMID: 24910706 DOI: 10.5812/hepatmon.18794]

56 **Quagliata L**, Matter MS, Piscuoglio S, Arabi L, Ruiz C, Procino A, Kovac M, Moretti F, Makowska Z, Boldanova T, Andersen JB, Hämmerle M, Tornillo L, Heim MH, Diederichs S, Cillo C, Terracciano LM. Long noncoding RNA HOTTIP/HOXA13 expression is associated with disease progression and predicts outcome in hepatocellular carcinoma patients. *Hepatology* 2014; **59**: 911-923 [PMID: 24114970 DOI: 10.1002/hep.26740]

57 **Jiang YJ**, Bikle DD. LncRNA profiling reveals new mechanism for VDR protection against skin cancer formation. *J Steroid Biochem Mol Biol* 2014; **144** Pt A: 87-90 [PMID: 24342142 DOI: 10.1016/j.jsbmb.2013.11.018]

58 **Li Z**, Zhao X, Zhou Y, Liu Y, Zhou Q, Ye H, Wang Y, Zeng J, Song Y, Gao W, Zheng S, Zhuang B, Chen H, Li W, Li H, Li H, Fu Z, Chen R. The long non-coding RNA HOTTIP promotes progression and gemcitabine resistance by regulating HOXA13 in pancreatic cancer. *J Transl Med* 2015; **13**: 84 [PMID: 25889214 DOI: 10.1186/s12967-015-0442-z]

59 **Cheng Y**, Jutooru I, Chadalapaka G, Corton JC, Safe S. The long non-coding RNA HOTTIP enhances pancreatic cancer cell proliferation, survival and migration. *Oncotarget* 2015; **6**: 10840-10852 [PMID: 25912306]

60 **Ji P**, Diederichs S, Wang W, Böing S, Metzger R, Schneider PM, Tidow N, Brandt B, Buerger H, Bulk E, Thomas M, Berdel WE, Serve H, Müller-Tidow C. MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer. *Oncogene* 2003; **22**: 8031-8041 [PMID: 12970751 DOI: 10.1038/sj.onc.1206928]

61 **Yang L**, Lin C, Liu W, Zhang J, Ohgi KA, Grinstein JD, Dorrestein PC, Rosenfeld MG. ncRNA- and Pc2 methylation-dependent gene relocation between nuclear structures mediates gene activation programs. *Cell* 2011; **147**: 773-788 [PMID: 22078878 DOI: 10.1016/j.cell.2011.08.054]

62 **Xu C**, Yang M, Tian J, Wang X, Li Z. MALAT-1: a long non-coding RNA and its important 3' end functional motif in colorectal cancer metastasis. *Int J Oncol* 2011; **39**: 169-175 [PMID: 21503572 DOI: 10.3892/ijo.2011.1007]

63 **Liu JH**, Chen G, Dang YW, Li CJ, Luo DZ. Expression and prognostic significance of lncRNA MALAT1 in pancreatic cancer tissues. *Asian Pac J Cancer Prev* 2014; **15**: 2971-2977 [PMID: 24815433 DOI: 10.7314/APJCP.2014.15.7.2971]

64 **Pang EJ**, Yang R, Fu XB, Liu YF. Overexpression of long non-coding RNA MALAT1 is correlated with clinical progression and unfavorable prognosis in pancreatic cancer. *Tumour Biol* 2015; **36**: 2403-2407 [PMID: 25481511 DOI: 10.1007/s13277-014-2850-8]

65 **Jiao F**, Hu H, Yuan C, Wang L, Jiang W, Jin Z, Guo Z, Wang L. Elevated expression level of long noncoding RNA MALAT-1 facilitates cell growth, migration and invasion in pancreatic cancer. *Oncol Rep* 2014; **32**: 2485-2492 [PMID: 25269958 DOI: 10.3892/or.2014.3518]

66 **Graham M**, Adams JM. Chromosome 8 breakpoint far 3' of the c-myc oncogene in a Burkitt's lymphoma 2; 8 variant translocation is equivalent to the murine pvt-1 locus. *EMBO J* 1986; **5**: 2845-2851 [PMID: 3024964]

67 **You L**, Chang D, Du HZ, Zhao YP. Genome-wide screen identifies PVT1 as a regulator of Gemcitabine sensitivity in human pancreatic cancer cells. *Biochem Biophys Res Commun* 2011; **407**: 1-6 [PMID: 21316338 DOI: 10.1016/j.bbrc.2011.02.027]

68 **Wolpin BM**, Rizzato C, Kraft P, Kooperberg C, Petersen GM, Wang Z, Arslan AA, Beane-Freeman L, Bracci PM, Buring J, Canzian F, Duell EJ, Gallinger S, Giles GG, Goodman GE, Goodman PJ, Jacobs EJ, Kamineni A, Klein AP, Kolonel LN, Kulke MH, Li D, Malats N, Olson SH, Risch HA, Sesso HD, Visvanathan K, White E, Zheng W, Abnet CC, Albanes D, Andreotti G, Austin MA, Barfield R, Basso D, Berndt SI, Boutron-Ruault MC, Brotzman M, Büchler MW, Bueno-de-Mesquita HB, Bugert P, Burdette L, Campa D, Caporaso NE, Capurso G, Chung C, Cotterchio M, Costello E, Elena J, Funel N, Gaziano JM, Giese NA, Giovannucci EL, Goggins M, Gorman MJ, Gross

M, Haiman CA, Hassan M, Helzlsouer KJ, Henderson BE, Holly EA, Hu N, Hunter DJ, Innocenti F, Jenab M, Kaaks R, Key TJ, Khaw KT, Klein EA, Kogevinas M, Krogh V, Kupcinskas J, Kurtz RC, LaCroix A, Landi MT, Landi S, Le Marchand L, Mambrini A, Mannisto S, Milne RL, Nakamura Y, Oberg AL, Owzar K, Patel AV, Peeters PH, Peters U, Pezzilli R, Piepoli A, Porta M, Real FX, Riboli E, Rothman N, Scarpa A, Shu XO, Silverman DT, Soucek P, Sund M, Talar-Wojnarowska R, Taylor PR, Theodoropoulos GE, Thornquist M, Tjønneland A, Tobias GS, Trichopoulos D, Vodicka P, Wactawski-Wende J, Wentzensen N, Wu C, Yu H, Yu K, Zeleniuch-Jacquotte A, Hoover R, Hartge P, Fuchs C, Chanock SJ, Stolzenberg-Solomon RS, Amundadottir LT. Genome-wide association study identifies multiple susceptibility loci for pancreatic cancer. *Nat Genet* 2014; **46**: 994-1000 [PMID: 25086665 DOI: 10.1038/ng.3052]

69 **Huang C**, Yu W, Wang Q, Cui H, Wang Y, Zhang L, Han F, Huang T. Increased expression of the lncRNA PVT1 is associated with poor prognosis in pancreatic cancer patients. *Minerva Med* 2015; **106**: 143-149 [PMID: 25668599]

70 **Hu P**, Shangguan J, Zhang L. Downregulation of NUF2 inhibits tumor growth and induces apoptosis by regulating lncRNA AF339813. *Int J Clin Exp Pathol* 2015; **8**: 2638-2648 [PMID: 26045769]

71 **Peng W**, Gao W, Feng J. Long noncoding RNA HULC is a novel biomarker of poor prognosis in patients with pancreatic cancer. *Med Oncol* 2014; **31**: 346 [PMID: 25412939 DOI: 10.1007/s12032-014-0346-4]

72 **Lu X**, Fang Y, Wang Z, Xie J, Zhan Q, Deng X, Chen H, Jin J, Peng C, Li H, Shen B. Downregulation of gas5 increases pancreatic cancer cell proliferation by regulating CDK6. *Cell Tissue Res* 2013; **354**: 891-896 [PMID: 24026436 DOI: 10.1007/s00441-013-1711-x]

73 **Sun YW**, Chen YF, Li J, Huo YM, Liu DJ, Hua R, Zhang JF, Liu W, Yang JY, Fu XL, Yan T, Hong J, Cao H. A novel long non-coding RNA ENST00000480739 suppresses tumour cell invasion by regulating OS-9 and HIF-1α in pancreatic ductal adenocarcinoma. *Br J Cancer* 2014; **111**: 2131-2141 [PMID: 25314054 DOI: 10.1038/bjc.2014.520]

74 **Zhu Z**, Xu Y, Zhao J, Liu Q, Feng W, Fan J, Wang P. miR-367 promotes epithelial-to-mesenchymal transition and invasion of pancreatic ductal adenocarcinoma cells by targeting the Smad7-TGF-β signalling pathway. *Br J Cancer* 2015; **112**: 1367-1375 [PMID: 25867271 DOI: 10.1038/bjc.2015.102]

75 **Zou Y**, Li J, Chen Z, Li X, Zheng S, Yi D, Zhong A, Chen J. miR-29c suppresses pancreatic cancer liver metastasis in an orthotopic implantation model in nude mice and affects survival in pancreatic cancer patients. *Carcinogenesis* 2015; **36**: 676-684 [PMID: 25863127]

76 **Liu N**, Sun YY, Zhang XW, Chen S, Wang Y, Zhang ZX, Song SW, Qiu GB, Fu WN. Oncogenic miR-23a in Pancreatic Ductal Adenocarcinogenesis Via Inhibiting APAF1. *Dig Dis Sci* 2015; **60**: 2000-2008 [PMID: 25701323]

77 **Ma J**, Fang B, Zeng F, Ma C, Pang H, Cheng L, Shi Y, Wang H, Yin B, Xia J, Wang Z. Down-regulation of miR-223 reverses epithelial-mesenchymal transition in gemcitabine-resistant pancreatic cancer cells. *Oncotarget* 2015; **6**: 1740-1749 [PMID: 25638153]

78 **Keklikoglou I**, Hosaka K, Bender C, Bott A, Koerner C, Mitra D, Will R, Woerner A, Muenstermann E, Wilhelm H, Cao Y, Wiemann S. MicroRNA-206 functions as a pleiotropic modulator of cell proliferation, invasion and lymphangiogenesis in pancreatic adenocarcinoma by targeting ANXA2 and KRAS genes. *Oncogene* 2015; **34**: 4867-4878 [PMID: 25500542 DOI: 10.1038/onc.2014.408]

79 **Kojima M**, Sudo H, Kawauchi J, Takizawa S, Kondou S, Nobumasa H, Ochiai A. MicroRNA markers for the diagnosis of pancreatic and biliary-tract cancers. *PLoS One* 2015; **10**: e0118220 [PMID: 25706130 DOI: 10.1371/journal.pone.0118220]

80 **Lin MS**, Chen WC, Huang JX, Gao HJ, Sheng HH. Aberrant expression of microRNAs in serum may identify individuals with pancreatic cancer. *Int J Clin Exp Med* 2014; **7**: 5226-5234 [PMID: 25664025]

81 **Sandhu V**, Bowitz Lothe IM, Labori KJ, Lingjærde OC, Buanes T, Dalsgaard AM, Skrede ML, Hamfjord J, Haaland T, Eide TJ, Børresen-Dale AL, Ikdahl T, Kure EH. Molecular signatures of mRNAs and miRNAs as prognostic biomarkers in pancreatobiliary and intestinal types of periampullary adenocarcinomas. *Mol Oncol* 2015; **9**: 758-771 [PMID: 25579086 DOI: 10.1016/j.molonc.2014.12.002]

82 **Hong TH**, Park IY. MicroRNA expression profiling of diagnostic needle aspirates from surgical pancreatic cancer specimens. *Ann Surg Treat Res* 2014; **87**: 290-297 [PMID: 25485236 DOI: 10.4174/astr.2014.87.6.290]

83 **Zhang Y**, Li M, Wang H, Fisher WE, Lin PH, Yao Q, Chen C. Profiling of 95 microRNAs in pancreatic cancer cell lines and surgical specimens by real-time PCR analysis. *World J Surg* 2009; **33**: 698-709 [PMID: 19030927 DOI: 10.1007/s00268-008-9833-0]

84 **Bloomston M**, Frankel WL, Petrocca F, Volinia S, Alder H, Hagan JP, Liu CG, Bhatt D, Taccioli C, Croce CM. MicroRNA expression patterns to differentiate pancreatic adenocarcinoma from normal pancreas and chronic pancreatitis. *JAMA* 2007; **297**: 1901-1908 [PMID: 17473300]

85 **Huang F**, Tang J, Zhuang X, Zhuang Y, Cheng W, Chen W, Yao H, Zhang S. MiR-196a promotes pancreatic cancer progression by targeting nuclear factor kappa-B-inhibitor alpha. *PLoS One* 2014; **9**: e87897 [PMID: 24504166 DOI: 10.1371/journal.pone.0087897]

86 **Xu Q**, Li P, Chen X, Zong L, Jiang Z, Nan L, Lei J, Duan W, Zhang D, Li X, Sha H, Wu Z, Ma Q, Wang Z. miR-221/222 induces pancreatic cancer progression through the regulation of matrix metalloproteinases. *Oncotarget* 2015; **6**: 14153-14164 [PMID: 25883224]

87 **Sarkar S**, Dubaybo H, Ali S, Goncalves P, Kollepara SL, Sethi S, Philip PA, Li Y. Down-regulation of miR-221 inhibits proliferation of pancreatic cancer cells through up-regulation of PTEN, p27(kip1), p57(kip2), and PUMA. *Am J Cancer Res* 2013; **3**: 465-477 [PMID: 24224124]

88 **Li A**, Omura N, Hong SM, Vincent A, Walter K, Griffith M, Borges M, Goggins M. Pancreatic cancers epigenetically silence SIP1 and hypomethylate and overexpress miR-200a/200b in association with elevated circulating miR-200a and miR-200b levels. *Cancer Res* 2010; **70**: 5226-5237 [PMID: 20551052 DOI: 10.1158/0008-5472.CAN-09-4227]

89 **Liu R**, Chen X, Du Y, Yao W, Shen L, Wang C, Hu Z, Zhuang R, Ning G, Zhang C, Yuan Y, Li Z, Zen K, Ba Y, Zhang CY. Serum microRNA expression profile as a biomarker in the diagnosis and prognosis of pancreatic cancer. *Clin Chem* 2012; **58**: 610-618 [PMID: 22194634 DOI: 10.1373/clinchem.2011.172767]

90 **Zhu W**, Xu B. MicroRNA-21 identified as predictor of cancer outcome: a meta-analysis. *PLoS One* 2014; **9**: e103373 [PMID: 25098165 DOI: 10.1371/journal.pone.0103373]

91 **Toste PA**, Li L, Kadera BE, Nguyen AH, Tran LM, Wu N, Madnick DL, Patel SG, Dawson DW, Donahue TR. p85α is a microRNA target and affects chemosensitivity in pancreatic cancer. *J Surg Res* 2015; **196**: 285-293 [PMID: 25846727 DOI: 10.1016/j.jss.2015.02.071]

92 **Kara M**, Yumrutas O, Ozcan O, Celik OI, Bozgeyik E, Bozgeyik I, Tasdemir S. Differential expressions of cancer-associated genes and their regulatory miRNAs in colorectal carcinoma. *Gene* 2015; **567**: 81-86 [PMID: 25925209 DOI: 10.1016/j.gene.2015.04.065]

93 **Hu Y**, Wang C, Li Y, Zhao J, Chen C, Zhou Y, Tao Y, Guo M, Qin N, Ren T, Wen Z, Xu L. MiR-21 controls in situ expansion of $CCR6^+$ regulatory T cells through PTEN/AKT pathway in breast cancer. *Immunol Cell Biol* 2015; **93**: 753-764 [PMID: 25735723 DOI: 10.1038/icb.2015.37]

94 **Gong B**, Liu WW, Nie WJ, Li DF, Xie ZJ, Liu C, Liu YH, Mei P, Li ZJ. MiR-21/RASA1 axis affects malignancy of colon cancer cells via RAS pathways. *World J Gastroenterol* 2015; **21**: 1488-1497 [PMID: 25663768 DOI: 10.3748/wjg.v21.i5.1488]

95 **Martin del Campo SE**, Latchana N, Levine KM, Grignol VP, Fairchild ET, Jaime-Ramirez AC, Dao TV, Karpa VI, Carson M,

Ganju A, Chan AN, Carson WE. MiR-21 enhances melanoma invasiveness via inhibition of tissue inhibitor of metalloproteinases 3 expression: in vivo effects of MiR-21 inhibitor. *PLoS One* 2015; **10**: e0115919 [PMID: 25587717 DOI: 10.1371/journal.pone.0115919]

96 **Go H**, Jang JY, Kim PJ, Kim YG, Nam SJ, Paik JH, Kim TM, Heo DS, Kim CW, Jeon YK. MicroRNA-21 plays an oncogenic role by targeting FOXO1 and activating the PI3K/AKT pathway in diffuse large B-cell lymphoma. *Oncotarget* 2015; **6**: 15035-15049 [PMID: 25909227]

97 **Wang LJ**, He CC, Sui X, Cai MJ, Zhou CY, Ma JL, Wu L, Wang H, Han SX, Zhu Q. MiR-21 promotes intrahepatic cholangiocarcinoma proliferation and growth in vitro and in vivo by targeting PTPN14 and PTEN. *Oncotarget* 2015; **6**: 5932-5946 [PMID: 25803229]

98 **Jones MF**, Hara T, Francis P, Li XL, Bilke S, Zhu Y, Pineda M, Subramanian M, Bodmer WF, Lal A. The CDX1-microRNA-215 axis regulates colorectal cancer stem cell differentiation. *Proc Natl Acad Sci USA* 2015; **112**: E1550-E1558 [PMID: 25775580 DOI: 10.1073/pnas.1503370112]

99 **Hemmesi K**, Squadrito ML, Mestdagh P, Conti V, Cominelli M, Piras IS, Sergi LS, Piccinin S, Maestro R, Poliani PL, Speleman F, De Palma M, Galli R. miR-135a Inhibits Cancer Stem Cell-Driven Medulloblastoma Development by Directly Repressing Arhgef6 Expression. *Stem Cells* 2015; **33**: 1377-1389 [PMID: 25639612 DOI: 10.1002/stem.1958]

100 **Ji Q**, Hao X, Zhang M, Tang W, Yang M, Li L, Xiang D, Desano JT, Bommer GT, Fan D, Fearon ER, Lawrence TS, Xu L. MicroRNA miR-34 inhibits human pancreatic cancer tumor-initiating cells. *PLoS One* 2009; **4**: e6816 [PMID: 19714243 DOI: 10.1371/journal.pone.0006816]

101 **Gao Y**, Liu T, Huang Y. MicroRNA-134 suppresses endometrial cancer stem cells by targeting POGLUT1 and Notch pathway proteins. *FEBS Lett* 2015; **589**: 207-214 [PMID: 25528443 DOI: 10.1016/j.febslet.2014.12.002]

102 **Cioffi M**, Trabulo SM, Sanchez-Ripoll Y, Miranda-Lorenzo I, Lonardo E, Dorado J, Reis Vieira C, Ramirez JC, Hidalgo M, Aicher A, Hahn S, Sainz B, Heeschen C. The miR-17-92 cluster counteracts quiescence and chemoresistance in a distinct subpopulation of pancreatic cancer stem cells. *Gut* 2015; **64**: 1936-1948 [PMID: 25887381 DOI: 10.1136/gutjnl-2014-308470]

103 **Lu Y**, Lu J, Li X, Zhu H, Fan X, Zhu S, Wang Y, Guo Q, Wang L, Huang Y, Zhu M, Wang Z. MiR-200a inhibits epithelial-mesenchymal transition of pancreatic cancer stem cell. *BMC Cancer* 2014; **14**: 85 [PMID: 24521357 DOI: 10.1186/1471-2407-14-85]

104 **Wang P**, Chen L, Zhang J, Chen H, Fan J, Wang K, Luo J, Chen Z, Meng Z, Liu L. Methylation-mediated silencing of the miR-124 genes facilitates pancreatic cancer progression and metastasis by targeting Rac1. *Oncogene* 2014; **33**: 514-524 [PMID: 23334332 DOI: 10.1038/onc.2012.598]

105 **Xu D**, Wang Q, An Y, Xu L. MiR-203 regulates the proliferation, apoptosis and cell cycle progression of pancreatic cancer cells by targeting Survivin. *Mol Med Rep* 2013; **8**: 379-384 [PMID: 23732815 DOI: 10.3892/mmr.2013.1504]

106 **Hu Y**, Ou Y, Wu K, Chen Y, Sun W. miR-143 inhibits the metastasis of pancreatic cancer and an associated signaling pathway. *Tumour Biol* 2012; **33**: 1863-1870 [PMID: 23070684 DOI: 10.1007/s13277-012-0446-8]

107 **Jiao LR**, Frampton AE, Jacob J, Pellegrino L, Krell J, Giamas G, Tsim N, Vlavianos P, Cohen P, Ahmad R, Keller A, Habib NA, Stebbing J, Castellano L. MicroRNAs targeting oncogenes are down-regulated in pancreatic malignant transformation from benign tumors. *PLoS One* 2012; **7**: e32068 [PMID: 22384141 DOI: 10.1371/journal.pone.0032068]

108 **Collins MA**, Pasca di Magliano M. Kras as a key oncogene and therapeutic target in pancreatic cancer. *Front Physiol* 2013; **4**: 407 [PMID: 24478710 DOI: 10.3389/fphys.2013.00407]

109 **Chang TC**, Wentzel EA, Kent OA, Ramachandran K, Mullendore M, Lee KH, Feldmann G, Yamakuchi M, Ferlito M, Lowenstein CJ, Arking DE, Beer MA, Maitra A, Mendell JT. Transactivation of miR-34a by p53 broadly influences gene expression and promotes apoptosis. *Mol Cell* 2007; **26**: 745-752 [PMID: 17540599]

110 **Kent OA**, Mullendore M, Wentzel EA, López-Romero P, Tan AC, Alvarez H, West K, Ochs MF, Hidalgo M, Arking DE, Maitra A, Mendell JT. A resource for analysis of microRNA expression and function in pancreatic ductal adenocarcinoma cells. *Cancer Biol Ther* 2009; **8**: 2013-2024 [PMID: 20037478]

111 **Habbe N**, Koorstra JB, Mendell JT, Offerhaus GJ, Ryu JK, Feldmann G, Mullendore ME, Goggins MG, Hong SM, Maitra A. MicroRNA miR-155 is a biomarker of early pancreatic neoplasia. *Cancer Biol Ther* 2009; **8**: 340-346 [PMID: 19106647]

112 **Farhana L**, Dawson MI, Murshed F, Das JK, Rishi AK, Fontana JA. Upregulation of miR-150* and miR-630 induces apoptosis in pancreatic cancer cells by targeting IGF-1R. *PLoS One* 2013; **8**: e61015 [PMID: 23675407 DOI: 10.1371/journal.pone.0061015]

113 **Bracken CP**, Gregory PA, Kolesnikoff N, Bert AG, Wang J, Shannon MF, Goodall GJ. A double-negative feedback loop between ZEB1-SIP1 and the microRNA-200 family regulates epithelial-mesenchymal transition. *Cancer Res* 2008; **68**: 7846-7854 [PMID: 18829540]

114 **Burk U**, Schubert J, Wellner U, Schmalhofer O, Vincan E, Spaderna S, Brabletz T. A reciprocal repression between ZEB1 and members of the miR-200 family promotes EMT and invasion in cancer cells. *EMBO Rep* 2008; **9**: 582-589 [PMID: 18483486 DOI: 10.1038/embor.2008.74]

115 **Mees ST**, Mardin WA, Wendel C, Baeumer N, Willscher E, Senninger N, Schleicher C, Colombo-Benkmann M, Haier J. EP300--a miRNA-regulated metastasis suppressor gene in ductal adenocarcinomas of the pancreas. *Int J Cancer* 2010; **126**: 114-124 [PMID: 19569050 DOI: 10.1002/ijc.24695]

116 **Wellner U**, Schubert J, Burk UC, Schmalhofer O, Zhu F, Sonntag A, Waldvogel B, Vannier C, Darling D, zur Hausen A, Brunton VG, Morton J, Sansom O, Schüler J, Stemmler MP, Herzberger C, Hopt U, Keck T, Brabletz S, Brabletz T. The EMT-activator ZEB1 promotes tumorigenicity by repressing stemness-inhibiting microRNAs. *Nat Cell Biol* 2009; **11**: 1487-1495 [PMID: 19935649 DOI: 10.1038/ncb1998]

117 **Li Y**, Vandenboom TG, Wang Z, Kong D, Ali S, Philip PA, Sarkar FH. miR-146a suppresses invasion of pancreatic cancer cells. *Cancer Res* 2010; **70**: 1486-1495 [PMID: 20124483 DOI: 10.1158/0008-5472.CAN-09-2792]

118 **Sun Y**, Zhang T, Wang C, Jin X, Jia C, Yu S, Chen J. MiRNA-615-5p functions as a tumor suppressor in pancreatic ductal adenocarcinoma by targeting AKT2. *PLoS One* 2015; **10**: e0119783 [PMID: 25856297 DOI: 10.1371/journal.pone.0119783]

119 **Patel K**, Kollory A, Takashima A, Sarkar S, Faller DV, Ghosh SK. MicroRNA let-7 downregulates STAT3 phosphorylation in pancreatic cancer cells by increasing SOCS3 expression. *Cancer Lett* 2014; **347**: 54-64 [PMID: 24491408 DOI: 10.1016/j.canlet.2014.01.020]

120 **Jiang J**, Li Z, Yu C, Chen M, Tian S, Sun C. MiR-1181 inhibits stem cell-like phenotypes and suppresses SOX2 and STAT3 in human pancreatic cancer. *Cancer Lett* 2015; **356**: 962-970 [PMID: 25444909 DOI: 10.1016/j.canlet.2014.11.007]

121 **Gao L**, He SB, Li DC. Effects of miR-16 plus CA19-9 detections on pancreatic cancer diagnostic performance. *Clin Lab* 2014; **60**: 73-77 [PMID: 24600978 DOI: 10.7754/clin.lab.2013.121210]

122 **Pan W**, Tang W, Yuan W, Yu Q, Zuo W, Xu C, Ma J. [Expression and clinical significance of plasma small RNA in patients with pancreatic cancer]. *Zhonghua Zhongliu Zazhi* 2014; **36**: 351-354 [PMID: 25030590]

123 **Komatsu S**, Ichikawa D, Takeshita H, Morimura R, Hirajima S, Tsujiura M, Kawaguchi T, Miyamae M, Nagata H, Konishi H, Shiozaki A, Otsuji E. Circulating miR-18a: a sensitive cancer screening biomarker in human cancer. *In Vivo* 2014; **28**: 293-297 [PMID: 24815829]

124 **Cote GA**, Gore AJ, McElyea SD, Heathers LE, Xu H, Sherman S, Korc M. A pilot study to develop a diagnostic test for pancreatic ductal adenocarcinoma based on differential expression of select

miRNA in plasma and bile. *Am J Gastroenterol* 2014; **109**: 1942-1952 [PMID: 25350767 DOI: 10.1038/ajg.2014.331]

125 **Wang J**, Paris PL, Chen J, Ngo V, Yao H, Frazier ML, Killary AM, Liu CG, Liang H, Mathy C, Bondada S, Kirkwood K, Sen S. Next generation sequencing of pancreatic cyst fluid microRNAs from low grade-benign and high grade-invasive lesions. *Cancer Lett* 2015; **356**: 404-409 [PMID: 25304377 DOI: 10.1016/j.canlet.2014.09.029]

126 **Yu J**, Li A, Hong SM, Hruban RH, Goggins M. MicroRNA alterations of pancreatic intraepithelial neoplasias. *Clin Cancer Res* 2012; **18**: 981-992 [PMID: 22114139]

127 **Wang HY**, Shen J, Jiang CP, Liu BR. How to explain the contradiction of microRNA 200c expression and survival in solid tumors? A meta-analysis. *Asian Pac J Cancer Prev* 2014; **15**: 3687-3690 [PMID: 24870778 DOI: 10.7314/APJCP]

128 **Passadouro M**, Pedroso de Lima MC, Faneca H. MicroRNA modulation combined with sunitinib as a novel therapeutic strategy for pancreatic cancer. *Int J Nanomedicine* 2014; **9**: 3203-3217 [PMID: 25061297 DOI: 10.2147/IJN.S64456]

129 **Joshi GK**, Deitz-McElyea S, Johnson M, Mali S, Korc M, Sardar R. Highly specific plasmonic biosensors for ultrasensitive microRNA detection in plasma from pancreatic cancer patients. *Nano Lett* 2014; **14**: 6955-6963 [PMID: 25379951 DOI: 10.1021/nl503220s]

130 **Bader AG**, Brown D, Winkler M. The promise of microRNA replacement therapy. *Cancer Res* 2010; **70**: 7027-7030 [PMID: 20807816 DOI: 10.1158/0008-5472.CAN-10-2010]

131 **Neesse A**, Gress TM. Emerging role of microRNAs to tackle drug resistance in pancreatic cancer. *Gut* 2015; **64**: 1842-1843 [PMID: 26041749 DOI: 10.1136/gutjnl-2015-309503]

132 **Oh JS**, Kim JJ, Byun JY, Kim IA. Lin28-let7 modulates radiosensitivity of human cancer cells with activation of K-Ras. *Int J Radiat Oncol Biol Phys* 2010; **76**: 5-8 [PMID: 20005451 DOI: 10.1016/j.ijrobp.2009.08.028]

133 **Zhao G**, Zhang JG, Liu Y, Qin Q, Wang B, Tian K, Liu L, Li X, Niu Y, Deng SC, Wang CY. miR-148b functions as a tumor suppressor in pancreatic cancer by targeting AMPKα1. *Mol Cancer Ther* 2013; **12**: 83-93 [PMID: 23171948 DOI: 10.1158/1535-7163.MCT-12-0534]

134 **Zhao G**, Wang B, Liu Y, Zhang JG, Deng SC, Qin Q, Tian K, Li X, Zhu S, Niu Y, Gong Q, Wang CY. miRNA-141, downregulated in pancreatic cancer, inhibits cell proliferation and invasion by directly targeting MAP4K4. *Mol Cancer Ther* 2013; **12**: 2569-2580 [PMID: 24013097 DOI: 10.1158/1535-7163.MCT-13-0296]

135 **Garofalo M**, Croce CM. MicroRNAs as therapeutic targets in chemoresistance. *Drug Resist Updat* 2013; **16**: 47-59 [PMID: 23757365 DOI: 10.1016/j.drup.2013.05.001]

136 **Ma L**, Reinhardt F, Pan E, Soutschek J, Bhat B, Marcusson EG, Teruya-Feldstein J, Bell GW, Weinberg RA. Therapeutic silencing of miR-10b inhibits metastasis in a mouse mammary tumor model. *Nat Biotechnol* 2010; **28**: 341-347 [PMID: 20351690 DOI: 10.1038/nbt.1618]

137 **Park JK**, Lee EJ, Esau C, Schmittgen TD. Antisense inhibition of microRNA-21 or -221 arrests cell cycle, induces apoptosis, and sensitizes the effects of gemcitabine in pancreatic adenocarcinoma. *Pancreas* 2009; **38**: e190-e199 [PMID: 19730150 DOI: 10.1097/MPA.0b013e3181ba82e1]

138 **Zhao Y**, Zhao L, Ischenko I, Bao Q, Schwarz B, Nieß H, Wang Y, Renner A, Mysliwietz J, Jauch KW, Nelson PJ, Ellwart JW, Bruns CJ, Camaj P. Antisense inhibition of microRNA-21 and microRNA-221 in tumor-initiating stem-like cells modulates tumorigenesis, metastasis, and chemotherapy resistance in pancreatic cancer. *Target Oncol* 2015; **10**: 535-548 [PMID: 25639539]

139 **Tay FC**, Lim JK, Zhu H, Hin LC, Wang S. Using artificial microRNA sponges to achieve microRNA loss-of-function in cancer cells. *Adv Drug Deliv Rev* 2015; **81**: 117-127 [PMID: 24859534 DOI: 10.1016/j.addr.2014.05.010]

140 **Trajkovski M**, Hausser J, Soutschek J, Bhat B, Akin A, Zavolan M, Heim MH, Stoffel M. MicroRNAs 103 and 107 regulate insulin sensitivity. *Nature* 2011; **474**: 649-653 [PMID: 21654750 DOI: 10.1038/nature10112]

141 **Finnerty JR**, Wang WX, Hébert SS, Wilfred BR, Mao G, Nelson PT. The miR-15/107 group of microRNA genes: evolutionary biology, cellular functions, and roles in human diseases. *J Mol Biol* 2010; **402**: 491-509 [PMID: 20678503 DOI: 10.1016/j.jmb.2010.07.051]

142 **Zhou H**, Rigoutsos I. MiR-103a-3p targets the 5' UTR of GPRC5A in pancreatic cells. *RNA* 2014; **20**: 1431-1439 [PMID: 24984703 DOI: 10.1261/rna.045757.114]

143 **Li Y**, VandenBoom TG, Kong D, Wang Z, Ali S, Philip PA, Sarkar FH. Up-regulation of miR-200 and let-7 by natural agents leads to the reversal of epithelial-to-mesenchymal transition in gemcitabine-resistant pancreatic cancer cells. *Cancer Res* 2009; **69**: 6704-6712 [PMID: 19654291 DOI: 10.1158/0008-5472.CAN-09-1298]

144 **Ma J**, Fang B, Zeng F, Pang H, Zhang J, Shi Y, Wu X, Cheng L, Ma C, Xia J, Wang Z. Curcumin inhibits cell growth and invasion through up-regulation of miR-7 in pancreatic cancer cells. *Toxicol Lett* 2014; **231**: 82-91 [PMID: 25256401 DOI: 10.1016/j.toxlet.2014.09.014]

145 **Ali S**, Ahmad A, Banerjee S, Padhye S, Dominiak K, Schaffert JM, Wang Z, Philip PA, Sarkar FH. Gemcitabine sensitivity can be induced in pancreatic cancer cells through modulation of miR-200 and miR-21 expression by curcumin or its analogue CDF. *Cancer Res* 2010; **70**: 3606-3617 [PMID: 20388782 DOI: 10.1158/0008-5472.CAN-09-4598]

146 **Xia J**, Duan Q, Ahmad A, Bao B, Banerjee S, Shi Y, Ma J, Geng J, Chen Z, Rahman KM, Miele L, Sarkar FH, Wang Z. Genistein inhibits cell growth and induces apoptosis through up-regulation of miR-34a in pancreatic cancer cells. *Curr Drug Targets* 2012; **13**: 1750-1756 [PMID: 23140286]

147 **Xia J**, Cheng L, Mei C, Ma J, Shi Y, Zeng F, Wang Z, Wang Z. Genistein inhibits cell growth and invasion through regulation of miR-27a in pancreatic cancer cells. *Curr Pharm Des* 2014; **20**: 5348-5353 [PMID: 24479798]

148 **Ma J**, Cheng L, Liu H, Zhang J, Shi Y, Zeng F, Miele L, Sarkar FH, Xia J, Wang Z. Genistein down-regulates miR-223 expression in pancreatic cancer cells. *Curr Drug Targets* 2013; **14**: 1150-1156 [PMID: 23834147]

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