Published in final edited form as:

Cancer Lett. 2010 June 1; 292(1): 8–16. doi:10.1016/j.canlet.2009.11.010.

MicroRNA in Pancreatic Cancer: Pathological, Diagnostic and Therapeutic implications

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Abstract

MicroRNAs (miRNAs) are a group of small non-coding RNA molecules of 20-22 nucleotides (nt) in length, predicted to control the activity of about 30% of all protein-coding genes in mammals. Altered expressions of miRNAs are reported in various cancers and may associate with cancer pathogenesis, apoptosis, and cell growth, thereby functioning as either tumor suppressors or oncogenes. Recent reports showed that deregulation of miRNA contribute to tumor development and progression and hence, have diagnostic and prognostic value in several human malignancies. This review discusses the current status of miRNA in pancreatic cancer development, progression, diagnosis, and therapy.

Keywords

microRNA; pancreatic cancer; diagnosis and therapy

1. Introduction

Cancer is the third leading cause of mortality worldwide [1], second only to cardiovascular diseases in the United States. Among cancers, pancreatic cancer is the fourth leading cause of cancer-related deaths in the United States [2], attributable to about 33,370 deaths in 2007 [3]. The incidence of pancreatic cancer in the United States is ~9 per 100,000 people [4] and with a mortality/incidence ratio of 0.99 [5]. Pancreatic cancer is uniformly fatal and is usually diagnosed at an advanced stage due to the lack of reliable early diagnostic markers. Therefore, there is an obvious need to discover a unique early detection marker(s) and molecular targets to combat the pancreatic cancer.

Recent studies have revealed that expression pattern of miRNAs are a richer source of pathogenomic tumor information as compared to messenger RNA expression profiles [6].

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Conflict of interest statement: The authors have no conflict of interest with any company or financial organization.

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Further, the expression patterns of miRNAs are unique to each tumor type and to their tissue of origin [6-12]. The miRNAs are a family of highly conserved, non-coding, 17-25 nucleotide [13] long RNA products, that regulate gene expression at the post-transcriptional level [13-16]. In 1993, Ambros and colleagues discovered *lin-4* in *Caenorhabditis elegans*, a gene known to control larval development timing that codes for a pair of small RNAs, which negatively regulates *lin-14* translation [13]. miRNAs play an important role in various physiological functions [17-19], and cell fate specification. The present review focuses on the current status of miRNA research, the differential expression pattern of miRNAs in pancreatic tumors and their use in diagnostic and therapeutic purposes.

2. Genomic organization and biosynthesis of miRNAs

The genomic organization of miRNAs is diverse and represents 1-3% of the human genome, [20;21] but they control about 20-30% of protein coding genes in the human genome. Most of the miRNAs (70%) are located in introns and/or exons (miR-10b, miR-33 and miR-198) [22-24], and the remaining 30% are situated in intergenic regions or gene deserts [22;25-27] and contain their own independent transcription units [28]. The miRNAs may be transcribed as monocistronic (e.g miR-21) [24] or polycistronic (e.g the miR-17-92-1 cluster) [29] messenger RNAs. Transcriptional regulation of miRNA expression is controlled by the host tissue genes, which make their expression tissue-specific [15;30;31], or regulated independently via their own regulatory elements [23].

Biosynthesis of miRNAs is a multi-step process, involving both the nuclear and cytoplasmic components. Initially, miRNAs are transcribed into a longer primary transcript (pri-miRNA) of several kilobases in length by RNA polymerase II. The transcript has the characteristic 5' 7-methyl guanylate (m7G) cap structure and 3' poly(A) tail [24;32;33]. The mature miRNA is the result of two endonuclease reactions [23;28;34]. The first processing occurs in the nucleus by Drosha/DGCR8, a ribonuclease III (RNase III) endonuclease that cleaves the pri-miRNA into a 65-70 bp stem-loop precursor miRNA (pre-miRNA) [24;34-39]. The pre-miRNA is then transported to the cytoplasm by Exportin-5-RanGTP dependent mechanism [40-42]. In cytoplasm, pre-miRNA is processed through a series of cuts to generate a mature 19-24 bp RNA duplex by RNase III endonuclease, Dicer/TRBP and AGO2 [40;43-48]. The helicase activity causes the RNA duplex to unwind and mature, single-stranded miRNA (one of the strand), then enters into the RNA-induced silencing complex (RISC) [49-51] and directs the complex to target mRNA through a poorly defined mechanism [52] (Figure 1). Perfect base pairing is extremely rare between the animal miRNAs and the target genes but in majority of the cases, strong base-pairing between the 5' half of the miRNA i.e the "seed" region, nucleotides 2-8, and its target may be sufficient to mediate mRNA regulation in animals [53-55]. Partial complementarity between the seed region of miRNA and the 3' UTR region of the target gene leads to translation inhibition [21], whereas perfect complementarity results in target mRNA degradation [44;56]. Therefore, each miRNA is predicted to target an average of 200 genes [57-60].

3. miRNAs and cancer

Genome-wide studies showed that miRNA genes are often located at genomic regions associated with cancer, chromosomal break points, as well as in the minimal regions of the loss of heterozygosity/amplifications, suggesting their role in human tumorigenesis. Several researchers reported that abnormal expression of miRNAs has been associated with cancers [7;61-69]. Previous studies have shown that some miRNAs are associated with tumor promotion (oncogenes) and some inhibit the tumor by reducing cell proliferation, survival (tumor suppressors) and cellular differentiation (Figure 1) [6;70]. Therefore, restoring the

expression of such miRNAs in tumor cells could possibly promote differentiation and provoke malignant cells into a benign or normal state.

The association of miRNAs and cancers came from a study characterizing the chromosome 13q14 deletion in human chronic lymphocytic leukemia (CLL). The chronic lymphocytic lymphoma and several solid tumors are associated with high incidence of chromosome 13q14 deletion [71]. This locus harboring a candidate gene for the cancer susceptibility is the miRNA cluster miR-15a–16, containing miR-15a and miR-16-1 and the expression of miR-15a and miR-16a was either absent or down-regulated in (68% cases) CLL patients [71-73]. These miRNAs act as tumor suppressors by targeting the anti-apoptotic gene BCL-2 [63]. A increase in apoptosis was observed when there was an ectopic expression of miR-15a–16 in lymphoma cells that harbor the 13q14 deletion. Later on, several groups reported an altered expression of miRNA in various cancers [66;74-79]

4. Differential expression of miRNAs in pancreatic cancer

The miRNA deregulation can be monitored by the profiling miRNAs at different stages of cancer. The expression pattern of miRNAs seems to be a better way to identify the cancer type than the messenger RNA expression patterns because these are more informative in developmental lineage, as well as during differentiation of different tumors [6]. Over the past years, a number of different approaches, including cDNA arrays [80;81], a modified Invader assay [82] and Real time PCR, [79;80;83] have been described to quantify miRNAs. Subsequently, nearly identical members of the let-7 family of miRNA isoforms were effectively discriminated by minor groove binder probes [84]. These techniques demonstrate the tissue-specific miRNA expression in several studies. For example, a profiling and clustering of 222 miRNA precursors in 32 cell lines of lung, breast, head and neck, colorectal, prostate, pancreatic, and hematopoietic cancers demonstrated that most of the cell lines were clustered into their respective tissues from which each cell line was derived [84]. Using these advanced technologies, several studies have recently shown the deregulation of miRNA expression in pancreatic cancer tumor tissues [10;80;85-89] (Table-I) and this differential miRNA expression might be useful in differential diagnosis of pancreatic cancer from other tumors. For instance, the miR-375 and miR-376 were expressed at significantly higher levels in the mouse pancreas and pancreatic islet cells compared with mouse brain, heart, and liver tissue [90]. The expression of the miR-376 precursor was highest in the human pancreatic cancer cell line, Panc1 compared to the other cell lines studied [11;84]. Large-scale miRNA profiling in (540 samples) solid tumors (breast, colon, lung, pancreas, prostate, and stomach) showed that the spectrum of miRNAs expression varied in different solid tumors and of normal cells (43 of 137 miRNAs, 31%). The miR-21, miR-191, and miR-17-5p were significantly over expressed in all of the six tumor types. Whereas, miR-218-2 was consistently down-regulated in colon, stomach, prostate, and pancreas cancers, but not in lung and breast carcinomas. This observation indicated that the colon, pancreas, prostate, and stomach have the most similar miRNA signatures, whereas, breast and lung were represented by different miRNA signatures. Similarly, up-regulation of miR-142-3p, miR-142-5p, miR-155, and miR-146a expression was observed in human pancreatic neuroendocrine tumors (PNETs) as compared with normal human islets[91]. Lee et al. (2007) reported that aberrantly expressed one hundred miRNA precursors in pancreatic cancer or desmoplasia, including the previously reported miRNA in other human cancers (miR-155, miR-21, miR-221 and miR-222) as well as the first reported miR-376a and miR-301 for the differential expression of cancer [87].

Similarly, using the QuantiMir system, the differential expression of 95 miRNAs was analyzed in 10 pancreatic cell lines and 17 pairs of pancreatic cancer/normal tissues. A significant up-regulation of miR-196a, miR-190, miR-186, miR-221, miR-222, miR-200b,

miR-15b, and miR-95 in most pancreatic cancer tissues and cell lines was reported. The up-regulation of these eight miRNAs ranged from 70–100% between normal control and tumor cells or tissues. In pancreatic cancer samples, the magnitude of these miRNAs overexpression was ranged from 3 to 2018-fold when compared to the normal control [92]. The miR-155 and miR-21 were significantly upregulated in the 15 intraductal papillary mucinous neoplasms (IPMNs) versus the matched controls[93]. Later on, they used Locked Nucleic Acid in situ hybridization (LNA-ISH) to confirm the expression pattern of miR-155 in 53 of 64 (83%) IPMNs compared to 4 of 54 (7%) normal ducts, and of miR-21 in 52 of 64 (81%) IPMNs compared to 1 of 54 (2%) normal ducts, respectively. Further, the up-regulation of miR-155 transcripts was observed by qRT-PCR in 6 of 10 (60%) IPMN-associated pancreatic juice samples compared to 0 of 5 (0%) disease controls. The expression of miR-216 has also shown to be specific to the pancreas [94;95]. Therefore, miRNAs play vital roles not only in different kinds and stages of pancreatic tumors but also in many diseases, including different cancers, cardiovascular diseases, and immune disorders. Epigenetic modification, DNA copy number change, and genetic mutations may be the factors that regulate the expression of miRNAs.

Gusev *et al.* (2007) analyzed predicted miRNA targets and recommended that co-expressed miRNAs collectively provide abnormal phenotypic changes in cancer cells by targeting the function and the signaling pathways known to be affected in a particular cancer [96;97]. This data added to the list of miRNAs with important cancer gene targets as previously shown by let-7::Ras interaction[66], miR-17-5p::E2F1[66;98] and miR-16::Bcl2 [63]. Similarly, let-7 miRNAs were expressed in pancreatic cancer cells but do not inhibit the epithelial mesenchymal transition [99]. A set of patient samples was tested to confirm the correlation between the expression of retinoblastoma (RB1) protein and miR-106a in gastric, prostate, and lung tumor samples, in which RB1 was down-regulated and miR-106a was found to be over expressed. But in breast tumor samples, miR-106a was slightly down-regulated and RB1 was expressed at higher levels than that of the paired normal control [11]. These experiments strengthen the hypothesis that the aberrant expression of miRNAs in solid tumors were crucial in regulating key cancer genes [12].

The expression of miRNAs can be regulated by epigenetic modification. CpG methylation is one of the epigenetic mechanisms for miRNA deregulation in cancer tissue. The miRNAs are significant components of the p53 transcriptional network and during DNA damage, some miRNAs exhibit p53-dependent up-regulation. The characterization of miR-34a primary transcript and promoter demonstrated that miR-34a is directly transactivated by p53 [100]. miR-34a expression causes reprogramming of gene expression and promotes apoptosis. Genes targeted by miR-34a, are highly enriched and play a crucial role in regulating cell-cycle progression, apoptosis, DNA repair, and angiogenesis. Therefore, miR-34a plays an important role in modulation and fine-tuning of the gene expression initiated by p53. Similarly, miR-34a expression was absent in several types of tumors due to the aberrant CpG methylation of its promoter [101]. Nineteen out of 24 primary prostate carcinomas displayed CpG methylation at the promoter sequence of the miR-34a gene, which resulted in the loss of its expression. The miR-34a promoter CpG methylation was also detected in breast, lung, colon, kidney, bladder, pancreatic carcinoma cell lines, melanoma cell lines and primary melanoma samples. After DNA damage, silencing of miR-34a was dominant over its transactivation by p53. Therefore, miR-34a acts as a tumor suppressor gene and is inactivated by CpG methylation and leads to transcriptional silencing in a broad range of genes in many tumors. The stress-induced gene, tumor protein 53-induced nuclear protein 1 (TP53INP1) is down-regulated in pancreatic cancer. The miR-155 is overexpressed in pancreatic cancer as well as in other tumors. The TP53INP1 expression was down-regulated during the early development of pancreatic ductal adenocarcinoma (PDAC) due to the suppression of its expression by over expressed miR-155 [86]. Similarly,

miR-17-92 cluster is up-regulated in lymphomas and breast, lung, colon, stomach and pancreatic cancers. This miRNA cluster targets the E2F1, BIM and PTEN leading to increased proliferation of cancer cells [11;102;103]. The miR-21 was significantly up-regulated in pancreatic cancer [85;93] and targets the Phosphatase and tensin homologue 2 (PTEN), programmed cell death 4 (PDCD4), trophomyosin 1 (TPM1) and tissue inhibitor of metalloproteinases 3 (TIMP3) leading to inhibition of apoptosis and therefore an increased tumorigenicity [104]. Ectopic expression of miR-107 in pancreatic cell lines MiaPACA-2 and Panc-1 revealed decreased growth rate due to down regulation of cyclin-dependent kinase 6 by miR-107 [105].

Similarly, over expression of miR-21 precursor in pancreatic cancer cells showed increased proliferation, invasion, and chemoresistance to gemcitabine compared with the control cells but the reverse was observed, when the miR-21 was knockdown in the pancreatic cancer cells [106]. Another study reported significant down regulation of let-7 in PDAC samples, as compared to adjacent tissue and its complete loss in poorly differentiated cancer samples. Overexpression of let-7 in pancreatic cancer-derived cell lines strongly inhibits cell proliferation, K-ras expression, and mitogen-activated protein kinase activation [107]. Transcriptional suppression of the miRNA-200 family members such as miR-141 and miR-200c by zinc-finger E-box binding homeobox 1 (ZEB1) [108] strongly activate epithelial differentiation in pancreatic, colorectal and breast cancer cells by targeting epithelial-mesenchymal transition (EMT) activators such as transforming growth factor beta 2 and ZEB1. These results indicate that ZEB1 triggers miRNA-mediated stabilization of EMT and promotes the invasion of cancer cells. Questions regarding the association of miRNAs and their role in cancer development remain unknown but it is suggested that a set of miRNAs might be associated with pancreatic tumorigenesis by acting as tumor suppressor or oncogene (Figure 1).

5. Agents altering miRNA expression in pancreatic cancer

The MTT-based cytotoxicity assay used to evaluate the influence of trichostatin A (TSA) treatment on the BxPC-3 cell viability showed the growth arrest of cells at the G(0)/G(1) phase. The inhibition of proliferation was observed in a time and dose-dependent manner which is accompanied by differential expression of miRNAs [109]. The results suggested that TSA may stimulate the expression of tumor suppressor miR-200c and miR-21 leading to the inhibition of proliferation in human pancreatic cancer cell line BxPC-3. In another study, curcumin changes the miRNA expression pattern in human pancreatic cells, by the up and down-regulation of miR-22 and miR-199a*, respectively [80]. Therefore, modulation of miRNA expression may be an important mechanism underlying the biological effects of curcumin. Similarly, exposure of MiaPACA-2 and Panc-1 with demethylating agent (5-aza-2'-deoxycytidine) or the histone deacetylase inhibitor (Trichostatin A) leads to the up-regulation of 14 microRNAs (miR-107, miR-103, miR-29a, miR29b and miR-320) at two fold or greater in each cell line. Forced expression of the miR-107 *in vitro* in MiaPACA-2 and Panc-1 results in a reduced growth rate due to the down-regulation of cyclin-dependent kinase by miR-107 [105]. Treatment of gemcitabine sensitive and gemcitabine-resistant pancreatic cancer cells with natural agents such as 3,3-diindolylmethane (DIM) or isoflavone results in significant down-regulation of miR-200b, miR-200c, let-7b, let-7c, let-7d, and let-7e in gemcitabine-resistant cells, which showed increased epithelial mesenchymal transition characteristics such as elongated fibroblastoid morphology, reduced expression of E-cadherin, and increased expression of mesenchymal markers such as vimentin and ZEB1 [110].

6. miRNAs used as a diagnostic markers

The expression patterns of 217 miRNAs may classify more accurately the 12 out of 17 tumors than the information based on ~16,000 messenger RNAs expression profiles (Lu et al., 2005). Decreased expression of let-7 in lung cancer was significantly associated with shortened post-operative survival, and was independent of disease stage [79]. Several reports indicated that miRNA expression profiles are useful in the diagnostic/prognostic of specific cancer types [6;8;72;75;78;79;111-113].

Expression profiles of miRNAs may also offer clues to pancreatic tumorigenesis and provide new diagnostic markers [87]. The common miRNA expression pattern may distinguish tumor type from the normal pancreas. Increased expression of miR-103 and miR-107, with decreased expression of miR-155 are useful to discriminate tumors from the normal pancreas [10]. Endocrine tumors from acinar type can be distinguished by a set of 10 miRNAs, which are possibly associated with either normal endocrine differentiation or endocrine tumorigenesis [10]. The miR-204 is chiefly expressed in insulinomas and it correlates with immunohistochemical expression of insulin [10]. Further, over expression of miR-21 is strongly associated with both a high Ki67 proliferation index and the presence of liver metastasis [10].

Previous studies showed that unique miRNA signatures in normal, chronic pancreatitis and cancer tissues. The profiling of miRNA expression in normal pancreas, chronic pancreatitis, and pancreatic ductal adenocarcinoma (PDAC) tissues and PDAC-derived cell lines showed that the presence of miR-216 and -217 and the lack of miR-133a expression was a characteristic feature of the pancreatic tissue, therefore, miRNA expression profiles differentiate between normal pancreas, chronic pancreatitis, and PDAC tissues. Further, in the same study it was reported that a total of 26 miRNAs were aberrantly expressed in PDAC, out of which, only miR-217 and -196a were found to be differentially expressed among the normal pancreas, chronic pancreatitis and cancerous tissues. This differential expression pattern have a potential utility for miRNAs based diagnostic procedures [88]. The expression pattern of miRNAs in pancreatic cancer and normal pancreas and chronic pancreatitis was studied and results showed that the over expression of 21 miRNAs and decreased expression of four miRNAs can correctly differentiate pancreatic cancer from benign pancreatic tissue in 90% of the samples. In addition, eight up-regulated and down-regulated miRNAs can differentiate the pancreatic cancer from chronic pancreatitis with 93% accuracy. A subgroup of six miRNAs was able to distinguish long-term survivors with node-positive disease from those dying within 24 months. Finally, over expression of miR-196a-2 was found to predict poor survival (median, 14.3 months [95% confidence interval, 12.4-16.2] vs. 26.5 months [95% confidence interval, 23.4-29.6]; $P = .009$) [85]. Therefore, unique miRNA expression pattern in pancreatic cancers may differentiate it from normal pancreas and chronic pancreatitis. Further, miRNA expression pattern may also be able to distinguish between long and short term survivors. The over expression of miR-99, miR-100, miR-100-1/2, miR-125a, miR-125b-1, miR-199a-1, and miR-199a-2 was observed in cancers as well as in chronic pancreatitis but not in normal pancreatic tissue. Similarly, it has been reported that the over expression of miR-21, miR-221, miR-222, miR-181a, miR-181b, miR-181d, and miR-155 in tumor samples compared to benign pancreatic tissue [85].

In situ hybridization showed a significant up-regulation of miR-21 in pancreatic cancers [114;115] but its expression did not correlate with tumor size, differentiation, nodal status, or tumor stage. The over expression of miR-21 was predictive of a poorer outcome compared to the absence or faint/focal miR-21 expression in patients. Therefore, in patients, over expression of miR-21 indicates the limited survival and may be an important biological

marker for prognosis [115]. The miR-196a and miR-217 can effectively distinguish between healthy tissue, PDAC, and chronic pancreatitis [116]. Furthermore, the expression of miR-196a is specific to PDAC cells and its expression is parallel to the progression of PDAC. Similarly, miR-196a-2 may also play a important role in predicting prognosis in pancreatic cancer [85].

Profiling of four miRNAs such as miR-21, miR-210, miR-155, and miR-196a in the plasma of pancreatic cancer patients revealed that elevated expression of miR-155 and miR-196a was observed with the parallel progression of disease. The assays for plasma levels analyses of these four miRNAs showed a sensitivity of 64% and a specificity of 89%. The study indicated that development of plasma miRNA profiling can be a sensitive and specific blood-based biomarker assay for pancreatic cancer [117]. Further, elevated levels of miR-155, miR-203, miR-210 and miR-222 expression in pancreatic tumors were significantly associated with increased risk (6.2-fold) of death compared to patients with tumors having reduced expression of these miRNAs [118].

7. miRNAs as a therapeutic agents in pancreatic cancer

If the PDAC Progression is due to miRNA overexpression/down regulation, the targeting of the mature miRNAs or their precursors by synthetic, chemically-modified antisense oligonucleotides or overexpression of miRNAs ectopically might be considered for therapy. The antisense oligonucleotides include Locked Nucleic Acid oligonucleotides or cholesterol conjugates of 2'-O-methyl, 2'-O-methoxyethyl (antagomirs).

Transfection of the synthetic miRNAs (Gli-1-miRNA-3548) and its corresponding duplex (Duplex-3548), significantly inhibits Gli-1 leading to the inhibition of the proliferation, delayed cell division and activation of late apoptosis in MiaPACA-2 cancer cells [89;119]. The expression of let-7 is higher in normal acinar pancreatic cells but it is lost in poorly differentiated cancer cells. Restoring the expression of the let-7 level in pancreatic ductal adenocarcinoma derived cells with plasmid based synthetic let-7 or lentiviral transduction *in vitro* and *in vivo* strongly inhibits the cell proliferation, K-ras expression, and mitogen-activated protein kinase activation, but it fails to inhibit tumor growth progression after intratumoral gene transfer [120]. Another study revealed that over expression of miR-21 and -221 enhanced the malignant phenotype of the pancreatic cancer cells. An inhibition of these miRNAs using antisense oligonucleotides revealed decreased proliferation and increased apoptosis (HS766T 3-6 fold) of pancreatic cancer cell lines compared to control oligonucleotides. Knock down of miR-21 and -221 expression with their corresponding antisense oligonucleotides in HS766T cells results in cell cycle arrest (G1 phase) which is accompanied by an increased expression of PTEN, RECK, and p27 respectively. Treatment of pancreatic cancer cells with the antisense oligonucleotides-gemcitabine combinations were synergistic [121]. Similarly, increased expression of miR-10a was reported in metastatic pancreatic adenocarcinoma and it promotes the metastatic potential of pancreatic tumor cells by suppressing the expression of HOXB1 and HOXB3 genes. Further, the retinoic acid receptor (RAR) antagonists effectively repress miR-10a expression that results in inhibition of pancreatic cancer cell metastasis [122]. Therefore, these studies provided early steps for miRNA replacement therapy for pancreatic cancer.

Ji et al. (2009) reported the over expression of miR-34 (miR-34 family members was found to be directly regulated by p53) in p53-mutant human pancreatic cancer cell lines (MiaPACA2 and BxPC3) by using miR-34 mimics or infection with lentiviral miR-34 construct and an observed down regulation of Bcl-2 and Notch1/2, which is accompanied by inhibition of pancreatic cancer cells clonogenicity and invasion, promotes apoptosis and cell cycle arrest at G1 and G2/M of the cells, which in consequence become more sensitive to the

chemotherapy and radiation. They also observed that miR-34 over expression leads to an 87% reduction of the tumor-initiating cell population, which is accompanied by inhibition of tumor growth *in vitro* and tumor formation *in vivo*. These results indicated that miR-34 may restore the tumor suppressing function of the p53 in p53-deficient human pancreatic cancer cells by modulating the downstream targets Bcl-2, Notch signaling pathway, and also plays an important role in pancreatic cancer stem cell self-renewal/cell fate. Therefore, miR-34 restoration in pancreatic cancer patients may be a novel molecular therapy [123].

8. Conclusions and Future Directions

Identification of unique patterns of deregulated miRNA expression in pancreatic cancer provides valuable information that may serve as molecular biomarkers for tumor diagnosis, identifying low and high risk populations of patients, disease prognosis, prevention of cancer, and prediction of therapeutic responses. The significant role of miRNAs in tumor development and progression emphasizes their importance as mechanism-based therapeutic targets in this malignant disease, which have yet to be fully exploited. The biological functions of several miRNAs are not known in normal and diseased conditions. The interpretation of miRNA profiling data and regulatory functions of miRNA in pancreatic cancer development and progression will be exploited. Therefore, miRNAs can serve as a valuable diagnostic markers and therapeutic target for numerous diseases including pancreatic cancer. Silencing, or antisense blocking, and miRNA modifications of oncogenic miRNAs provide new avenues for treatment of pancreatic cancer as well as other type of cancers.

Acknowledgments

The authors on this work are supported by grants from the National Institutes of Health (CA78590, CA111294, CA133774 and CA131944).

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Figure 1.

Overview of miRNA biosynthesis and its role in pancreatic cancer. miRNAs upregulated and downregulated in pancreatic cancer are depicted in red (left) and green (right), respectively.

Table 1
Important miRNA expression patterns in pancreatic cancer (PC) cell lines and tissues.

miRNA	Expression	microRNA targeted genes	Reference
miR-196a, 190, 186, 221, 222, 200b, 15b, and 95.	Up-regulation	Hoxb8, ZEB1 and SIP1.	[92]
miR-155	Up-regulation	TP53INP1	[86;93]
miR-221, 424, 301, 100, 376a, 125b-1, 21, 16-1, 181a, 092-1, 15b, 155, 212, 107, 24-1, let-7f-1&let-7d	Up regulation		[87]
miR-345, 142-P, 139	Down-regulation		[87]
miR-196a-2, 221, 181a, 155, 21, 213, 181b, 222, 181b-2, 21, 181b-1, 181c, 220, 181d, 223, 100-1/2, 125a, 143, 10a, 146, 99, 100, 199a-1, 10b, 107, 103-2, 1 25b-1, 205, 23a and 23b	Up-regulation	Hoxb8	[85]
miR-148a, 148b and 375	Down-regulation		[85]
miR-21	Up-regulation	PDCD4	[85;87;93;106;115; 124]
miR-155	Down-regulation		[10;11]
miR-17, 20, 92-1,-99a, 99b, 100,103, 107, 125a, 125b-1, 125b-2, 129-2, 130a, 132, 204, 211 and 342.	Up-regulation	MYC gene	[10]
miR-34a	Down-regulation	CDK6, P53,	[100;101]
miR-93, 196a, 196b, 205, 203, 210, 224, 221, 222, 145, 150, 143, 155, 146a, 141 223, 31, & 18a	Up-regulation	TIMP3, ZNF462 TP53INP1, ZNF563, STAT3, Kit	[88;116]
miR-29c, 30a-3p, 96, 130b, 141, 148a, 148b, 216, -217, 375 and 494, 130b,	Down-regulation	cyclin-dependent kinase inhibitor 1B (p27, Kip1) and 1C (p57, Kip 2)	[88;116]
miR-21, 17-5p, 191 29b-2, 223 128b, 199a-1, 24-1, 24-2, 146, 181b-1, 20a, 107, 32 3, 92-2, 214, 30c, 25, 221 &106a	Up-regulation		[11]
Let-7	Down-regulation	K-ras and MAPK	[120]
miR-376	Up-regulation		[84]