Critical role of miRNAs in pancreatic cancer

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1. ABSTRACT

Pancreatic cancer (PC) is an aggressive malignancy with a high mortality rate and poor prognosis. Numerous investigations have shown that microRNA (miRNA) plays a vital role in PC. Thousands of miRNAs have been screened in PC and altered miRNAs, including circulating miRNAs, are associated with PC proliferation, apoptosis, metastasis, chemosensitivity, and radiosensitivity. Several studies have shown that miRNAs can act as potential diagnostic and prognostic markers. The present review focuses on recent advances regarding the roles of miRNAs in PC and their practical value.

2. INTRODUCTION

Cancer originating from the pancreas, a glandular organ located behind the stomach, is a highly aggressive malignancy with a poor prognosis (1). Pancreatic cancer (PC) has one of the highest mortality rates of all cancers. Infiltrating pancreatic ductal adenocarcinoma (PDAC) is the most common type of PC, accounting for up to 90% of cases (2). In the early stages of PC there are usually no symptoms, and symptoms which are specific for suspicion of PC often do not appear until the disease is at an advanced stage. At the time of diagnosis the cancer has usually spread to other parts of the body (3, 4). Signs and symptoms of PC may include yellow skin, abdominal and back pain, unexplained weight loss, light colored stools, dark urine and loss of appetite (5). Many risk factors can contribute to PC, including smoking, obesity, diabetes, and certain rare genetic conditions such as multiple endocrine neoplasia type 1 and hereditary nonpolyposis colon cancer among others (6).

The development of PC may involve the overexpression of several oncogenes, inactivation of tumor suppressor genes or the deregulation of various signaling proteins. Many investigations have demonstrated that aberrant expression of kirsten rat sarcoma viral oncogene (KRAS) and p53 play critical roles in PC (7). In addition, specific mutations can lead to pancreatic carcinoma (8). The genetic mutations that cause PC have been well characterized. Genetic analysis of PC tissue has indicated that multiple mutations accumulate over time. The most common mutations are located in the KRAS gene (about 90%) (9, 10), p16/CDKN2A gene (about 75%) (11), tumor protein p53 gene (about 65%) (12, 13), SMAD4 gene (about 50%) (11, 14) and the SWI/SNF gene (35%) (15, 16). However, blocking the activity of these frequently mutated genes was not found to be a promising therapeutic strategy. Chemotherapy is considered the main treatment option for patients with unresectable PC, and chemo-radiotherapy may improve survival and quality of life. However, even with advancements in medicine, PC is still extremely

resistant to the currently available regimens (17, 18). The burden of PC is expected to increase over time. This situation represents a challenge for scientists to identify the best active regimen with the fewest side effects. Therefore, there is an urgent need to understand the molecular mechanisms and biomarkers underlying this disease, including the genetic and epigenetic networks influencing the malignant transformation, metastasis and chemo-resistance mechanisms of PC. Recent studies have shown that dysregulation of microRNA (miRNA) has key relevance in pancreatic tumorigenesis (19, 20). Consequently, the evaluation of miRNAs as therapeutic targets and biomarkers in the diagnosis and prognosis of PC is of interest. The current review focuses on recent advances in miRNA research in PC and the potential practical value of miRNAs.

3. EPIDEMIOLOGY OF PANCREATIC CANCER

PC is the seventh leading cause of death due to cancer worldwide (21). Compared with the developing world, the disease occurs more often in the developed world, where approximately 65% of new cases occur annually. In the United States, PC is the fourth most common cause of cancer-related death with an estimated 30,700 new cases and 30,000 deaths expected in 2013 (22, 23). Although the incidence and mortality of some other cancers have slowly declined in recent years, PC still has a high occurrence and mortality rate. PC exhibits aggressive features and has a shorter 5-year relative survival rate of 4%. For all stages combined, the 1-year relative survival rate is only 21%. Even patients who undergo complete resection, chemotherapy, and radiation have a 5-year survival of only 20% (24, 25). Lack of early alarm symptoms, rapid local or distant metastasis, highly malignant phenotypes, and innate resistance to conventional chemotherapeutics are the major reasons for the high mortality rate of PC patients (26). PC is a highly heterogeneous disease. A large scale genetic analysis revealed that PC is defined by numerous exomic alterations in diverse signaling pathways (27). In fact, the deregulation mechanisms of PC are unknown and the detailed molecular mechanism requires further clarification. Therefore, there is an urgent need to understand the molecular mechanisms involved in the occurrence and progression of PC, and to develop new diagnostic and therapeutic strategies to improve the outcome of patients suffering from this malignant disease.

4. THE CHARACTERISTICS OF miRNAs

microRNAs (miRNAs), which were first discovered in *Caenorhabditis elegans* in 1993, constitute an evolutionarily conserved class of small, non-coding RNAs that regulate gene expression at the posttranscriptional level (28). They are negative regulators of gene expression through base pair interactions with the 3′untranslated region (3′UTR) of protein-coding

mRNAs (29). Perfect complementarity between the miRNAs and the 3′UTR of the target transcripts leads to degradation of mRNAs, while partial complementarity results in inhibition of translation. The majority of interactions between miRNA and mRNA in animals are only partially complementary, thus translational inhibition predominates. miRNAs are predicted to regulate the activity or gene expression of approximately 30% of all the protein-coding genes in mammals. To date, more than 700 human miRNAs have been identified (29, 30).

The biogenesis of miRNAs involves a complicated process. miRNAs are initially transcribed from genomic DNA into large primary miRNAs (pri-miRNAs). pri-miRNAs are then cleaved by Drosha RNase III endonuclease in the nucleus, known as precursor miRNA (pre-miRNA), which is a hairpin loop structure of up to 70 nucleotides in length. Pre-miRNAs are subsequently transported into the cytoplasm by a nuclear membrane transporter, Exportin 5, where they are further processed by another RNase III Dicer into mature miRNAs, a class of 21–25 nucleotides in length. Single-stranded mature miRNAs are then incorporated into the RNA-induced silencing complex (RISC). Mature miRNAs guide the RISC to find specific target mRNAs by complementary base pairing interactions with the 3′UTRs of target mRNAs. The RISC eventually causes degradation of target mRNAs and/or translational down-regulation, thus inhibiting gene expression (31-33).

5. ABERRANT EXPRESSION OF miRNA IN PC

miRNAs are involved in cellular processes such as cell proliferation, cell migration and cell metabolism (28, 34); therefore, aberrant expression of miRNAs can result in many human diseases, including the occurrence of cancer and metabolism disorder. A number of approaches have been described to quantify miRNA levels. These approaches have revealed distinct cell- and tissue-specific miRNA expression in PC specimens, which suggests that miRNAs play a role in the development of PC (35).

The earliest investigation of miRNAs in the pancreas showed that miR-375 and miR-376 were expressed at higher levels in mouse pancreas and pancreatic islet cells than in other mouse tissues such as brain, heart, and liver tissue (36). A subsequent study found that the expression of miR-376 precursor in the Panc-1 PC cell line was the highest of the cell lines studied, while expression of miR-375 in the two PC cell lines studied were similar to the other cell lines (37). Real-time PCR is the traditional strategy for measuring miRNA expression. Lee EJ *et al*. profiled more than 200 microRNA precursors in specimens of human PC, paired benign tissue, and normal pancreas using real-time PCR (38). Approximately 100 miRNA precursors were aberrantly expressed in PC or desmoplasia, including miR-155,

miR-21, miR-221, miR-222, miR-376a and miR-301. Most of the major aberrantly expressed miRNAs displayed increased expression in tumors. Mature miRNA showed that three of the major differentially expressed miRNAs (miR-221, miR-376a, and miR-301) were localized to tumor cells and not to stroma, normal acini, or ducts (38).

In the past decade, microarray has been used to detect global miRNA expression. Roldo *et al*. profiled the global miRNA expression using microarray and found that a common pattern of miRNA expression distinguishes any PC type from normal pancreas (39). Specifically, the expression of miR-103 and miR-107, accompanied by a lack of expression of miR-155, distinguishes PC from normal tissue; a set of miRNAs discriminates endocrine from acinar tumors and is possibly associated with either normal endocrine differentiation or endocrine tumorigenesis; and the overexpression of miR-21 is strongly associated with both a high Ki67 proliferation index and the presence of liver metastasis; miR-204 is primarily expressed in insulinomas and correlates with immunohistochemical detection of insulin (39). These results suggest that alterations in miRNA expression might prove useful in distinguishing tumors with different clinical behaviors (35, 39). In another study, Bloomston *et al*. demonstrated that a series of miRNAs were impaired in PC compared with normal pancreas and pancreatitis tissue samples, with up-regulation of miR-155, miR-181a,b,c,d, miR-21, miR-196a, and miR-221, and down-regulation of miR-148a,b and miR-375 (40). Briefly, the expression of miR-196a was up-regulated and inversely correlated with survival in PC patients in these investigations (40, 41); strong expression of miR-21 and miR-200c was associated with poor survival of PC patients (42-44); miR-21 expression was predictive of poorer outcomes compared with absent or faint/focal miR-21 expression in patients with node-negative disease (43); in the high miR-200c expression group, the 5-year survival rate was 33.5%, but was 11.2% in the low miR-200c expression group (44).

In addition to the miRNAs dysregulated in PC tissues, many circulating miRNAs are also affected during PC progression. Kong *et al*. found that serum miR-196a was a potential noninvasive marker for PDAC prognosis and selection for laparotomy (45). Another investigation by Wang *et al*. showed that the expression levels of four miRNAs in plasma including miR-21, miR-210, miR-155, and miR-196a, were significantly higher in patients with PC than in a healthy control group (46). Collectively, the miRNAs most frequently reported in the literature to exhibit aberrant expression in PC were mir-15b, miR-146a, miR-21, miR-155, miR-181b, miR-196a, miR-200, and miR-221/222.

6. FUNCTION OF miRNAs IN PC

MiRNAs regulate a number of genes involved in PC development by binding directly to the 3′UTR of these critical mRNAs. The altered expression of miRNAs in PC is crucial in regulating key cancer genes. These genes targeted by miRNAs are highly enriched and play a crucial role in regulating the proliferation, migration, invasion, and apoptosis of PC cells (28, 34). These functions of the miRNAs in PC affect the prognosis of PC patients.

6.1. miRNAs modulate proliferation or apoptosis of PC cells

Cell proliferation and apoptosis are essential to PC growth. Deregulation of proliferation or apoptosis, however, can lead to pathological states, including uncontrolled cell growth, as in cancer, or cell loss as in neurodegenerative diseases. It has been reported that miRNAs play critical roles in PC cell proliferation and apoptosis (Figure 1). Specifically, miR-21 was significantly up-regulated in PC, where it targets phosphatase and tensin homologue 2 (PTEN), programmed cell death 4, tropomyosin 1 (TPM1), and tissue inhibitor of metalloproteinase 3 (TIMP3), leading to inhibition of apoptosis and consequent increased tumorigenicity (47, 48). miR-21 overexpression enhanced the malignant phenotype of PC cells. Consistently, inhibition of miR-21 decreased proliferation and increased apoptosis of PC cell lines (49).

miR-221 was shown to be significantly up-regulated in PC cell lines and tumor tissues compared to normal pancreatic duct epithelial cells and normal pancreas tissues. Inhibition of miR-221 suppressed the proliferative capacity of PC cells with concomitant up-regulation of PTEN, p27(kip1), p57(kip2), and p53 upregulated modulator of apoptosis (PUMA), which are the tumor suppressors and the predicted targets of miR-221 (50, 51). Most importantly, treatment of PC cells with the isoflavone mixture (G2535), formulated 3,3'-diindolylmethane, or the synthetic curcumin analogue down-regulated the expression of miR-221 and consequently up-regulated the expression of PTEN, p27(kip1), p57(kip2), and PUMA, leading to the inhibition of cell proliferation and migration of MiaPaCa-2 and Panc-1 cells (50, 51).

miR-34a is a significant component of the p53 transcriptional network and during DNA damage (52, 53). miR-34a is commonly deleted in human PC. Characterization of the miR-34a primary transcript and promoter demonstrated that this miRNA is directly transactivated by p53 (52, 53). Expression of miR-34a causes marked reprogramming of gene expression and promotes apoptosis. miR-34a responsive genes are highly enriched in those that regulate cell-cycle progression, apoptosis, DNA repair, and angiogenesis (52, 53).

miR-96 is considered a potential tumor suppressor, as it directly targets and down-regulates the KRAS oncogene (54). In PC, miR-96 is significantly down-regulated when compared with normal pancreatic
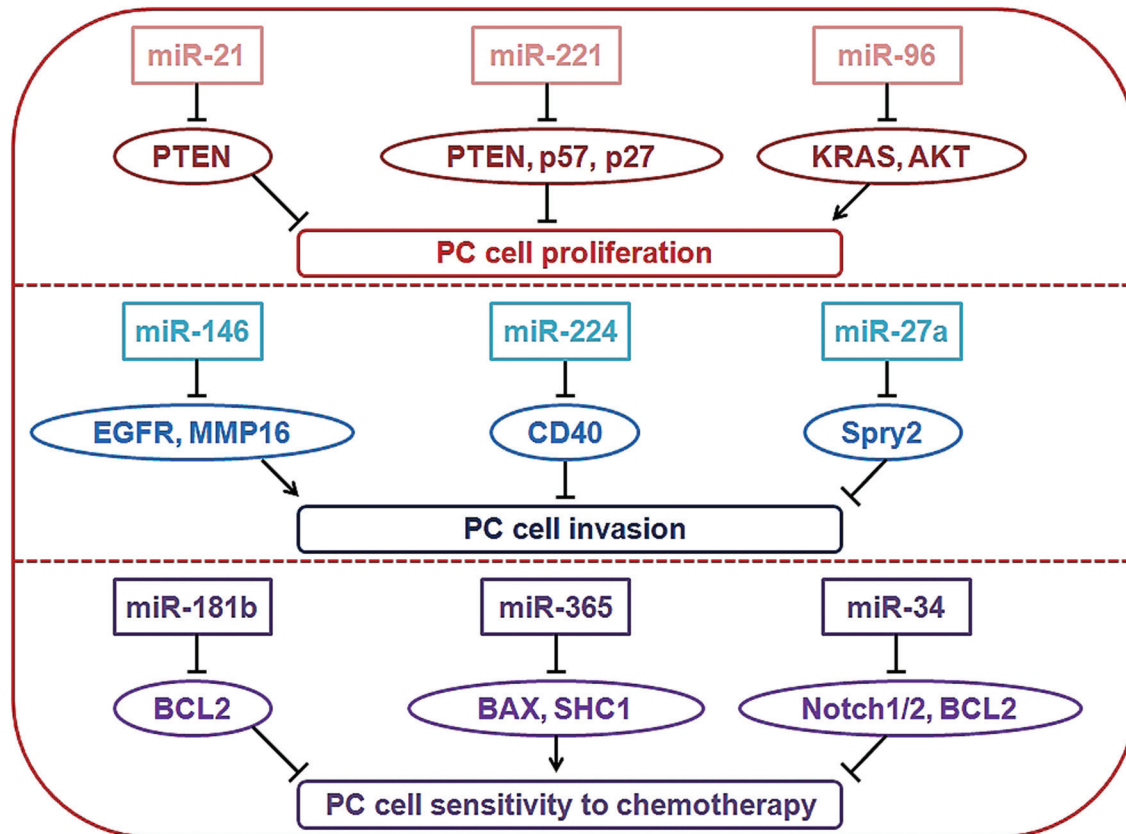
Figure 1. Many miRNAs are link to the proliferation, invasion and sensitivity to chemotherapy of PC. MiR-21, miR-221 and miR-96 regulate PC proliferation by targeting PTEN, P27, and AKT, respectively. MiR-146, miR-224 and miR-27a modulate PC cell invasion by inhibiting their targets as shown. And miR-181b, miR-365 and miR-34 regulate PC cell sensitivity to chemotherapy by inhibiting these genes such as BCL2 and BAX.

tissues (55). Ectopic expression of miR-96 has been shown to induce apoptosis in the PC cell lines Panc-1 and MiaPaCa-2; this is mediated by the inhibition of KRAS and RAC-alpha serine/threonine-protein kinase signaling (54). In human clinical specimens, an inverse correlation between miR-96 and KRAS expression was observed. Thus, miR-96 may have potential therapeutic use in KRAS-driven PC.

6.2. miRNAs regulate migration and invasion of PC cells

PC is an aggressive malignancy due to its high metastatic potential, which is dependent on the migration and invasion activity of PC cells. The propensity of PC for early invasion, and a lack of effective methods for screening and early diagnosis, usually results in a diagnosis when the disease is at an advanced stage; therefore, it is important to identify new factors that regulate PC cell metastasis.

6.2.1. miRNAs act as inhibitors of PC cell migration and invasion

miR-146a, an inhibitor of metastasis in other types of cancer, also inhibited the invasive capacity of

PC cells (56). The expression of miR-146a in PC cells is lower compared with normal human pancreatic duct epithelial cells. Re-expression of miR-146a inhibited the invasive capacity of PC cells with concomitant down-regulation of the epidermal growth factor receptor and the NF-kappaB regulatory kinase interleukin 1 receptor-associated kinase 1, which are important factors in the regulation of metastasis (56). Moreover, a similar study showed that miR-146b-5p may be involved in PC cell migration and invasion by targeting matrix metallopeptidase 16 (57) (Figure 1); miR-20a, a member of the miR-17-92 family, regulates signal transducers and activators of transcription 3 at the post-transcriptional level, with consequent inhibition of cell proliferation and invasion of PC. The PC cell lines, Panc-1 and BxPC-3, stably overexpressing microRNA-20a showed reduced proliferation and invasion capacity *in vitro* and *in vivo* (58); miR-520h had an inhibitory effect on PC cell migration and invasion. This may be mediated through direct binding and inhibition of ATP-binding cassette subfamily G member 2 gene expression, which is also known as the breast cancer resistance protein. In addition, miR-31 expression led to reduced cell migration and invasion in PC (59).

6.2.2. miRNAs act as promoters of PC cell migration and invasion

miR-10a is one of the promoters of PC invasion (60). miR-10a was overexpressed in PC cells isolated from a subset of primary tumors compared with precursor lesions and normal ducts using microdissection analysis. *In vitro* experiments revealed that miR-10a inhibitors decreased the invasiveness of PC cells, but had no effect on their proliferation. Inhibition of homeobox-A1, a target of miR-10a, promoted the invasiveness of PC cells (60); miR-224 and miR-486 also appear to promote PC metastasis (61). It was revealed that miR-224 and miR-486 showed significantly higher expression in highly invasive PDAC than in low invasive PDAC (61). Cluster of differentiation (CD) 40, the target of miR-224 and miR-486, is a member of the tumor necrosis factor receptor family which is important in anti-tumor immune responses. Thus, up-regulation of the miRNAs targeting CD40 may represent an important factor in PC metastasis (Figure 1) (62, 63); miR-27a is abnormally upregulated in PC. Functional inhibition of miR-27a has been shown to suppress growth, colony formation, and migration of the PC cell lines Panc-1 and MiaPaCa-2. A validated target gene of miR-27a is sprouty homolog (Spry) 2, which is a member of the Sprouty family (Figure 1) (64, 65). Functionally, overexpression of Spry2 inhibits tumor growth and metastases through Ras/MAPK pathway inactivation (66). Collectively, a variety of miRNAs are relevant to PC cell migration and invasion, and they play an important role in PC metastasis, suggesting that these miRNAs may be useful in treating and improving the prognosis of patients with PC.

6.3. miRNAs affect PC cell sensitivity to radiotherapy or chemotherapy

The sensitivity of tumor cells to radiotherapy or chemotherapy is an important prognostic factor in patients with cancer. A series of miRNAs have been shown to play a role in the chemosensitivity or radiosensitivity of PC cells (Figure 1). It was found that gemcitabine induced higher levels of apoptosis in PC cells transfected with miRNA-181b mimics (67). Nude mouse xenograft assay data showed that miR-181b transfection also sensitized PC cells to gemcitabine treatment *in vivo*. Further study showed reduced B-cell lymphoma (BCL) -2 expression following miR-181b transfection and enhanced caspase-3 activity in miRNA-181b mimic-transfected PDAC cells, indicating that miRNA-181b may sensitize PDAC cells to gemcitabine by targeting BCL-2 (67); miR-34 also appears to sensitize PC cells to chemotherapy and radiotherapy (68, 69). It has been reported that miR-34 expression is significantly lower in PC cell lines than in normal pancreatic ductal epithelial cell lines. Ji *et al*. showed that miR-34 potently inhibits BCL-2 expression and cell growth, and increases cell death and response to radiotherapy in the overall population of MIA-PaCa-2 cells (53).

Moreover, several miRNAs have been demonstrated to be involved in PC chemoresistance. In addition to promoting PC cell proliferation, miR-21 also appears to induce chemoresistance to gemcitabine in PC cell lines. For example, PC cell lines such as Panc-1, LPc111, and LPc006 transfected with the miR-21 precursor were resistant to gemcitabine treatment, showing reduced apoptosis or increased proliferation (42, 70). In contrast, the inhibition of miR-21 induced more apoptosis and decreased proliferation in the PC cell line SUIT-2, which expresses relatively high levels of miR-21. Hwang *et al*. also demonstrated that miR-21 may be a useful biomarker for the prediction of chemoresistance, as PC cells with lower miR-21 expression had higher chemosensitivity to 5-fluorouracil (71). In addition, Hamada *et al*. found that miR-365 was highly expressed in invasive PDAC and induced gemcitabine resistance in PC cells. The authors suggested that miR-365 may induce chemoresistance by directly targeting adaptor protein Src homology 2 domain containing 1 (SHC1) and apoptosis-promoting BCL2-associated X protein (BAX) (72). Knockdown of SHC1 and BAX increased gemcitabine resistance, indicating that the miR-365/SHC1/BAX axis may influence the survival of PC cells (72). MiR-200 may also be involved in chemoresistance. Ali *et al*. reported that treatment with curcumin, a major chemical component in turmeric, up-regulated miRNA-200b and miRNA-200c in both gemcitabine-sensitive (BXPC-3) and gemcitabine-resistant (MIA-PaCa-E and MIA-PaCa-M) cell lines, which were associated with induction of apoptosis (73).

As discussed above, miRNAs affect PC proliferation, apoptosis, invasion, prognosis, and treatment by regulating tumor-related gene expression, including p53, KRAS, PTEN, BCL2 and p27. The discovery of miRNAs provides a new opportunity for studying the tumorigenesis and metastatic mechanisms of PC. An increased understanding of these processes may contribute to the development of systemic delivery systems for miRNAs to treat metastatic PC.

7. miRNAs AS DIAGNOSTIC MARKERS FOR PANCREATIC CANCER

Poor survival of PC is partially attributed to the advanced stage of the cancer at diagnosis. At the time of diagnosis, less than 15% of patients have surgically resectable disease. Thus, there is an urgent need to develop minimally invasive biomarker assays for early detection and effective clinical management of PC. As indicated in many investigations, increased expression of miR-103 and miR-107 along with decreased expression of miR-155 are useful in discriminating tumors from normal pancreas (39); miR-21, miR-221, miR-222, miR-181a, miR-181b, miR-181d, and miR-155 may be potential markers as they are overexpressed in PC samples compared with benign pancreatic tissue (40). In addition, it was reported that miR-196a combined

with miR-217 can be used to classify benign versus malignant pancreatic tissues in pancreatic fine-needle aspirates (74).

Compared with tissues samples, serum and plasma from PC patients and PC cells are the most readily available samples for diagnostic testing and, hence, are attractive media for biomarker testing to screen for early-stage disease. As a marker of hypoxia, miR-210 has been detected in the serum of PC patients, and its expression levels were fourfold higher in these patients than in normal controls (75, 76). A recent investigation also showed that the expression levels of four miRNAs in plasma, miR-21, miR-210, miR-155, and miR-196a, was significantly higher in patients with PC than in a healthy control group (46). In addition, miR-1290 demonstrated the best diagnostic performance of all the significantly elevated circulating miRNAs, yielding an area under the curve of 0.96 [95% confidence interval, 0.91–1.00], 0.81 (0.71–0.91), and 0.80 (0.67–0.93), for subjects with PC relative to healthy controls, subjects with chronic pancreatitis, and pancreatic neuroendocrine tumors, respectively (77, 78). In conclusion, early diagnosis of PC requires markers with high sensitivity and specificity. Serum and plasma miRNAs, for example, miR-21, miR-155, miR-210, and miR-196a, are promising biomarkers for the early detection of PDAC, especially in combination with serum salivated Lewis blood group antigen CA19-9 levels (79).

8. miRNAs AS PROGNOSTIC AND PREDICTIVE MARKERS OF PANCREATIC CANCER

Poor survival is a hallmark feature of PC. Several studies have suggested the prognostic significance of miRNAs expression profiles in PC. Bloomston *et al*. reported that the six miRNAs, miR-452, miR-105, miR-127, miR-518a-2, miR-187, and miR-30a-3p, are differentially over-expressed in patients with a longer survival time (greater than 2 years) (40). In addition, miR-219 and miR-196a-2 can predict poor prognosis in patients with PC (46, 80). Tumors with high expression of miR-219 result in a median survival of 13.6 months compared with 23.8 months for those with low expression. Furthermore, median survival in patients with high expression of miR-196a-2 was 14.3 months compared with 26.5 months for those with low expression; miR-21 appears to confer chemoresistance in PDAC cell lines. Strong miR-21 expression was predictive of poorer outcomes compared with absent or faint/focal miR-21 expression in patients with node-negative PDAC (median 15.2 versus 27.7 months) (70, 81). Jamieson *et al*. also found that miR-21 was associated with poor prognosis (82). In addition, high expression of miR-212 and miR-675, and low expression of miR-148a, miR-187 and let-7g predicted short overall survival of patients who underwent surgery for PC (83).

9. CONCLUSION

It is well established that miRNAs are key players in a wide variety of biological processes, including development, metabolism, cellular proliferation, apoptosis, invasion, and prognosis. Altered expression patterns of miRNAs can result in disease occurrence. Recently, the stability of miRNAs in serum has been verified, opening up the possibility of using these miRNAs as circulating biomarkers of disease. Large numbers of miRNAs, including circulating miRNAs, have aberrant processing and expression profiles in PC, suggesting that these miRNAs may be used in the diagnosis and prognosis of PC, especially for early, presymptomatic disease. However, the precise mechanisms controlling the processes mentioned earlier remain unclear. Further investigations should explore the interpretation of miRNA profiling data and the regulatory functions of miRNAs in PC development and progression. Despite numerous studies on the function of miRNAs in PC, the transfer of these miRNAs for the clinical therapy of PC is a complex process. Chemically modified antisense oligonucleotides or ectopic overexpression of miRNAs may be considered for the therapy of PC. In order to achieve transient over-expression or suppression of a miRNA, local or systemic delivery of miRNA mimics or miRNA antagomirs require further investigation. In addition, large scale prospective validation studies to test the diagnostic and prognostic value of miRNAs are needed to develop miRNAs as biological markers of PC.

10. ACKNOWLEDGEMENT

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Abbreviations: 3′UTR, 3′untranslated region; BAX, BCL2-associated X protein; BCL, B-cell lymphoma; CD, cluster of differentiation; KRAS, kirsten rat sarcoma viral oncogene; miRNA, microRNA; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; pre-miRNA, precursor miRNA; pri-miRNAs, primary miRNAs; PTEN, phosphatase and tensin homologue 2; PUMA, p53 upregulated modulator of apoptosis; RISC, RNA-induced silencing complex; SHC1, homology 2 domain containing 1; Spry, sprouty homolog; TPM1, tropomyosin 1; TIMP3, tissue inhibitor of metalloproteinase 3

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