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Insights into the Role of microRNAs in Pancreatic Cancer Pathogenesis: Potential for Diagnosis, Prognosis, and Therapy

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Abstract

Pancreatic cancer is a highly lethal malignancy and a fourth leading cause of cancer-related death in the United States. Poor survival of pancreatic cancer patients is largely because of its asymptomatic progression to advanced stage against which no effective therapy is currently available. Over the years, we have developed significant knowledge of molecular progression of pancreatic cancer and identified several genetic and epigenetic aberrations to be involved in its etiology and aggressive behavior. In that regard, recent lines of evidence have suggested important roles of microRNAs (miRNAs/miRs) in pancreatic cancer pathogenesis. microRNAs belonging to a family of small, noncoding RNAs are able to control diverse biological processes due to their ability to regulate gene expression at the posttranscriptional level. Accordingly, dysregulation of miRNAs can lead to several disease conditions, including cancer. There is a long list of microRNAs that exhibit aberrant expression in pancreatic cancer and serve as key microplayers in its initiation, progression, metastasis, and chemoresistance. These findings have suggested that microRNAs could be exploited as novel biomarkers for diagnostic and prognostic assessments of pancreatic cancer and as targets for therapy. This book chapter describes clinical problems associated with pancreatic cancer, roles that microRNAs play in various aspects of pancreatic

cancer pathogenesis, and envision opportunities for potential use of microRNAs in pancreatic cancer management.

Keywords

microRNAs; Pancreatic cancer; Initiation; Metastasis; Chemoresistance; Diagnosis and prognosis; Therapy

Introduction

microRNAs (miRNAs) have received considerable attention because of their potential to regulate diverse biological processes such as cell development, cell differentiation, and survival. Moreover, significance of miRNAs has been recognized in various human cancers within past decade. miRNAs are small (~19–25 nucleotide long) noncoding RNA molecules, which are generated from endogenous hairpin transcripts, and serve as negative regulators of gene expression by binding to the 3'-UTRs of target mRNA with partial or full complementarity. This target mRNA-miRNA binding typically results in either translational repression or causes target mRNA decay [1, 2]. To date, in humans approximately 2469 miRNAs have been identified [3], and it is estimated that around one-third of all the genes are regulated by miRNAs [4]. Majority of the target mRNAs contain multiple binding sites for different miRNAs, which suggest that individual mRNA can be regulated by many miRNAs [5]. On the other hand, a single miRNA can also potentially regulate the expression of multiple genes [5–7].

Pancreatic cancer is a highly lethal malignancy and is the eighth leading cause of cancer-related deaths globally [8]. In the United States, it is currently the fourth leading cause of cancer-related death and predicted to become second on the list by 2030 [9, 10]. Post-diagnosis median survival of pancreatic cancer patients is nearly 2–8 months, and only ~6 % of all patients survive more than 5 years [11]. Such a poor prognosis is largely due to late diagnosis of disease, when it is either locally advanced or has already metastasized to distant organ sites [6, 12]. Moreover, currently, there is a complete lack of an effective therapy to treat metastatic pancreatic cancer. Even small pancreatic tumors at the time of diagnosis harbor several genetic or epigenetic alterations that cooperatively promote their aggressiveness and therapeutic-resistance [13, 14]. In view of this grim scenario, there has been increasing interest to define genetic and epigenetic landscape of pancreatic cancer and understand molecular mechanisms underlying its initiation, aggressive progression, and therapy resistance. Clearly, miRNAs have emerged as important biomolecules regulating pancreatic cancer pathobiology.

This book chapter summarizes currently available information on the significance of miRNAs in pancreatic cancer with major emphasis on their roles in disease initiation, progression, and chemoresistance. We also highlight the diagnostic, prognostic, and therapeutic potential of miRNAs in pancreatic cancer and their prospective utility in clinics.

Pancreatic Cancer: A Major Clinical Problem

Pancreatic cancer has the worst prognosis among all cancers. It is referred as a “silent killer” because of the lack of any symptoms in its early stages of progression and its diagnosis is often considered as “death sentence” to the patient. The appeared symptoms are often indistinguishable and share commonality with other abdominal or gastrointestinal (GI) tract pathologies [15, 16]. Consequently, we are still struggling to develop a sensitive and specific diagnostic for pancreatic cancer that would be clinically feasible [17]. Due to these limitations, specific sets of biomarkers are required which could be potentially used for diagnosis and prognosis of pancreatic cancer. Therapy of pancreatic cancer also remains a major challenge in clinics due to highly advanced and metastatic disease at the time of diagnosis. Thus, surgical resection followed by adjuvant therapy, which could be curative, is not an option in most pancreatic cancer patients. Even in some early stage cases, surgical resection largely fails to manage the disease [18]. Chemotherapeutic options for the advanced stage patients are limited and provide minimal survival benefit at best. Gemcitabine as a single-agent drug for the treatment of pancreatic cancer shows only a meager improvement in the median survival by only few weeks [19]. Erlotinib, an epidermal growth factor receptor (EGFR) inhibitor when given in combination with gemcitabine, modestly prolonged the mean survival rates of pancreatic cancer patients as compared to gemcitabine treatment alone [20]. In a phase III study it was shown that combination treatment of gemcitabine with cisplatin did not increase the survival benefits [21]. Moreover, in a multicenter phase II/III trial on patients with metastatic pancreatic adenocarcinoma, FOLFIRINOX in combination with gemcitabine increased median survival to 11.1 months as compared to 6.8 months in the gemcitabine treatment group [22]. Recently, based on the findings from a phase III clinical trial, albumin-bound paclitaxel (nab-paclitaxel) in combination with gemcitabine was introduced. The median overall survival was increased to 8.5 months in patients treated with nab-paclitaxel and gemcitabine as compared to 6.7 months for gemcitabine treatment alone. Moreover, the median progression-free survival was 5.5 months compared to 3.7 months for patients treated with combination and gemcitabine alone, respectively [23]. These studies suggest that so far there is no major stride made that could effectively treat pancreatic cancer. Therefore, there is an urgent clear need for the identification and development of specific and sensitive biomarkers for diagnosing this asymptomatic disease in its early phase.

Deregulation of miRNAs in Pancreatic Cancer

Mounting evidence suggest that miRNAs are aberrantly expressed and highly deregulated in pancreatic cancer [6]. Poy and colleagues first identified specific miRNA signature for the normal pancreas [24]. Since then, extensive studies on miRNAs have been conducted and several differentially expressed miRNAs identified in pancreatic cancer. Pancreatic cancer-based miRNA screening was clearly able to distinguish pancreatic ductal adenocarcinoma (PDAC) from normal pancreas and pancreatitis [12]. The study identified 100 miRNAs to be differentially expressed in pancreatic cancer including miR-155, miR-21, miR-221, and miR-222, which are also known to be aberrantly expressed in other human cancers [25]. Furthermore, miRNA profiling identified significantly high levels of miR-196a, miR-186, miR-190, miR-95, miR-221, miR-222, miR-200b, and miR-15b in pancreatic tumors [26].

Moreover, we recently provided the evidence that miR-150 is significantly downregulated in pancreatic cancer [27]. Study carried out in the serum samples of pancreatic cancer patients identified miR-2 to be overexpressed in pancreatic cancer [28]. Microarray-based miRNA study revealed that 21 miRNAs were upregulated, and 4 downregulated in pancreatic cancer [29]. Interestingly, this expression pattern differentiated pancreatic cancer from normal/benign pancreatic tissues. In pancreatic neuroendocrine tumors, expression of miR-155, miR-146a, miR-142-3p, and miR-142-5p were high as compared to its normal counterpart [30]. In 15 different pancreatic cancer cell lines, miR-10a, miR-92, and miR-17-5p were observed to be overexpressed [31]. Furthermore, elevated levels of miR-155 and miR-21 were reported in the clinical specimens of intraductal papillary neoplasms. Another similar study suggested that activation of miR-155 is an “early” event in the pancreatic cancer progression, and the expression level of miR-155 increases with the progression from PanIN-2 to PanIN-3 [32]. Similarly, expression of miR-218 was shown to decrease with the progression of pancreatic cancer [33]. Working on the same line, Yu et al., reported altered expression of miRNAs with the pancreatic cancer progression [34]. In low-grade PanINs (PanIN-1 or PanIN-2), miR-133a, miR-151-5p, miR-148a/b, miR-34c-5p, miR-130b, miR-200c, miR-185, miR-331-3p/5p, miR-330-3p, miR-423-5p, miR-378, and miR-129-3p were significantly elevated, while miR-196b was found to be overexpressed in PanIN-3 lesions [34]. Morimura and colleagues identified a specific miRNA signature in the blood specimen of pancreatic cancer patients. They identified significantly higher levels of miR-20a, miR-18a, miR-155, miR-22, miR-21, miR-99a, miR-24, miR-185, miR-25, miR-885-5p, miR-191, miR-642b, and miR-196a in the blood of pancreatic cancer patients’ as compared to that from normal donors [35]. miRNA expression analysis in fine-needle aspirates showed upregulation of miR-196a, miR-217, miR-451, and miR-486-5p with downregulation of let-7c, let-7d, let-7f, and miR-200c in pancreatic cancer [36]. Overall these studies suggest that miRNAs are aberrantly expressed in pancreatic cancer and their deregulation could influence the development and progression of pancreatic cancer.

Role of miRNAs in Pancreatic Cancer

Accumulating data over the past several years have defined important roles of miR-NAs in pancreatic cancer pathobiology (Fig. 5.1). A number of miRNAs are known to promote early events of pancreatic carcinogenesis, while several others are involved in its metastatic progression and chemoresistance as discussed below.

miRNAs in Pancreatic Cancer Initiation and Promotion

There are several reports indicating a role of miRNAs in pancreatic cancer initiation and promotion. The levels of miR-34 were shown to be significantly downregulated in pancreatic cancer, and its overexpression influenced various processes such as angiogenesis, apoptosis, cell cycle progression, and even metastatic potential [37, 38]. Ji et al. also reported the role of miR-34 in tumor initiation by demonstrating that restoration of miR-34 resulted in the inhibition of tumor-initiating cells [38].

Ample amount of data is available that advocate the significance of miRNAs in controlling the pancreatic cancer growth. For example, Yu and coworkers reported that restoration of

miR-96 resulted in K-Ras inhibition followed by pancreatic cancer cell death [39]. Forced expression of miR-143/145 decreased cell proliferation [40]. Furthermore, it was shown that expression level of miR-145 progressively decreased from precursor lesions to late PDAC, and restoration of miR-145 abrogated cell proliferation [41]. Keklikoglou and colleagues reported that restitution of miR-206 was enough to inhibit angiogenesis and tumor growth in pancreatic cancer [42]. Guo et al., reported that overexpression of tumor suppressor miR-410 led to inhibition of angiogenesis in pancreatic tumor model [43].

Moreover, inhibition of miR-21 and miR-210 was also shown to inhibit migration and invasion of pancreatic cancer cells and suppressed angiogenesis [44]. In another report, a role of miR-217 in inhibition of pancreatic cancer growth in vitro and in vivo was demonstrated [45]. Several other miRNAs, such as miR-130a, miR-301a, and miR-454, are also reported to be upregulated in pancreatic cancer and to negatively regulate SMAD4 expression to promote tumor growth [46, 47]. Let-7 is largely known to be either completely lost or downregulated in pancreatic cancer [48] and functional study demonstrated that the overexpression of let-7 caused the inhibition of pancreatic cancer cell proliferation through inhibiting MAPK and K-Ras signaling [48]. Tsuda et al. provided the evidence that synthetic miR-3548 retarded the growth of MiaPaCa-2 cells by targeting Gli-1 [49]. Cell cycle progression is indispensable for cancer cell growth and studies suggest that miRNAs regulate several cell-cycle-related proteins, such as cyclin-dependent kinase, CDK6 by miR-107 [50], CDC25B by miR-148a [51], and CDKN1B by miR-221 [52].

Transfection with inhibitor of miR-221 in pancreatic cancer cells upregulated CDKN1B, and suppressed their growth [53]. miR-424-5p is overexpressed in pancreatic cancer cells and reported to promote the proliferation and apoptosis resistance [54]. Recently, we also identified miR-150 to be a tumor suppressor miRNA in pancreatic cancer cells and demonstrated its tumor suppressor function. Restoration of miR-150 suppressed the growth and malignant potential of pancreatic cancer cells via downregulating MUC4 [27]. Xu et al. demonstrated that restoration of miR-203 caused apoptosis and cell cycle arrest [55]. Moreover, miR-203 also caused significant reduction in tumor growth [55]. Altogether, these reports clearly suggest that miRNAs are of important significance in pancreatic cancer initiation and progression.

miRNAs in Pancreatic Cancer Metastasis

Pancreatic cancer is a highly aggressive malignancy characterized by extensive near and distant metastasis. So far, several molecular targets have been identified that could potentially drive the aggressive nature of this malignancy. Recently, miRNAs have also gained significant attentions for their role in regulating the metastatic processes, and involved miRNAs are often referred as metastamiRs [6]. Two miRNAs, miRNA-218 and miR-155, has been shown to be associated with lymphatic metastasis of pancreatic cancer [33, 56]. Moreover, Mees and colleagues have reported that miR-194, miR-200b, miR-200c, and miR-429, which are overexpressed in highly metastatic pancreatic cancer cells, regulate metastasis by targeting metastatic suppressor gene EP300 [57]. Another study reported that miR-10a is an important mediator in pancreatic cancer metastasis and its repression effectively inhibits the invasion and metastasis of pancreatic tumor cells [58].

Ouyang et al. reported that increased level of miR-10b in pancreatic cancer made pancreatic tumor cells invasive by activating epidermal growth factor (EGF) and transforming growth factor-beta (TGF- β) signaling [59]. Another study identified overexpression of miR-10b in pancreatic cancer, and suggested its role in the aggressive phenotype associated with metastasis [60]. Giovannetti and coworkers reported that patients exhibiting upregulated level of miR-21 had a shorter survival [61]. Moreover, miR-21 helped in the invasion and metastasis of pancreatic cancer cells by regulating matrix metalloproteinases and vascular endothelial growth factor [61]. Another study showed that deregulated miR-21 expression in pancreatic cancer was associated with high proliferation index and liver metastasis [62].

Kadera et al. also demonstrated the role of miRNAs in pancreatic tumor invasion and metastasis [63]. miRNA expression profile data suggested that levels of miR-100 was significantly higher in metastatic pancreatic cell lines as compared to non-metastatic ones suggesting its role in metastasis of pancreatic cancer [56]. Moreover, miR-146a was also reported to be significantly downregulated in pancreatic cancer, and its restoration inhibited the invasiveness of pancreatic cancer cells by suppressing the expression of EGFR and interleukin-1 receptor-associated kinase 1 (IRAK-1) [64].

The expression of tumor suppressor miRNA, miR-143, is lost or downregulated in many cancers, including pancreatic cancer, and its overexpression in pancreatic cancer cells downregulated various genes associated with tumor growth and metastasis. Furthermore, findings suggested that the restoration of miR-143 blocked pancreatic cancer cell migration and invasion in vitro and inhibited liver metastasis and tumor growth in vivo [65]. Downregulation of miR-126 was shown to be a crucial event for attaining an invasive phenotype in PDAC and its re-expression decreased the pancreatic cancer invasiveness [66]. Similarly, Hamada et al. have reported a role of miR-126 in regulating pancreatic tumor invasiveness [67]. Decreased level of miR-34b is associated with tumor-node-metastasis stage and lymph-node metastasis [68]. Taken together, these studies clearly suggest critical roles of miRNAs in the metastatic progression of pancreatic cancer.

miRNAs in Chemoresistance of Pancreatic Cancer

The growing evidence suggests that miRNAs play important role in the chemoresistance of pancreatic cancer. Bhutia et al. demonstrated that overexpression of precursor-let-7 inhibited RRM2 level in pancreatic cancer cells and induced chemo-sensitization [69]. Similarly, preclinical data demonstrated that increased miR-21 expression in pancreatic cancer cells enhanced therapeutic efficacy of gemcitabine by reducing RRM2 level [70]. Recently, it was shown that miR-1246 promoted pancreatic cancer growth and induced drug resistance [71]. Furthermore, Singh and colleague observed the upregulation of miR-146 and downregulation of miR-205 and let-7 in gemcitabine-resistant pancreatic cancer cell lines and clinical samples, suggesting their involvement in the development of chemoresistance [72]. Another study regarding the role of miRNAs suggested that miR-17-5p was upregulated and imparted gemcitabine resistance to pancreatic cancer cells by targeting pro-apoptotic protein, Bim at the posttranscriptional level [73]. The inhibition of this miRNA in Panc-1 and BxPC3 cells sensitized them to gemcitabine toxicity by inducing apoptosis [73]. miR-21 is also shown to play an important role in the chemoresistance of cancer cells.

A study carried out by Giovannetti and colleagues showed that miR-21 was upregulated in gemcitabine-resistant pancreatic cancer cells, and it modulated the expression of genes associated with survival and invasion and sensitized the cells to gemcitabine therapy [61]. Moreover, this study also revealed that overexpression of miR-21 was associated with poor therapeutic outcome in pancreatic cancer patients treated with gemcitabine. Additional support for the role of miR-21 in chemoresistance came from a study in which it was shown to regulate the expression of anti-apoptotic BCL2 protein [74]. Another study reported that miR-125b was overexpressed in gemcitabine-resistant derivative cell line of BxPC3 (BxPC3- GZR) as well as in advanced PDAC samples and its inhibition sensitized the BxPC3- GZR to gemcitabine [75]. In another recent study, Khan et al. demonstrated that overexpression of miR-145 significantly enhanced the gemcitabine cytotoxicity through downregulation of MUC13 [41]. miR-155 is also reported to be overexpressed in pancreatic cancer, and gets upregulated in pancreatic cancer cells upon gemcitabine treatment further supporting its possible involvement in chemoresistance [25]. Another study revealed that re-expression of miR-200 sensitized pancreatic cancer cells to gemcitabine [28].

Moreover, miR-142-5p and miR-204 were also reported to be significantly downregulated in gemcitabine-resistant PDAC and established cell lines [76]. In a recent report, it was shown that expression level of miR-320c was significantly elevated in gemcitabine-resistant pancreatic cancer lines suggesting its role as a regulator of chemoresistance [77]. Overall, these studies suggest that miRNAs are involved in the chemoresistance in pancreatic cancer.

Opportunities for the Clinical Use of miRNAs in Pancreatic Cancer Management

The widely recognized hurdle in the treatment of pancreatic cancer is its late detection and the lack of effective therapies. Recent studies have provided considerable evidence showing the use of miRNA expression profiles in the diagnosis and prognosis of pancreatic cancer; moreover, miRNAs are also emerging as promising targets for cancer therapy as shown in Fig. 5.2. Below we discuss related data on these aspects to understand the clinical potential of miRNAs in pancreatic cancer.

miRNAs as Diagnostic Markers

It is now becoming evident that miRNAs have the potential to be utilized as bio-markers for cancer diagnosis. For example, certain miRNAs such as miR-376a, miR-301, miR-155, miR-21, miR-221, and miR-222 are overexpressed in pancreatic cancer and their expression is restricted to tumor cells only with no expression in normal acini or ducts [25]. Moreover, differential expression of miR-96 [39], miR-34a [38], and miR-21 [78] was shown to accurately discriminate between pancreatic cancer and normal adjacent tissue. Another expression analysis study between normal pancreas and PDAC suggested that the presence of miR-216 and miR-217 and absence of miR-133a is unique for healthy pancreas [29]. On the other hand, increased expression of miR-103 and miR-107 with low expression of miR-155 is also another signature profile for pancreatic tumors [62].

Bloomston et al. successfully identified 21 overexpressed and 4 downregulated miRNAs in pancreatic cancer, which correctly differentiated 90 % of the malignant cases from the normal tissue. Similarly, using a subset of 15 overexpressed and 8 downregulated miRNAs, they could also accurately discriminate between 93 % of samples as chronic pancreatitis and pancreatic cancer [29].

Furthermore, Szafranska et al. [79] identified 20 additional miRNAs that were able to discriminate pancreatic cancer from chronic pancreatic diseases and normal pancreas. The expression analysis of miR-196a and miR-217 in fine-needle aspirates categorized malignant pancreatic cancer from benign lesions [80]. Later, Kong et al. [81] observed elevated level of miR-196a in the serum samples of pancreatic cancer compared with control groups. This study led to the identification of serum miR-196a as a potential marker for pancreatic cancer and selection for laparotomy [81]. Yu et al. [34] identified a signature of 35 miRNAs in PanIN-3 lesion, and miR-196b was found to be the best biomarker for detection of these lesions.

Kawaguchi et al. [52] found that pancreatic cancer patients with higher plasma concentration of miR-221 exhibited significant correlation with distant metastasis. In a study measuring 735 circulating miRNAs in pancreatic cancer and control sera, miR-1290 was demonstrated to exhibit the best diagnostic performance among other upregulated circulating miRNAs [82]. Lewis blood group antigen CA19-9 is currently being widely used as standard serum marker for the identification of pancreatic cancer. However, its utilization is limited to monitor response to therapy and it is not a sensitive or specific marker for diagnosis [83, 84].

Interestingly, combination of miR-16 and miR-196a with CA19-9 was demonstrated to be more accurate in discriminating pancreatic cancer from normal tissue with a sensitivity and specificity of 92.0 % and 95.6 %, respectively. Habbe et al. [85] identified miR-155 to be the potential biomarker for detecting early stage of pancreatic cancer. Altogether, these studies highlight the potential of miRNAs to be used as a valuable tool for discriminating pancreatic tumors from normal pancreas and classifying the tumor stage and grade, either alone or in combination with other biomarkers.

miRNAs in Prognostic Assessment

With accumulating data, it is now becoming more obvious that apart from the significance of miRNAs in pancreatic cancer diagnosis, they can also be utilized as potential prognostic biomarkers. An elevated level of miR-21 was shown to be associated with poor therapeutic outcome in patients undergoing gemcitabine therapy [61]. Furthermore, overexpression of miR-21 in PDAC is reported to be correlated with the shorter overall survival in node negative patients and is strongly associated with liver metastasis [78]. Interestingly, patients with low miR-21 expression have been observed to benefit from gemcitabine treatment [86]. Ohuchida et al. [87] demonstrated downregulated expression of miR-204 and miR-142-5p in gemcitabine-resistant pancreatic tumor samples; furthermore, they identified a positive correlation of these miRNAs with prolonged survival of patients with pancreatic cancer. Thus, miR-142-5p was identified to be a predictive marker for gemcitabine response.

Bloomston et al. [29] demonstrated that a set of six miRNAs could distinguish long-term survivors with node-positive disease dying within 2 years. Furthermore, their study suggested that, high miR-196a-2 level could predict poor survival. Others have shown that overexpression of miR-155, miR-200, miR-203, miR-205 [81], miR-212, and miR-675 [31] miR-200c [80], miR-21 [54], and reduced expression of miR-34a, miR-30d [54], miR-130b [88], miR-148a, miR-187 and let-7g [87] in PDAC are associated with poorer survival rate. Ikenaga et al. identified miR-203 as a new prognostic marker of pancreatic adenocarcinoma patients, who underwent resection [89]. Like miR-21, the expression of miR-155, miR-196a, and miR-10b was also correlated with enhanced invasiveness and poor overall survival of pancreatic cancer patients [60]. Moreover, poor prognosis of pancreatic cancer was also observed in patients expressing high levels of miR-17-5p clusters. Together, these studies highlight the significance of miRNAs in pancreatic cancer prognosis.

miRNAs as Therapeutic Targets

Extensive miRNA-based preclinical studies have been conducted in pancreatic cancer to clearly highlight the role of miRNAs in the initiation, progression, and chemoresistance. Thus, there is wide scope to exploit miRNAs for the development of novel therapeutic strategies against pancreatic cancer. For example, nanoparticle- based delivery of miR-143, miR-145, or miR-34a in mouse model of pancreatic cancer significantly inhibited the tumor growth [90]. Inhibition of miR-21 and miR-221 using antisense approach was also shown to enhance gemcitabine cytotoxicity in pancreatic cancer cells [91]. Similarly, repression of miR-10a in pancreatic cancer cells was able to inhibit tumor growth and metastasis [58]. In another study, it was demonstrated that inhibition of miR-132 and miR-212 by antisense miRNA oligonucleotides decreased the pancreatic tumor growth [92].

Restoration of a tumor suppressor miR-204 resulted in the downregulation of Mcl-1 and caused pancreatic cancer cell death [76]. Similarly, Yan et al. demonstrated that the restoration of miR-20a could potentially downregulate Stat3 at the posttranscriptional level leading to the inhibition of cell proliferation of pancreatic carcinoma [93]. Furthermore, viral vector-mediated delivery of miR-145 or miR-143 effectively inhibited pancreatic cancer development [40]. Hu et al. using adenovirus-mediated delivery of miR-143 demonstrated significant reduction of cancer metastasis [65]. Moreover, we also demonstrated that delivery of miR-150 mimics significantly inhibited pancreatic cancer cell growth and metastatic potential [27]. Similarly, restoration of tumor suppressor let-7 miRNA in cancer-derived cell lines strongly reduced their proliferation via downregulating K-Ras and mitogen- activated protein kinase activation [48]. Yu et al. [39] demonstrated that the delivery of miR-96 mimics inhibited in vivo tumorigenesis [39].

Wang and colleague reported that miR-23b is downregulated in radioresistant pancreatic cancer cells and restoration of miR-23b sensitized pancreatic cancer cells to radiation therapy [94]. Another study demonstrated that re-expression of tumor suppressor miR-141 in pancreatic cancer cells blocked tumor cell growth, invasion, clonogenicity, and increased chemosensitivity [95]. Recently, Guo et al. demonstrated that the delivery of miR-410 mimics inhibited tumor formation in xenograft mouse model [43]. Delivery of anti-miR-21 and anti-miR-221 oligonucleotides inhibited the growth and sensitized pancreatic tumor

cells to anticancer drugs, 5-Fluorouracil, and gemcitabine [96]. Thus, these studies provide strong rationale towards the exploitation of miRNAs as effective therapeutic targets for the treatment of pancreatic cancer.

Conclusion and Future Perspectives

microRNAs have undoubtedly established themselves as a novel class of gene regulators, and accumulating data support their roles in multiple biological processes. In fact, what we know today may just be the glimpse of pleiotropic functions that miRNAs can perform, and coming era may unfold many new discoveries. Pancreatic cancer remains a highly lethal malignancy lacking in almost all areas (diagnosis, prognosis, and therapy) of clinical management. Therefore, continued identification of novel, differentially expressed miRNAs and delineation of their important patho-biological functions may open up new possibilities for early and specific diagnosis as well as provide future cancer therapeutics for this devastating malignancy.

We would need to develop clinically feasible, cost-effective systems for sensitive detection of miRNAs to realize miRNA-based cancer diagnosis. Restoration or inhibition of miRNAs involved in malignant cancer phenotypes and chemoresistance through innovative approaches would also be required to enable powerful and effective miRNA-based therapeutic strategies against pancreatic cancer.

Clearly, interest in miRNA research continues to grow in all branches of biological sciences and have encouraged interdisciplinary collaborations to exploit their utility for human health applications. Remarkable progress thus far has built a strong foundation to forthcoming clinical and translational research and the diagnostic/prognostic tools and therapies that will emerge in near future. The expectation is that we will be able to curb pancreatic cancer-related deaths by developing improved understanding of its biology and identification of novel therapeutic targets. The existing data thus far provide great hope from these small, functionally involved biomolecules to prominently impact pancreatic cancer management.

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Fig. 5.1.

Involvement of miRNAs in pancreatic cancer pathogenesis. Several miRNAs are demonstrated to be involved in pancreatic cancer cell initiation, promotion, metastasis and chemoresistance, and thus greatly impact this malignancy

Fig. 5.2.

Clinical significance of miRNAs in pancreatic cancer. Specific expression pattern of miRNAs could be used for diagnosis and prognosis of pancreatic cancer. miRNAs could also be used for pancreatic cancer therapy by restoration of tumor suppressor miRNAs or inhibition of oncogenic miRNAs