

The role of miRNAs in the diagnosis, chemoresistance, and prognosis of pancreatic ductal adenocarcinoma

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Abstract: Pancreatic ductal adenocarcinoma (PDAC) remains a very challenging malignancy with late presentation, metastatic potential, chemoresistance, and poor prognosis. Therefore, there is an urgent need for novel diagnostic and prognostic biomarkers. miRNAs are small noncoding RNAs that regulate the expression of multitude number of genes. Aberrant expression of miRNAs has been linked to the development of various malignancies, including PDAC. A series of miRNAs have been defined as holding promise for early diagnostics, as indicators of therapy resistance, and even as markers for prognosis in PDAC patients. In this review, we summarize the current knowledge on the role of miRNAs in diagnosis, chemoresistance, and prognosis in PDAC patients.

Keywords: pancreatic ductal adenocarcinoma, miRNA, diagnosis, prognosis, chemoresistance

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of death by cancer in the USA, with 53,670 new cases expected in 2017, a number that has been steadily increasing for more than a decade.¹ Due to a late diagnosis and the lack of effective treatment measures, PDAC has an extremely poor prognosis and its 5-year survival rate does not exceed 5%.² Numerous studies have indicated that among those patients who were found occasionally through imaging modalities to have early-stage carcinoma, the improved 5-year survival rate is 30% for those with a 2 cm carcinoma, 57% for those with a 1 cm carcinoma, and 100% for patients with a ductal epithelium tumor measuring <1 cm.³ Thus, in light of the disappointing statistics in the prognosis of PDAC, there is an urgent, unmet need for development of valid, reliable biomarkers for early detection and monitoring of PDAC. The current most widely used biomarkers for PDAC are carbohydrate antigen 19-9 (CA19-9),⁴ carcinoembryonic antigen,⁵ and/or genetic markers such as K-RAS and p53.⁶ However, these markers are neither sensitive nor specific for screening, but are used to follow known disease if they were initially elevated, and are not recommended for screening and diagnosis of early disease.⁷

miRNAs are a class of short, non-coding RNAs ranging approximately from 17 to 25 nucleotides, which contain a seed sequence for binding to imperfect complementary regions in the 3' untranslated region of the target mRNAs, inhibiting their translation or leading to their degradation.^{8,9} Collective evidences have demonstrated that miRNAs have a critical regulatory role in the development, differentiation, and apoptosis of normal cells, as well as in the expression of many target mRNAs simultaneously, playing a critical role in tumorigenesis, invasion, metastasis, and chemoresistance of

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cancer cells.¹⁰ Indeed, miRNAs exhibit tissue-specific and disease-specific expression that could provide the basis for their development as novel diagnostic, prognostic, and/or therapeutic targets, as well as chemoresistance.^{11,12}

Since abnormal expression of miR-15 and miR-16 was reported in chronic lymphocytic leukemia,¹³ more and more evidences have shown that miRNA mutations or misexpression correlates with various human cancers and indicate that miRNAs can act as either tumor suppressors or oncogenes.¹⁴ Remarkably, miRNAs have been profiled in many different malignancies including breast,¹⁵ lung,¹⁶ and PDAC,^{17,18} and differential expression was detected with these malignancies, all of which have made miRNAs promising biomarkers. The aim of this review is to present the evidence on the utility of miRNAs in the diagnosis, chemoresistance, and prognosis of PDAC.

Role of miRNAs in the diagnosis of PDAC

miRNAs in tissues and fluids have several exceptionally appealing characteristics – they are stable as they are resistant to cleavage by ribonucleases and survive extreme pH and temperature conditions, their isolation is noninvasive, and their amplification is technically easy and inexpensive.^{13,19} Accumulating evidence is showing that altered levels of miRNAs in tissues, blood, and body fluids can distinguish patients with cancer from healthy individuals.²⁰

Many researches are engaged in analysis of aberrant expression of miRNAs in normal pancreatic tissue and PDAC. For the first time in 2007, Bloomston et al showed that PDAC may have a distinct miRNA expression pattern that may differentiate it from normal pancreas (NP) and chronic pancreatitis (CP).²¹ Particularly, the results revealed that 21 miRNAs with increased expression and 4 with decreased expression were identified that correctly differentiated PDAC from NP in 90% of samples by cross-validation. Moreover, 15 overexpressed and 8 underexpressed miRNAs differentiated PDAC from CP with 93% accuracy.²¹ Similarly, Schultz et al used a diagnostic classifier including 19 miRNAs to discriminate pancreatic and ampullary adenocarcinomas from CP and NP with a sensitivity of 98.5% and a positive predictive value of 97.8% with an accuracy of 97.0%.²² For the single miRNA as a diagnostic biomarker, miR-21 has been considered a very promising biomarker for the reason that overexpression of miR-21 was persistently observed in PDAC compared to healthy tissues and/or tissues of CP in several studies.^{23–25} Zhang et al recently demonstrated that miR-132 was downregulated in PDAC compared to their

respective benign tissues by TaqMan miRNA assays.²⁶ Another diagnostic biomarker is miR-96, which is downregulated in pancreatic cancer as compared to normal tissues.²⁷

With the lack of reliable approaches based on imaging techniques and routine tumor markers, the detection of miRNAs in peripheral body fluids, especially blood or serum, has currently a considerable potential for use in clinical practice.²⁸ Compared to traditionally used markers, serum miR-1290 distinguished patients with low-stage PDAC from controls better than CA19-9 did.²⁹ Moreover, blood samples collected from pancreatic cancer patients had higher expression levels of miR-192 with sensitivity toward cancer at 76% and specificity at 55%.³⁰ Another potential biomarker is miR-155, which occurs at high levels in the plasma of 80% of early pancreatic lesions (stage II) in microdissected pancreatic intraepithelial neoplasias tissues.³¹ In addition, circulating miR-18a in the plasma of 36 PDAC patients was found to be significantly increased when compared to 30 healthy volunteers.³²

Other studies are focused on using combination of several circulating miRNAs to increase the diagnostic accuracy rate. It has been reported that the combination of miR-196a and miR-217 expression patterns differentiated PDAC from healthy controls and CP cases.³³ Moreover, plasma levels of miR-16 and miR-196a in combination with CA 19-9 have been shown to work very efficiently for improving the prognostic prediction of early PDAC.⁵ Furthermore, another group of researchers observed much higher levels of circulating miR-200a, 200b, and 210 in the plasma of PDAC patients.³⁴

The main miRNAs isolated from the histologic samples, serum or plasma, stool, and pancreatic juices with a potential role in diagnosis of pancreatic cancer are shown in Table 1. These reports indicate the importance of miRNAs as potential biomarkers for the diagnosis of pancreatic cancer.

Role of miRNAs in the chemoresistance of PDAC

Chemotherapy (eg, gemcitabine) represents an important therapeutic strategy for most patients with PDAC.⁶⁰ However, it has been shown that the limited response to current chemotherapy results in an exceptionally poor prognosis.⁶¹ Despite investigations into the mechanisms underlying chemoresistance over the past 50 years, the exact mechanism of this phenomenon is still unknown. It has been suggested cancer chemoresistance can arise from physiological barriers to drug absorption or penetration into the target tissues or from biologic mechanisms within individual tumor cells which reduce the effectiveness at their intended site of action,

Table 1 Selected miRNA candidates which are correlated to diagnosis in PDAC

miRNA	Histologic samples	Serum or plasma	Stool	Pancreatic juice
miR-10b	↑ ³⁵	↑ ³⁶		
miR-16		↑ ³⁷		
miR-18a		↑ ^{32,38}		
miR-20a		↑ ³⁹		
miR-21	↑ ²³⁻²⁵	↑ ^{39,40}		↑ ²⁵
miR-24		↑ ³⁹		
miR-25		↑ ³⁹		
miR-27a-3p		↑ ⁴¹		
miR-29c	↓ ⁴²			
miR-30a-3p				
miR-30c				
miR-31				
miR-34a	↑ ²³ ↓ ⁴³	↓ ⁴³		
miR-96	↓ ²⁷			
miR-99a		↑ ³⁹		
miR-101				
miR-103	↑ ⁴⁴			
miR-106b				
miR-107	↑ ⁴⁴			
miR-130b				
miR-132	↑ ⁴⁵ ↓ ²⁶			
miR-135b				
miR-139-3p				
miR-141	↓ ⁴⁶			
miR-143	↑ ⁴⁶		↓ ⁴¹	
miR-145	↑ ⁴⁶			
miR-146a	↑ ⁴⁶			
miR-148a	↓ ^{46,47}			
miR-148b	↓ ⁴⁶			
miR-150	↓ ⁴³	↓ ⁴³		
miR-155	↑ ^{24,25}	↑ ⁴⁰	↓ ⁴¹	↑ ²⁵
miR-181a	↑ ²¹			
miR-181b	↑ ²¹		↑ ⁴⁸	
miR-181d	↑ ²¹			
miR-185		↑ ³⁹		
miR-191		↑ ³⁹		
miR-192		↑ ^{30,49}		
miR-194		↑ ⁴⁹		
miR-196a	↑ ⁴⁶	↑ ^{37,40,50}	↓ ⁴¹	
miR-196b	↑ ⁵¹	↑ ⁵⁰		
miR-200a		↑ ⁵²		
miR-200b		↑ ⁵²		
miR-203	↑ ⁵³	↑ ⁵⁴		
miR-210	↑ ²²	↑ ^{40,55}	↑ ⁴⁸	
miR-212	↑ ⁵⁶			
miR-216	↓ ⁴⁶			
miR-216a			↓ ⁴¹	
miR-217	↓ ²³ ↓ ⁴⁶			
miR-222	↑ ^{21,46,56}			
miR-223	↑ ⁴⁶			
miR-369-5p		↑ ⁵⁴		
miR-373		↓ ⁵⁷		

(Continued)

Table 1 (Continued)

miRNA	Histologic samples	Serum or plasma	Stool	Pancreatic juice
miR-375		↓ ⁵⁴		
miR-376a		↑ ⁵⁴		
miR-492		↓ ⁵⁸		
miR-494	↓ ⁴⁶			
miR-663a		↓ ⁵⁸		
miR-1246		↑ ⁵⁹		
miR-1290		↑ ²⁹		
miR-3976		↑ ⁵⁹		
miR-4306		↑ ⁵⁹		
miR-4644		↑ ⁵⁹		

Notes: ↑, upregulated; ↓, downregulated.**Abbreviation:** PDAC, pancreatic ductal adenocarcinoma.

such as increased expression of enzymes involved in drug catabolism or antiapoptotic proteins.⁶²

Recent studies have indicated that miRNAs appear to be critical regulators of chemoresistance in PDAC cells.⁶³ The levels of the oncogenic miR-155 were shown to increase after pancreatic cancer cells were treated with gemcitabine.⁶⁴ Moreover, downregulation of miR-200 family expression was observed in gemcitabine-resistant pancreatic cancer cells.⁶⁵ Furthermore, miR-34 is reported to involve in the self-renewal of pancreatic cancer stem cells, while the loss of miR-34 in pancreatic cancer is associated with an enrichment of cancer stem cells that are insensitive to chemotherapy.⁶⁶ miRNAs with a putative impact on chemoresistance are shown in Table 2.

The mechanisms through which miRNAs induce chemoresistance have been clarified in several studies. It has been shown that miR-365 induced chemoresistance through directly targeting the adaptor protein Src Homology 2 Domain Containing 1 and apoptosis-promoting protein BAX.⁶⁷ Another study showed that miR-1246 expression induced chemoresistance through downregulating CCNG2, a family of cyclins.⁶⁸ In addition, a recent study also indicates that miRNAs might regulate the epithelial–mesenchymal transition (EMT) through the regulation of cadherin1 and other molecules,⁶⁹ which mediate various types of cellular drug resistance mechanisms. Many members of the let-7 family are downregulated in EMT-type cells that are resistant to gemcitabine. In an investigation of the expression levels of miR-200 and let-7 in EMT-phenotype pancreatic cancer cells that are resistant to gemcitabine, re-expression of the downregulated miR-200 family upregulates cadherin1 and downregulates ZeB1 and vimentin (EMT inducers).⁷⁰ Table 3 and Figure 1 show the mechanisms by which miRNAs cause chemoresistance. These results clearly suggest the potential role of miRNAs as novel targets to improve chemoresistance.

Table 2 miRNA candidates which are correlated to chemoresistance in PDAC

miRNA	Gemcitabine	Cisplatin	5-fluorouracil	Docetaxel	Irradiation
miR-let-7	↓ ⁷⁰				
miR-10b	↑ ⁷¹				
miR-21	↑ ⁷²⁻⁷⁶		↑ ^{72,77}		
miR-29a	↑ ⁷⁸				
miR-34	↓ ⁶⁶	↓ ⁶⁶		↓ ⁶⁶	↓ ⁶⁶
miR-99b					↑ ⁷⁹
miR-101-3p	↓ ⁸⁰				
miR-125b	↑ ⁸¹				
miR-142-5p	↓ ⁸²				
miR-155	↑ ^{83,84}				
miR-181b	↑ ⁸⁵				
miR-200a	↓ ⁷⁰				
miR-200b	↓ ⁷⁰				
miR-204	↓ ⁸²				
miR-210	↓ ⁸⁶				
miR-214	↑ ⁸⁷				
miR-221	↑ ⁷²		↑ ⁷²		
miR-320a			↑ ⁸⁸		
miR-320c	↑ ⁸⁹				
miR-365	↑ ⁶⁷				
miR-374b		↓ ⁹⁰			
miR-1246	↑ ⁶⁸				

Notes: ↑, upregulated; ↓, downregulated.

Abbreviation: PDAC, pancreatic ductal adenocarcinoma.

Role of miRNAs in the prognosis of PDAC

As one of the most lethal human cancers, PDAC is known for its very poor overall prognosis.⁹¹ Thus, finding prognostic

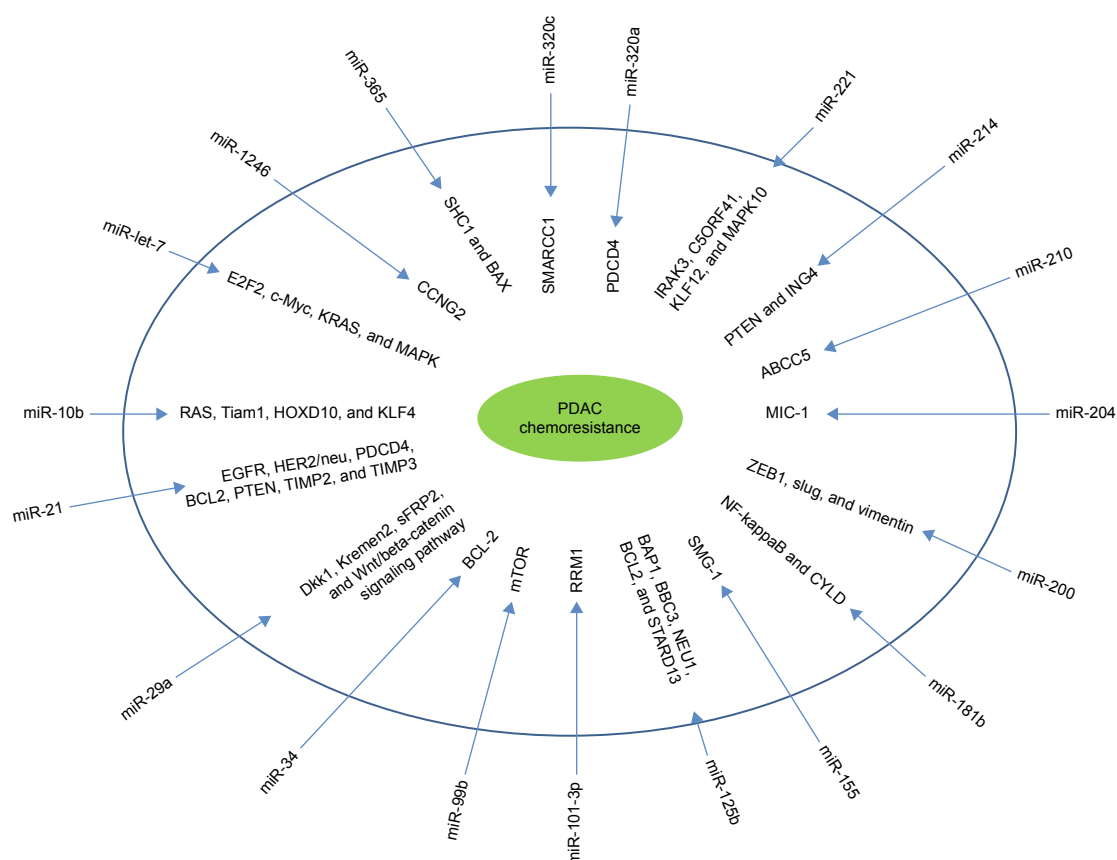
markers to assess probable course of the disease prior to treatment is highly desirable. A number of literature reports are devoted to the use of miRNAs as prognostic markers in PDAC.

In particular, many studies have been carried out on RNA extraction of histologic tissue. A meta-analysis involving 1,525 patients has shown that overall and/or disease-free survivals were significantly shorter in patients with high tumoral miR-21.⁹² Multivariate analyses have confirmed that a low level of miR-218 expression was an independent predictor of poor prognosis in PDAC patients.⁹³ Similarly, low expression of miR-497 was also an independent adverse prognostic factor of PDAC.⁹⁴ Recently, Zou et al showed that miR-29c expression was significantly lower in the PDAC tissue of 109 patients compared with pair-matched adjacent paracancerous tissues, suggesting that a lower level of miR-29c is associated with a poor prognosis.⁹⁵

miRNAs as prognostic biomarkers have also been evaluated in the serum or plasma of PDAC patients. It was reported that serum miR-196a expression level had a potential value in predicting the median survival time of PDAC patients (high-level miR-196a, 6.1 months versus low-level miR-196a, 12.00 months; $p=0.007$), indicating that serum miR-196a could be a potential noninvasive marker for PDAC prognosis.⁹⁶ More recently, Hua et al demonstrated that serum

Table 3 The mechanisms through which miRNAs induce chemoresistance

miRNA	Mechanisms	Reference
miR-let-7	E2F2, c-Myc, KRAS, and MAPK	70
miR-10b	RAS, Tiam1, HOXD10, and KLF4	71
miR-21	EGFR, HER2/neu, PDCD4, BCL2, PTEN, TIMP2, and TIMP3	73, 74
miR-29a	Dkk1, Kremen2, sFRP2, and Wnt/beta-catenin signaling pathway	78
miR-34	BCL-2	66
miR-99b	mTOR	80
miR-101-3p	RRM1	80
miR-125b	BAPI, BBC3, NEU1, BCL2, and STARD13	81
miR-155	SMG-I	83
miR-181b	NF-kappaB and CYLD	85
miR-200	ZEB1, slug, and vimentin	70
miR-204	MIC-1	82
miR-210	ABCC5	86
miR-214	PTEN and ING4	87
miR-221	IRAK3, C5ORF41, KLF12, and MAPK10	72
miR-320a	PDCD4	88
miR-320c	SMARCC1	89
miR-365	SHC1 and BAX	67
miR-1246	CCNG2	68



Abbreviation: PDAC, pancreatic ductal adenocarcinoma.

Table 4 (Continued)

miRNA	Histologic samples	Serum or plasma	Pancreatic juice
miR-203	↑ ^{53,106}		
miR-205			↑ ²⁰
miR-210	↑ ¹⁰⁶		↑ ²⁰
miR-212	↑ ⁹⁷		
miR-218	↓ ⁹³		
miR-219	↑ ¹⁰⁹		
miR-222	↑ ^{106,110}		
miR-223	↑ ¹¹¹	↑ ¹¹¹	
miR-326	↑ ¹⁰⁷		
miR-373		↓ ⁵⁷	
miR-452	↓ ²¹		
miR-492			↑ ²⁰
miR-497	↓ ⁹⁴		
miR-518a-2	↓ ²¹		
miR-675	↑ ⁹⁷		
miR-1207-3p	↑ ¹⁰²		
miR-1247	↓ ¹¹²		↑ ²⁰
miR-1249	↑ ¹⁰²		
miR-1274a	↑ ¹⁰²		
miR-1290	↑ ¹⁰²		
miR-1914	↑ ¹⁰²		
miR-4281	↑ ¹⁰²		

Abbreviation: PDAC, pancreatic ductal adenocarcinoma.

miR-373 expression was greatly downregulated in a total of 103 PDAC patients who had shorter 5-year overall survival.⁵⁷ Consistent with the predictive role of miR-21 isolated from the histologic samples in poor prognosis, it has been shown that serum miR-21 levels in PDAC patients were also significantly associated with overall survival.³⁹

The main miRNAs isolated from the histologic samples, serum or plasma, and pancreatic juices with a potential role in poor prognosis of pancreatic cancer are shown in Table 4. These data demonstrate that miRNA-based biomarker can serve as an effective approach for PDAC prognosis.

Conclusion

Taken together, accumulating evidence supports the view that miRNAs have proven effective for PDAC diagnosis, chemoresistance, and prognosis. Despite the many efforts that have been taken, a practical application to be used in the clinic is still lacking. Additional studies in larger homogeneous populations with validated methodology using the emerging miRNAs as markers within prospective trials, to see if they can aid clinical decision making are needed.

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Disclosure

The authors report no conflicts of interest in this work.

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