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Extracellular and intracellular microRNAs in pancreatic cancer: from early diagnosis to reducing chemoresistance

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Abstract

Pancreatic cancer (PaC) is one of the most aggressive malignancies. The dismal survival rate of PaC patients is mainly due to the late diagnosis and their resistance to conventional chemotherapies. Emerging evidence suggests that miRNA can serve as a potential new diagnostic and therapeutic weapon to fight against PaC. Circulating miRNAs represent the most promising noninvasive tools for diagnosis owing to their high stability in blood. Combinations of circulating miRNAs with other serum indicators such as carbohydrate antigen 19–9 (CA19–9) were demonstrated to be valuable biomarkers for early PaC diagnosis. As miRNAs can regulate epithelial-mesenchymal transition (EMT) and the progression of cancer stem cells (CSCs), two critical factors in PaC drug resistance, selectively manipulating miRNAs may improve the sensitivity of certain PaC chemotherapeutic agents, such as gemcitabine. Therefore, the investigations of miRNAs in PaC may provide potential novel approaches for both tumor diagnosis and treatment.

Keywords: Pancreatic cancer, Circulating microRNAs, Biomarkers, Epithelial-mesenchymal transition, Chemoresistance

Introduction

Pancreatic Cancer (PaC) is currently the 3rd cause of cancer-associated deaths in the U.S. surpassing breast cancer [1], with ~ 53,670 new diagnoses (greater than 90% is pancreatic ductal adenocarcinoma, PDAC) and ~ 43,090 deaths predicted to occur in 2017 [2, 3]. Only 24% of patients survive for 1 year after diagnosis with PaC, even in countries with the best standard of care [4]. Currently, owning to no effective early screening test, about 80% of PaC patients are too late to do the potentially curative resection [5]. In addition, PaC is highly resistant to conventional chemotherapies (gemcitabine), which led to the high mortality of PaC patients. According to clinical trials, conventional chemotherapy treatment only increase 5 weeks of survival in patients diagnosed with advanced PaC [6, 7]. Therefore, the patients presenting with advanced PaC have extremely low survival times, underlines the urgent need to improve both early diagnosis and further understanding of drug-resistant mechanisms of PaC.

MicroRNA (miRNA) is a class of small noncoding RNAs that negatively regulate target gene expression at post-transcriptional level [8, 9]. As tiny but powerful players in cell regulation, miRNAs are almost involved in all biologic processes in mammals [10, 11]. Aberrant miRNA expressions are observed in PaC, thus, targeting miRNAs may provide fundamentally new approaches to reduce chemoresistance in PaC. Moreover, studying of the stably expressed circulating miRNAs in blood may provide us a gold mine of noninvasive biomarkers in cancer [10]. Since the change of miRNA expressions usually occurs during early tumorigenesis, we thus describe the possibility of using circulating miRNAs for early PaC detection, which can be applicable diagnostic and prognostic markers in PaC [12–15]. The roles of miRNAs in epithelial-mesenchymal transition (EMT), cancer stem cells (CSCs), and their biological significances in PaC and possible applications to reduce chemoresistance are also discussed.

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Extracellular miRNAs: Potential biomarkers for early detection of PaC

Current diagnosis of PaC

'The silent killer' PaC often shows no symptoms in the early stages unless the primary tumor is located in the pancreas head [16, 17]. This leads to PaC being diagnosed until when it has spread beyond the pancreas itself [5]. Clinical trials showed that for the patients who are able to remove their pancreatic tumor, their 5-year survival rate are significantly improved by adjuvant chemotherapy [18–20]. Unfortunately, when diagnosis, only less than 15% of patients were surgically resectable [21].

Abdominal pain, unusual bloating, belching, heartburn, altered bowel habits, symptoms of biliary obstruction are the most commonly symptoms before PaC diagnosis, unfortunately, usually only advanced PaC exerts enough specific symptoms [22]. Therefore, early detection of PaC is urgently needed [23]. Current noninvasive imaging techniques such as ultrasound, contrast-enhanced multidetector CT, and MRI are unable to detect tumor < 1–2 cm in size [24]. Carbohydrate antigen 19–9 (CA19–9), the most extensively used biomarker in PaC diagnosis, is also used to predict tumor recurrence [25, 26]. However, it still lack of sensitivity, and often shows false-positive elevation in the presence of obstructive jaundice [25]. Thus, it is urgent to devise better diagnostic markers for PaC. Despite a large number of potential markers have been identified in PaC, such as cytokeratin, glycoprotein, few have proven advantageous when compared to the currently used CA19–9 serum testing [25, 27–32].

Over the past decade, miRNAs were found to be important regulators in carcinogenesis process [11]. Many studies have demonstrated that miRNAs were either oncogenic or acted as tumor-suppressors [33]. Due to their stability in fresh and formalin-fixed paraffin-embedded samples, the deregulated tissue miRNAs represent feasible diagnostic or prognostic markers for PaC [34, 35].

Currently, the noninvasive blood-based test is still the most convenient early diagnostic approach. In addition, the ideal blood PaC biomarkers would allow for diagnosis before it spreads to other organs [16, 36]. In this part, we focus on the amazing discovery that a large amount of miRNAs are stably expressed in the circulation, which might provide an easy and promising early diagnosis strategy for PaC [11, 37–39]. Studies by several independent groups clearly show that the circulating miRNAs are protected from endogenous ribonuclease activity because binding to proteins [40–42], or being packed by secretory exosomes [43, 44].

Single circulating miRNA as potential biomarker

Allen et al. first found that circulating miR-210 was significantly elevated in plasma samples from PaC patients [45]. In the same year Ang et al. reported that both tissue and serum miR-200a/b were up-regulated in PaC patients [46]. As shown in Table 1, identification of these circulating miRNA-based biomarkers opens up a promising field of using the expression profile of circulating miRNAs for PaC diagnosis. Otsuji's group found that the miR-18a and miR-221, which belong to the oncogenic miR-17/92 and miR-221/222 clusters, were highly expressed in both PaC tissue and plasma samples [47–49]. Zhang et al. [50, 51] demonstrated that the circulating miR-192 and miR-194 in serum may be potential sensitive diagnostic biomarkers for PDAC. Kong et al. showed that serum miR-196a could be used to select possible surgical candidates, because elevated miR-196a level was closely related to poor survival PaC [52, 53]. Their results were proven later by Bartsch and co-workers [54]. Sun et al. also revealed that downregulation of serum of miR-124 was linked to the poor prognosis in patients with PDAC [55]. Michael et al. found that the elevated level of serum miR-1290 could sensitively distinguish patients with low-stage PaC from controls [56]. Tessa et al. showed that circulating miR-485-3p and miR-938 could discriminate PDAC patients from healthy individuals and patients with chronic pancreatitis (CP) [57–59]. miR-25 has also been demonstrated to be a potential novel biomarker for the early PaC diagnosis [60]. By analyzing the expression levels of 6 miRNAs that up-regulated in PDAC, Alemar et al. showed that miR-21 and miR-34a are potentially useful in diagnosing PDAC [61]. By assessing miR-182 in 109 PaC and 38 CP as well as 50 healthy controls, Chen et al. suggested that miR-182 may be a potential marker for both diagnosis and prognosis of PaC, with a sensitivity of 64.1% and a specificity of 82.6% [62].

Panels of circulating miRNAs as potential biomarkers

Recent years, accompanied by the development of microarray techniques, miRNAs were systemically investigated in PaC patients. Wang et al. profiled four miRNAs, miR-21, miR-210, miR-155 and miR-196a as blood-based biomarkers of PaC, with sensitivity of 64% and specificity of 89% [63, 64]. By comparing the miRNA expressions in PaC with normal pancreas/chronic pancreatitis in human tissue specimens and blood samples, Bauer et al. revealed that several miRNAs (miR-148a, miR-216a, miR-217, miR-181a/c, miR-324, miR-146a, miR-210, miR-345 and miR-574) were able to differentiate between PaC and normal/inflamed pancreas in tissue and blood specimens [10, 65]. Notably, when they assessed miRNAs in blood samples only, they found that 36 miRNAs were able to distinguish PaC from healthy controls with sensitivity of 97.3% and specificity of 95%. Liu et al. compared serum miRNA expressions of PaC patients with matched cancer-free controls and observed that seven miRNAs (miR-20a, miR-21, miR-24, miR-25, miR-99a, miR-185 and miR-191) were significantly altered in PaC patients [12, 66].

Table 1 MiRNAs as early diagnostic markers for pancreatic caner

Biomarker	Source	Sample size			Diagnostic utility		Ref.
		PaC	CP	Normal	Sensitivity	Specificity	
miR-18a	plasma	36		30	N/A	N/A	[44]
miR-192	serum	70		40	76.00%	55.00%	[46]
miR-196a	serum	35	15	15	100.00%	75.00%	[48]
miR-210	plasma	11		11	N/A	N/A	[41]
miR-221	plasma	47		30	74.00%	78.00%	[45]
miR-1290	serum	41	35	19	N/A	N/A	[52]
miRNA-192,-194	serum	N/A		N/A	84.00%	75.00%	[47]
miR-196a,b	serum	24	10	10	100.00%	90.00%	[50]
miR-200a	serum	45	11	32	84.40%	87.50%	[42]
miR-200b	serum	45	11	32	71.10%	96.90%	[42]
miR-148a, −216a,-217,181a/c, −324-5p, −146a,-210,-345,-574	blood	45	38	33	N/A	N/A	[61]
miR-20a,-21,-24,-25,-99a,-185,-191	serum	95		81	94.00%	93.00%	[62]
miR-21, −210, −155, −196a	plasma	28		19	64.00%	89.00%	[59]
miR-22,-642,-885-5p	blood	11		11	91.00%	91.00%	[64]
CA 19–9 and miR-27a-3p	serum/PBMCs	129	103	60	85.30%	81.60%	[66]
CA 19–9 and miR-16,-196a	serum/plasma	140	111	68	92.00%	95.60%	[67]
CA 19–9 and miR-145, −150, −223, −636	serum/blood	86	7	44	74.00%	96.00%	[68]
CA 19–9 and miR-26b, −34a, −22, −126-5p, −145, − 150, − 223, −505, − 636, − 885-5p	serum/blood	86	7	44	73.00%	97.00%	[68]

CA 19–9 Carbohydrate antigen 19–9, *PaC* Pancreatic cancer, *CP* Chronic pancreatitis

Ganepola et al. developed a panel of blood-based diagnostic biomarkers consisting of miR-642b, miR-885-5p and miR-22 for PaC early detection, with sensitivity of 91% and specificity of 91% [67, 68]. These findings indicate that combinations of miRNAs may proven to be more accurate at diagnosing and/or predicting outcome in PaC patients.

Combination of panels of miRNAs with CA19–9 as biomarkers

The idea of combining circulating miRNAs with CA19–9 for PaC early detection has also been raised up by some researchers. Wang et al. investigated miRNA expression levels in PBMCs in healthy, benign pancreatic/peripancreatic disease, and PaC cohorts. They found that the combination of miR-27a in PBMCs and serum CA19–9 levels showed higher diagnostic accuracy [69]. Liu et al. also elucidated the supplementary effect of plasma miRNAs with serum CA19–9 in early PaC diagnosis, and they demonstrated that miR-16 and miR-196a can discriminate PaC patients from healthy and CP patients. Moreover, the combination of miR-16, miR-196a and CA19–9 was more effective, with a sensitivity of 92% and specificity 95.6% for discriminating PaC patients from healthy controls, and a sensitivity of 88.4% and specificity of 96.3% for discriminating PaC from CP patients. Of note, the combination was sensitive in identifying in Stage 1 PaC (85.2%) [70]. Schultz et al. have performed the largest screening of the whole blood miRNAs in PaC patients. In their study, the blood samples of 409 PaC patients and 312 healthy participant and 25 patients with CP were tested. The test characteristics for the training cohort were index I (miR-145, miR-636, miR-223, and miR-150) and index II (miR-26b, miR-126-5p, miR-34a, miR-145, miR-22, miR-223, miR-150, miR-636, miR-505, and miR-885-5p). For CA19–9 and index I, the sensitivity was 74% and specificity was 96% [71]. For CA19–9 and index II, the sensitivity was 73% and specificity was 97%. Although most of the studies assessed circulating miRNAs in blood, study by Wang et al. investigated the miRNA profile in exocrine pancreatic secretions (pancreatic juice) from PaC patients [11]. Inclusion of serum CA19–9 with the profiles of four circulating miRNAs (miR-205, miR-210, miR-492, and miR-1427) was successfully discriminate pancreatic juice patients from PaC group, with a sensitivity to 91% and the specificity to 100% [72].

Exosomal miRNAs as new promising biomarkers

Exosomes, membrane vesicles ranging from 30 to 120 nm [73–76], are emerging as important intercellular communicators between tumor cells and their microenvionment via information transfer, including nucleotides and proteins [77–80]. Current clinical applications for exosomes in cancer are primarily early detection biomarkers and prognosis assessment. Because the relatively stable vesicle structure in the circulation, exosomes possess great potential for replacing or supplementing the currently used

but unsatisfying biomarker CA19–9 [81–85]. Melo et al. showed that the expression of glypican-1 (GPC1) in PaC-derived exosomes can be used in early PaC diagnosis [86, 87]. In addition, *Silva* et al. reported that PDAC secreted exosomes induced liver metastatic burden, and could be served as a potential prognostic marker for detecting PDAC liver metastasis [77]. Compared with exosomal miRNAs that have been reported in several types of cancers, such as breast cancer and lung cancer, lesser studies focused on miRNAs in PaC secreted exosomes [84]. Que. et al. conducted a PaC exosome case-control study and found that exosomal miR-17-5p and miR-21 were enriched in the serum of PaC patients [88]. A study by Madhavan et al. showed that combination of a panel of proteins (CD44v6, Tspan8, EpCAM, MET and CD104) and four exosomal miRNAs (miR-1246, miR-4644, miR-3976 and miR-4306) markedly increased the diagnostic accuracy of PaC [89]. Recently, by exploring the new technology of label-free nanoplsmonic-based small noncoding RNA, Joshi et al. discovered that exosomal miR-10b was significantly increased in PaC patients [84, 90, 91]. Taken together, exosomal miRNAs show their potential as early detection and prognostic biomarkers in PaC, however, larger numbers of extensive studies are necessary before the clinical application.

Intracellular miRNAs: Potential therapeutic targets for chemoresistance of PaC

Molecular pathogenesis in PaC chemoresistance

Another major barrier in successfully treating PaC is chemoresistance, which can cause the failure of the treatment and lead to high mortality of PaC. Statistic studies implicate that over 80% of the PaC patients showed local invasion or metastasis when diagnosed, which made them inoperable [92–94]. Thus, effective chemotherapy is extremely important for the treatment of advanced PaC patients. Of the numerous chemotherapeutic molecules that have been investigated, gemcitabine is used as the standard clinical drug used in PaC patients, and it usually combined with other adjuvant drugs in the treatment [94–99]. Although FLOFRINOX, another combination of four drugs has increased about 5 months survival than single gemcitabine treatment, this modest and incomplete benefit is unsatisfied, and there is still an urgent need for new drugs to combat chemoresistance in PaC patients [100].

The investigation of the underlying mechanisms of drug resistance has been lasted for half a century. It has been well-established that drug resistance could be either intrinsic (innate) or acquired during the treatment [101]. Conventionally, it is believed that the microenvironment surrounded tumor cells are responsible for innate drug resistance [102], while due to insensitivity to drug-induced apoptosis and the induction of drug-detoxification mechanisms, the drug resistance is acquired [103]. To date, a variety of distinct molecular mechanisms have been implicated to participate in PaC pathogenesis, including many genes, such as oncogenes and tumor suppressor genes [104–106], and several signaling pathways such as Notch, EGFR, Akt, NF-κB, TGF-β, JNK, and hedgehog [107–116]. These efforts trying to elucidate mechanisms of drug resistance prompted the development of new targeted agents. However, due to the highly complex nature of drug resistance, the current single agent or multiple drug combinations are often ineffective. The disappointing outcome demands a comprehensive understanding of drug-resistant mechanisms of PaC. Recent studies have pointed out that the intracellular miRNAs may play important roles in cells with EMT-phenotype and cancer stem cells (CSCs) [117–119], making them as potential targets for reducing drug resistance.

Role of intracellular miRNAs in PaC

miRNAs are small RNAs that function as guide molecules in RNA silencing by base pairing with their target mRNAs, this posttranscriptional gene regulatory mechanism makes miRNAs as either “oncomiRs” or “tumor suppressors” [94, 120]. miRNA Profiling in PaC also has showed some of the aberrantly expressed miRNAs, including several miRNAs act as tumor suppressors, whereas others as oncomiRs [121–127]. Therefore, restoring the decreased tumor suppressor miRNAs enables reinstating “normal cellular programs” and hinders the “oncogenic progression”. On the contrary, oncomiRs, are potential the therapeutic targets by RNA silencing. Notably, recent evidence suggests that miRNAs also play important roles in drug resistance, such as downregulation of miR-200 family is synonymous with gemcitabine-resistant PaC cells [128]. Meanwhile, tumor suppressor miR-145 directly targeted p70S6K1 and inhibited its expression, subsequently reverse the gemcitabine resistance [129]. Mikamori et al. revealed that long-term exposure of gemcitabine increase miR-155 expression in PDAC cell. These miR-155 not merely facilitated the anti-apoptotic activity in cells, but were also delivered by exosomes into other PDAC cells, therefore spreading the drug resistance widely [130].

The EMT-like phenotype and miRNAs in PaC

The epithelial cells can transformed from a cobblestone phenotype to a mesenchymal phenotype, which enables the epithelial cells to invade the extracellular matrix [6, 131]. EMT was first described in early 1980s, but hasn’t been paid enough attention until realizing it is closely related to tumor cell invasion and metastasis [132, 133]. When epithelial cells undergo an EMT process, the expression levels of E-cadherin 1 and junction plakoglobin are decreased, while the mesenchymal markers are increased, including vimentin, fibronectin and N-cadherin [134, 135]. Moreover,

the activity of matrix metalloproteinases (MMPs) of epithelial cells were also increased, which contributes to the acquisition of invasiveness [134, 135]. Many studies have proven that EMT played an important role in chemoresistance [136, 137]. Arumugnam et al. reported that several pancreatic cell lines which showed high levels of epithelial markers were sensitive to chemotherapeutic drugs such as gemcitabine, whereas the cell lines resistant to these drugs showed the mesenchymal markers [138, 139].

Aberrant signaling pathways, cytokines and transcriptional factors contribute to the EMT process, thus targeting the EMT network could be a feasible approach to overcome chemoresistance [94, 140]. Recent studies proven that the EMT process is regulated by different miRNAs, which function as critical regulators of the pathologic processes during cancer cell development [128] (Table 2). Philip et al. found that during the TGF-β-induced EMT process, miR-200 family and miR-205 were significantly decreased in cells [141, 142]. Overexpression of the miR-200 family could prevent TGF-β-stimulated cell EMT through inhibiting the expression levels of E-cadherin transcriptional repressors [143]. Following studies also confirmed that ectopic expression of miR-200 family played a determinant role in EMT. Restored miR-200 expression resulted in morphological reversal of EMT phenotype [128, 141, 144]. Sureban et al. illustrated the direct regulatory links between doublecortin-like kinase-1 (DCAMKL-1), miRNAs and EMT in PaC [145]. They found that knockdown of DCAMKL-1 induced miR-200a expression in human PaC cells, and consequently results in downregulation of EMT phenotypic transcription factors. Lzumchenko et al. demonstrated that the TGFβ-miR-200-MIG6 network helps the EMT-kinase switch, which led to resistance to EGFR inhibitors [146]. Bao et al. found that activation of Notch-1signaling contributes to the switch of EMT phenotype through regulating miR-200b expression [147]. Hamada et al. reported the tumor suppressor role of miR-126 in PaC cells by targeting disintegrin and ADM9 [148]. Recently, they also found that miR-197 stimulated EMT process in PaC cells by targeting p120 catenin [149]. Mody et al. found that histone methylation reversal agents, which were used to treat solid tumors, could attenuate TGFβ-1 induced EMT features via restoring miR-663 and miR-4787-5p expression levels [150]. Other miRNAs have also been proven to participate in modulating cell EMT process. For example, let-7 was demonstrated to inhibit HMGA2 expression and maintain RAS-induced EMT [151–153]. Moes et al. found that the miR-203/SNAIL feedback loop regulates EMT process [154]. Ma et al. also reported that knockdown of miR-223 could attenuate drug resistance through reversing EMT phenotype [155].

Cancer stem cells and miRNAs in PaC

The CSC theory suggests that cancer cells can be divided into several different types of cells, including the large proportion of normal tumor cells and a small number of cancer stem cells (CSCs). However, these CSCs live longer, can generate new tumor cells, even cause relapse and distant metastasis [156]. This CSC theory explains why in many cancers, including PaC, drugs that seem to rapidly reduce tumor size but failed to improve long-term survival [156–162]. Now it has been well established that CSCs are responsible for tumor initiation, propagation, and most importantly, they are chemoresistance, which cause the relapse of cancer [163].

Cell surface markers CD44, CD24, CD133, CXCR4 and ESA are expressed by PaC stem cells (approximately 1% of the tumor) [117, 163]. Notably, even high doses of gemcitabine were unable to eliminate CSCs, although the majority of PaC cells were killed in the culture [117]. Studies suggest that the deregulated miRNAs may also contribute to pancreatic stem cells generation [156, 164, 165] (Table 3).

Table 2 Deregulated miRNAs in pancreatic cancer and their functions in the EMT process

miRNAs	Targets	Status	Functions in the EMT process		Ref.
			Activation	Inhitibion	
miR-200a	ZEB1	down	TGF-β induced EMT Vimentin	P53 network E-cadherin	[126]
miR-200b	ZEB2/SIP1				[188]
miR-200c	Slug				[189]
miR-141	SIRT				[139]
miR-429					[142]
miR-126	ADM9	down	Cellular migration invasion	E-cadherin	[146]
miR-197	P120 catenin	up	EMT process		[147]
miR-205	ZEB2/SIP1	down		E-cadherin	[139]
Let-7	HMGA2	down	RAS signaling		[149, 150]
miR-217	SIRT1	down	TGF-β induced EMT		[151]
miR-203	SNAI1	down	EMT process		[152, 154]

EMT Epithelial-mesenchymal transition

Table 3 Deregulated miRNAs and their functions in pancreatic cancer stem cells

miRNAs	Targets	Status	Functions in CSCs		Ref.
			Activation	Inhibition	
miR-200a	Suz12	down	CD44 induction CSC formation CSC self-renewal	E-cadherin	[167]
miR-200b	Bmi 1				[169]
miR-200c	Notch 1				[168]
miR-141	Lin28B				[166]
miR-429	FoxM1				[145, 170, 171, 173]
miR-34a	HDAC1/2	down	cell migration invasion		[165]
miR-101	EZH2/MCL-1/Fos	down	cell proliferation invasion		[175]
miR-125b	BAK1	up		apoptosis	[178]
Let-7a	HMGA2	down			[152]

CSCs Cancer stem cells

miR-34a was found to play a key role in PaC progression by inhibiting CSC characteristics, and restoration of miR-34a expression strongly inhibited the proliferation and invasion of PaC CSCs [166]. Wu et al. demonstrated that miR-34 regulates drug resistance via targeting HDAC1 and HDAC2 [167]. Bao et al. showed that metformin could decrease the CSC marker expression via reversal of miRNAs that are significantly decreased in PaC, such as let 7 and miR-200 family [168]. Here, miR-200 family has also been shown to inhibit Suz12 and Bmil, two essential genes responsible for the stem cell maintenance [144, 169–171]. Notch signaling pathway has been demonstrated to be key regulator in the CSC formation. MiR-200b could repress Lin28b and Notch 1 to inhibit the CSC proliferation and up-regulate CD44 expression [147, 172–174]. Bao et al. demonstrated that overexpression of miR-200b also inhibited the FoxM1 and increased cell migration [175, 176]. By studying the tumor suppressor miR-101, Konno et al. reported that miR-101/EZH2/MCL-1/Fos axis induces the apoptosis and senescence of cancer cell [177]. Yang et al. found that let-7a increase the drug sensitivity via downregulate HMGA2 [178]. Jung et al. showed several miRNAs were significantly altered in pancreatic CSCs, such as miR-99a, miR-100 etc. [179]. Inhibition of apoptosis via downregulating BAK1 was reported recently by Chen and co-workers [180]. Recently, Haseqawa et al. reported that miR-1246 contributed to drug resistance and CSC properties in PaC, furthermore, it could be promising prognosis marker for PaC patients [181].

Targeting specific miRNAs to reduce chemoresistance

Accumulating evidences suggest the pivotal roles of EMT-type cells and CSCs in drug resistance, as miRNAs appear to exert ubiquitous regulatory roles in EMT and CSCs, inhibiting or restoring the deregulated miRNAs could become a novel approach for PaC treatment by eliminating of CSCs or EMT-like cells [6]. For example, inhibition of the aberrantly expressed miR-221 and miR-21 significantly improved gemcitabine sensitivity in PaC cells [122, 182], whereas introduction of miR-200 family could make the gemcitabine-resistance cells become sensitive to gemcitabine again [121, 183, 184]. Some researchers reported that natural agents isolated from common food, such as curcumin, isoflavone and idole-3-carbinol, could reverse EMT-phenotype by regulating miRNAs, which could be an easy and safe way for treating PaC patients [185, 186].

Conclusion and future perspective

Intracellular miRNAs are closely correlated with the pathogenesis of PaC. Targeting specific miRNAs become new potential strategy to treat PaC and reduce drug-resistance. In addition, in the recent decade, the detection of stably expressed circulating miRNAs in blood is a 'booming' field in biomarker world [68]. The high stability of miRNAs in circulation postulate the possibility of using them as sensitive and specific biomarkers for PaC early diagnosis and prognosis, from single miRNA to a panel of miRNAs profiling, and in certain cases, from miRNA expression profile alone to a combination of miRNA profile with other clinic PaC indicators such as CA19–9. However, although these findings have the potential to improve clinical early diagnosis in the future, it is fair to say that all these potential biomarkers still need rigorous validation before using in routine management. Circulating miRNAs also show the implication of chemoresistance in several cancers such as breast cancer [187]. Several circulating miRNAs present functional significance in predicting the resistance to chemotherapy [188, 189]. Thus, it is reasonable to further explore the role of circulating miRNAs in the development of chemoresistance in PaC. Despite the promising therapeutic advantages of miRNAs, there are several critical issues, such as avoiding "off-target" effects, optimizing the miRNA dosing and devising effective delivery approaches, need to be fully addressed before it can benefit PaC patients.

Abbreviations
ADM9: Metalloproteinase domain-containing protein 9; Akt-2: v-akt murine thymoma viral oncogene homolog 2; BAK1: B-cell lymphoma 2-antagonist/killer 1; Bcl-6: B-cell lymphoma 6; CA19–9: Carbohydrate antigen 19–9; CCNG-2: Cyclin G2; CSC: Cancer stem cell; DCAMKL-1: Deouble ecortin-like kinase-1; EGFR: Epidermal growth factor receptor; EMT: Epithelial-mesenchymal transition; ESA: Epithelial-specific antigen; Hh: Hedgehog; HMG2: High-mobility group protein 2; JNK: c-Jun N-terminal kinases; K-ras: V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; MIA: Melanoma inhibitory activity; MIG6: Mitogen-inducible gene 6; MMP: Metalloproteinase; Myb: Myelobastosis oncogene; NF-κB: Nuclear factor-k-gene binding; P16: Cyclin-dependent kinase inhibitor 2A; P53: Tumor protein 53; PaC: Pancreatic cancer; PBMC: Peripheral blood mononuclear cell; PRC: Polycomb repressor complexe; Pten: Phosphatase and tensin homolog; S100P: S100 calcium binding protein P; Slug: Snail homolog 2; Smad4: Mothers against DPP homolog 4; Src: Sarcoma oncogene; TGF-β: Transforming growth factor; ZEB: Zinc finger E-box binding homeobox

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XJ, JL and DH wrote the manuscript. ZW and SZ contributed to the discussion. XJ, JL and YZ revised the manuscript and approved the final version to be published. All authors read and approved the final manuscript.

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Not applicable.

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