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REVIEW

MicroRNA in pancreatic cancer

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Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies. Patients with PDAC are often asymptomatic, and many have lymph node and distant metastases as well as vessel invasion upon diagnosis. Surgery and current chemotherapy have limited efficacy for improving prognosis, which accounts for overall median survival of 8.6 months and a 9.7% 5-year survival rate. MicroRNAs (miRNAs) are attracting increasing attention because of their association with tumour progression. At least 50% of miRNAs that are aberrantly expressed in tumours have important roles as post-transcriptional regulators and exhibit oncogenic or tumour suppressive activities by directly binding to their target messenger RNAs. Various techniques are available to identify miRNAs that are differentially expressed in cancerous vs normal tissues. In this review, we summarise the miRNA profiles of normal pancreatic tissue and cancer tissue of patients with PDACs and characterise the expression of miRNAs associated with tumour progression. Further, we highlight the target genes and signalling pathways of miRNAs that are aberrantly expressed in PDACs. This knowledge may lead to the development of preventive and therapeutic strategies for treating this deadly disease.
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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies and accounts for >200 000 deaths annually worldwide.[1] Patients with PDAC are often asymptomatic, and many have lymph node or distant metastasis as well as vessel invasion upon diagnosis.[2] The prognosis is very poor for Japanese patients with PDAC who undergo pancreatectomy (overall median survival, 11.7 months; 13.4%, 5-year survival).[3] Moreover, the current chemotherapeutic regimen employing gemcitabine is limited in its efficacy for improving prognosis,[4] which accounts for the 8.6-month overall median survival of all patients and 9.7% 5-year survival.[3]

KRAS, *TP53* and *SMAD* act as oncogenes in PDAC.[5,6] However, most are not therapeutic targets for PDAC, and further studies are required to identify anticancer molecules. MicroRNAs (miRNAs) attract much attention because of their association with the proliferation, migration, invasion and chemoresistance of tumour cells. miRNAs are endogenous small (19–24 nucleotides) noncoding RNAs that regulate gene expression through base-pairing to complementary sites in the 3′-untranslated region (UTR) of target messenger RNAs (mRNAs), leading to translational repression or degradation of the target mRNAs.[7,8] At least 50% of miRNAs are aberrantly expressed in many tumours, have important roles as post-transcriptional regulators and exhibit oncogenic or tumour suppressive functions by directly binding to target mRNAs.[9]

Several miRNA databases such as Targetscan (http://www.targetscan.org/vert_70/), miRBase (http://www.mirbase.org/) and microRNA.org (http://www.microrna.org/microrna/home.do) are available for predicting miRNA targets, and successful predictions may lead to the identification of new oncogenes and signalling pathways in cancer cells.[10] Moreover, to identify miRNA expression in cancer and to determine whether miRNAs are differentially expressed by cancer cells vs their normal counterparts, researchers employ techniques such as real-time quantitative reverse transcription-PCR (qRT-PCR), microarray assays and next-generation nucleotide sequencing. Here we review miRNA profiles of normal and malignant pancreatic tissues in patients with PDAC and identify miRNAs associated with tumour progression. Further, we highlight target genes and signalling pathways in PDAC that are affected by aberrantly expressed miRNAs. This knowledge may lead to the development of preventive and therapeutic strategies for treating this deadly disease.

miRNA PROFILES OF PDAC

Numerous studies report miRNA profiling of PDAC tissue using techniques such as those described above to analyse tumour, benign and normal frozen tissue that are acquired from formalin-fixed paraffin-embedded (FFPE) tissue and fine-needle aspiration biopsies (FNABs). These studies identified from several hundreds to thousands of miRNAs. In the present review, we chose to review the findings of 10 microarray analyses and one PCR array analysis of normal and cancer tissue of patients with PDAC (Table 1).[11–21] Eight microarray analyses employed RNA samples extracted from frozen resected tumours, another study analysed FFPE samples,[12] and two studies utilised RNA isolated from FFPE-FNAB and fresh FNAB samples.[17,20]

Analyses of the 11 microarrays identified 483 differentially expressed miRNAs, including 276 and 207 that were upregulated or down-regulated, respectively, in at least one analysis. Among these miRNAs,

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Table 1 Summary of miRNA profiling on PDAC tissue

No.	*Assay type*	*Number of probes*	*Sample type*	*Number of samples (tumour/normal)*	Reference
1	mirVana miRNA Bioarrays (Ambion)	377	Resected tissue	8/5	11
2	Ohio State University custom miRNA microarray	1100	FFPE	65/65	12
3	Agilent Human miRNA microarray (v2.0)	723	Resected tissue	48/10	13
4	Toray 3D Gene miRNA microarray	>900	Resected tissue	5/5	14
5	Affymetrix Gene Chip miRNA Array	866	Resected tissue	17/17	15
6	Geniom Biochip miRNA *Homo sapiens*	863	Resected tissue	94/16	16
7	LC Sciences Houston miRNA microarray	NR	FFPE from FNAB	29/15	17
8	miRCURY LNA human microRNA Array	<1200	Resected tissue	20/20	18
9	Taqman Array Human MicroRNA A+B Cards v2.0	664	Resected tissue	170/28	19
10	miRCURY LNA Array	NR	FNAB	11/11	20
11	Agilent Human miRNA microarray (V12.0)	NR	Resected tissue	14/6	21

Abbreviations: FFPE, formalin-fixed paraffin-embedded; FNAB, fine-needle aspiration biopsy; NR, not reported.

Table 2 Analyses of cancerous and noncancerous tissues of PDACs: downregulated miRNAs detected using 10 microarrays and one PCR array

miRNA	*Number of study*	*Target genes*	*Summary*	*Reference*
miR-217	7	*SIRT1*	Regulate the EMT process	99
		KRAS	Inhibits cell growth and colony formation	25
miR-141	6	*MAP4K4*	Inhibits proliferation, colony formation and invasion by Inhibits G1-phase arrest and apoptosis	100
		YAP1	Inhibits proliferation, colony formation and apoptosis	97
		TM4SF1	Inhibits invasion and migration	101
miR-148a	6	*DNMT1*	Inhibits proliferation and metastasis of ASPC-1 cells	102[a]
		CCKBR, Bcl-2	Inhibits growth and apoptosis	103[a]
		CDC25B	Inhibits cell survival	67
		None	Hypermethylation of the DNA region encoding miR-148a in PanIN	104
miR-375	6	*PDK1*	Inhibits cell growth proliferation and promote apoptosis	33,34
		None	Inhibits proliferation	105[a]
miR-29c	5	*ITGB1*	Inhibits cell growth, invasion and migration	106
		MMP2	Inhibits migration, invasion and liver metastasis in nude mice and affects survival of patients	107
		FRAT2, LRP6, FZD4, FZD5	Inhibit migration and stem cell like phenotype and TGF—β/SMAD3 signalling inhibits miR-29c	47
miR-130b	5	*STAT3*	Inhibits proliferation and invasion	43
miR-200c	5	*MUC4, MUC6*	Direct targets of miR-200c	37
		E-cadherin	Inhibits invasion and increases proliferation	36
		None	Downregulates ZEB1, slug and vimentin	53
miR-216a	5	*JAK2*	Inhibits proliferation and promote apoptosis	42
		JAK2	Inhibits proliferation	21
		Beclin-1	Enhances radiosensitivity	108[a]
miR-216b	5		No report	
miR-30a	4		No report	
miR-30d	4		No report	
miR-26a	3	*p53*	Inhibits proliferation by phosphorylation of p53	109[a]
		Cyclin E2	Inhibits proliferation and patient survival	58
miR-148b	3	*AMPKα1*	Arrests cell cycle and inhibits cell growth	65
		DNMT1	Modifies methylation of tumour suppressor genes	95
miR-335	3	*OCT4*	Inhibits progression and stem cell properties	110[a]
miR-365	3	*SHC1, BAX*	Induce gemcitabine resistance	111
miR-30a*[b]	3		No report	
miR-30b	3		No report	
miR-30c	3		No report	
miR-30e	3		No report	
miR-379	3		No report	
let-7d	3		No report	
let-7f	3		No report	

Abbreviations: EMT, epithelial-mesenchymal transition; TGF, transforming growth factor.
[a]Abstract only.
[b]*means a miRNA-star form.

Table 3 Upregulated miRNAs by 10 microarray and one PCR array analysis between cancerous and noncancerous tissues in PDAC

miRNA	*Number of study*	*Target genes*	*Summary*	*Reference*
miR-21	8	*Bcl-2*	Reduces apoptosis and induce gemcitabine resistance	70,71
		FasL	Reduces apoptosis and induce gemcitabine resistance	112
		FoxO1	Promotes tumour growth	90
		PDCD4	Promotes proliferation and reduce cell death	14,73
		PTEN, RECK	Enhance the progression of cell cycle and promote proliferation	30
miR-155	7	*Foxo3a, KRAS, ROS*	Enhance proliferation induced by ROS generation	91
		SEL1L	Downregulates SEL1L	113
		MLH1	Downregulates MLH1	114
		SOCS1	Promotes invasion and migration	44
		TP53INP1	Promotes tumour growth	75
miR-100	6	*FGFR3*	Inhibits proliferation and increase sensitivities to cisplatin	115[a,b]
miR-222	6	*p57*	Promotes proliferation	63
		MMP2, MMP9	Promote proliferation and invasion while inhibiting apoptosis	116
miR-31	6	None	Promotes proliferation, invasion and migration	117
miR-10a	5	*HOXA1*	Promotes invasion	118
miR-23a	5	*APAF1*	Promotes proliferation and reduce apoptosis	82
		FZD5, HNF1B, TMEM92	Increase EMT-like cell shape transformation	48
miR-107	5	*CDK6*	Inhibits growth	57
miR-143	5	*ARHGEF1, ARHGEF2, K-RAS*	Inhibit the migration, invasion and liver metastasis	119[a,b]
miR-146a	5	*EGFR, IRAK1, MTA-2*	Inhibit invasion	120[a]
		EGFR	Inhibits invasion	121[a]
miR-221	5	*p27kip1*	Enhances the progression of cell cycle and promote proliferation	30
		PTEN, p27kip1, p57kip2, PUMA	Promote proliferation	31
		TIMP2	Promotes proliferation and invasion while inhibiting apoptosis	116
		TRPS1	Mediates EMT phenotype, migration and growth	122
miR-210	5		No report	
miR-145	4	*KRAS, RREB1*	Inhibit tumour growth	27[a]
		ROR	Inhibits proliferation, invasion and cell cycle	123[a]
		MUC13	Inhibits tumour growth and invasion	124[a]
miR-150	4	*MUC4*	Inhibits growth, clonogenicity, migration and invasion, and enhances intercellular adhesion	125[a]
miR-181a	4	*PTEN, MAP2K4*	Promote migration	32
		TNFAIP1	Promotes proliferation and migration	126[b]
miR-214	4	*ING4*	Decreases the sensitivity of tumour cells to gemcitabine	85
miR-1246	4		No report	
let-7i	4		No report	
miR-15b	3	*SMURF2*	Promotes EMT	55
miR-23b	3	*ATG12*	Regulates autophagy associated with radioresistance	127[a]
miR-24	3	*Bim*	Promotes cell growth	88
		FZD5, HNF1B, TMEM92	Increase EMT-like cell shape transformation	48
miR-92a	3	*DUSP10*	Promotes proliferation	128
miR-181b	3	*BCL-2*	Sensitises SW1990/CFPAC-1 cells to gemcitabine	72
		CYLD	Increases gemcitabine resistance of MiaPaca2 cells	129
miR-196a	3	*NFKBIA*	Promotes proliferation and migration	130
		ING5	Promotes proliferation and migration and reduces apoptosis	86
miR-27a	3	*Sprouty2*	Promotes growth, colony formation and migration	26
miR-223	3	*FBw7*	Acquires EMT phenotype	59
miR-34a	3		No report	
miR-140-3p	3		No report	
miR-199a-3p	3		No report	
miR-199b-3p	3		No report	
miR-199a-5p	3		No report	
miR-331-3p	3		No report	
miR-342-3p	3		No report	
miR-505	3		No report	
miR-708	3		No report	
miR-886-5p	3		No report	

[a]Reported as a tumour suppressive microRNA.
[b]Abstract only.

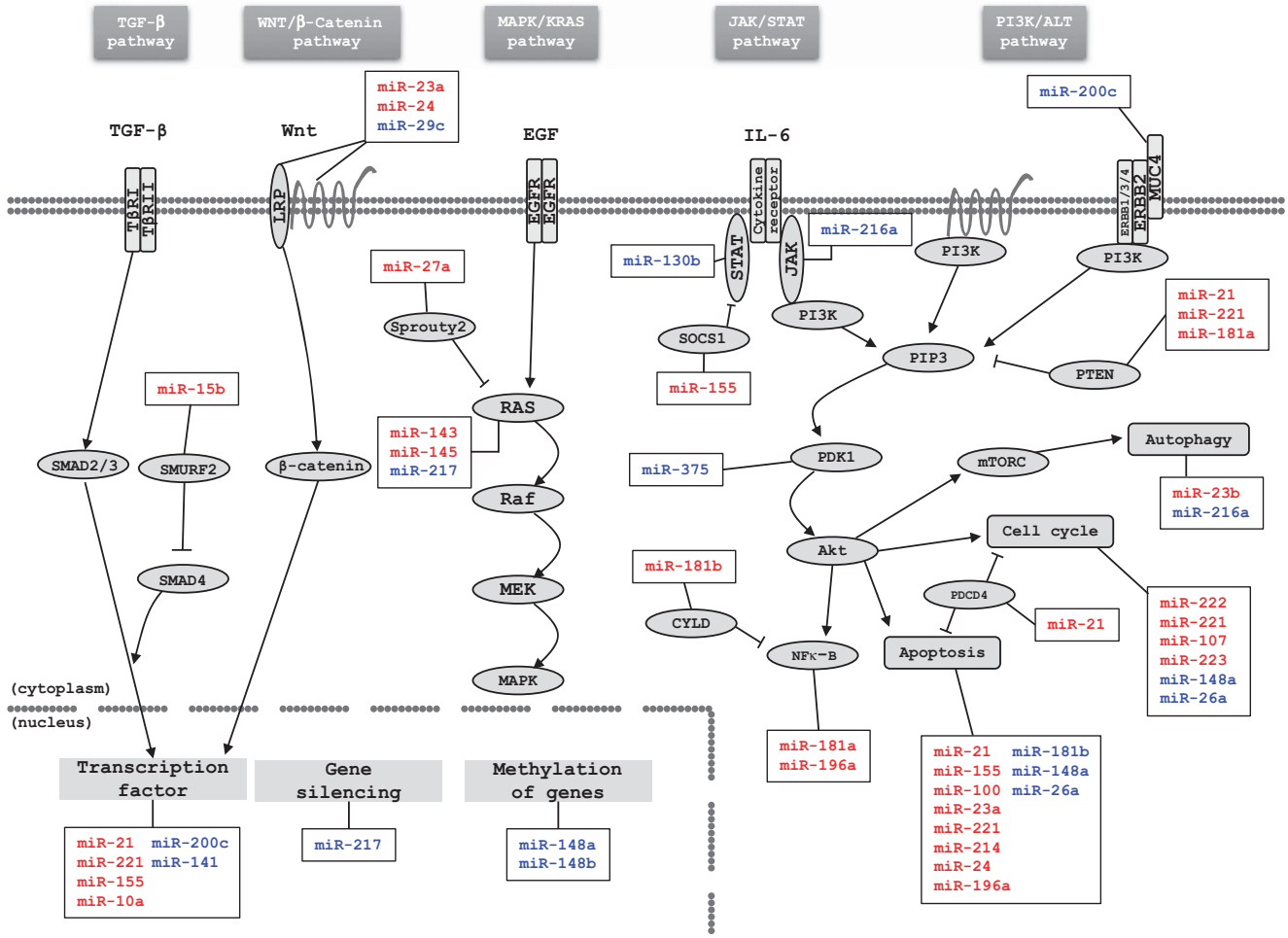

Figure 1 Expression profiles of miRNAs in pancreatic ductal adenocarcinoma (PDAC) cells. This highly simplified model indicates the most significant information about the known and potential interactions of miRNAs with signal transduction pathways in PDAC cells. Red or blue text indicates upregulated or downregulated miRNAs, respectively.

36 and 22 miRNAs are upregulated or downregulated, respectively, in at least three studies (Tables 2 and 3). miR-21 is upregulated in eight studies, miR-155 is upregulated in seven studies, and miR-222, miR-100 and miR-31 are upregulated in six studies. In contrast, miR-217 is downregulated along with miR-141, miR-148a and miR-375. The functions, target genes and signalling pathways of certain miRNAs in PDAC are identified in numerous studies (Figure 1). The regulation of the activities of signalling pathways that influence PDAC progression is reviewed in the sections that follow.

MAPK/KRAS SIGNALLING

KRAS is a small GTPase (21 kDa), which cycles between GTP-bound active and GDP-bound inactive states. Activated KRAS stimulates downstream signalling components such as MAP2K1/MEK, MAPK1/ERK2 and has significant roles in cell survival, proliferation and migration. Mutant forms of KRAS, which are present in at least 90% of PDACs, induce the constitutive activation of downstream signalling cascades.[22–24] miR-217 is significantly downregulated in PDAC tissues and cell lines, and a dual-luciferase reporter assay revealed that *KRAS* mRNA is the direct target of miR-217 *in vitro*. Overexpression of miR-217 in a PDAC cell line decreases KRAS levels, reduces the constitutive phosphorylation of the downstream signal transducer AKT and inhibits cell proliferation.[25] Further, miR-27a expression is abnormally upregulated in PDAC, and inhibition of miR-27a suppresses the growth, colony formation and migration of pancreatic cancer cells. A reporter assay revealed that the mRNA encoding Sprouty2, which regulates KRAS, is the target of miR-27a.[26]

Activated KRAS represses the miR-143/145 cluster in PDAC cells, and overexpression of these miRNAs regulates tumour growth. Moreover, downregulation of miR-143/145 requires the KRAS-responsive element-binding protein (RREB1), which represses the miR-143/145 promoter. The mRNAs encoding KRAS and RREB1 are targets of miR-143/miR-145, revealing a feed-forward mechanism that potentiates KRAS signalling.[27] Some of the miRNAs that are not listed in are reported to be associated with this signalling. These studies show that these miRNAs suppress KRAS and downstream signalling. Restoration of these miRNAs may be a therapeutic strategy for treatment of PDAC.

PI3K/AKT SIGNALLING

The PI3K/AKT pathway resides downstream of KRAS signalling pathways and is involved in the inhibition of apoptosis and stimulation of cell proliferation.[28] PTEN, which suppresses PI3K-AKT-mTOR signalling and controls many cellular processes,[29] is targeted by miR-21, miR-221 and miR-181a.[30–32] miR-21 contributes to the inhibition of cell cycle arrest, apoptosis, and gemcitabine sensitivity.[30] Inhibition of

miR-221 expression leads to the inhibition of cell proliferation and migration of MiaPaCa-2 and Panc-1 cells.[31] Enforced expression of miR-181a promotes the migration of pancreatic cancer cells.[32] In contrast, miR-375 and miR-200c, which are listed up in PI3K/AKT signalling, function as tumour suppressors. PDK1 is a kinase downstream of PI3K, and its mRNA is the direct target of miR-375 in PDAC.[33,34] miR-375 inhibits the malignant phenotype of PDAC cells through the AKT signalling pathway rather than MAPK signalling pathways. miR-200c expression in PDACs is associated with the epithelial-mesenchymal transition (EMT)[35,36] as well as MUC4.[37] MUC4 stabilises HER2 and activates AKT, leading to the activation of downstream including N-cadherin.[38,39] Overexpression of miR-200c causes significant downregulation of *MUC4* mRNA and protein.[37]

JAK/STAT SIGNALLING

Signalling through the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway, which is triggered by growth factors and cytokines, stimulates cell proliferation, differentiation, cell migration and apoptosis.[40,41] miR-216a is the third listed downregulated miRNA (Table 2), which is involved in the JAK/STAT pathway.[21,42] These studies cited show that *JAK2* mRNA is the direct target of miR-216a and that the inhibition of JAK2 expression reduces tumour volume. Further, treating PDAC cells with miR-216a inhibits growth and the transcription of genes that encode downstream components of the JAK/STAT pathway, such as survivin, and promotes apoptosis.[42] miR-130b is downregulated in PDAC (Table 2) and binds directly to the 3′-UTR of *STAT3* mRNA.[43] Further, the downregulation of miR-130b correlates with poor prognosis and tumour progression, and the overexpression of miR-130b suppresses the proliferation of PDAC cells.[43] In contrast, miR-155 is associated with the JAK/STAT pathway as an oncogenic miRNA. Thus, miR-155 negatively regulates SOCS1, which functions as tumour suppressor in JAK/STAT signalling and activates STAT3 to promote the invasion and migration of PDAC cells.[44]

WNT/β-CATENIN SIGNALLING

The WNT/β-catenin signalling pathway has important roles in the proliferation, differentiation, invasion and migration of cancer cells. WNT binds to a heterodimeric receptor complex composed of frizzled (FZD) and a single transmembrane lipoprotein receptor-related protein (LRP)-5 or -6 co-receptor. Binding of WNT leads to the inactivation, cytoplasmic accumulation and translocation of β-catenin to the nucleus to enhance the transcription of target genes.[45,46] miR-29c, which is downregulated according to the results of five microarray analyses, directly regulates the regulators upstream of WNT as follows: FZD4, FZD5, FRAT2 and LRP-6. Further, transforming growth factor (TGF)-β suppresses the expression of miR-29c, leading to WNT activation.[47] PDAC cell lines are classified into two groups according to their capacity to integrate into the mesothelial monolayer, and microarray analysis revealed that miR-23a, miR-24 or both, target the mRNAs that encode FZD5, HNF1B and/or TMEM92.[48] Moreover, western blot analysis revealed that cells with high integration capacity cells express E-cadherin and β-catenin at levels lower compared with cells with low integration capacity.[48]

TGF-β SIGNALLING PATHWAY

The TGF-β signalling pathway has critical roles in cellular functions. TGF-β binds to type II TGF-β receptors (TβRII), which leads to the phosphorylation of the kinase domain of TβRI. Phosphorylated TβRI activates, in turn, the phosphorylation and activation of the downstream mediators SMAD2 and SMAD. Phosphorylated SMAD2 and SMAD3 form a complex with SMAD4 that translocates to the nucleus to regulate the transcription of target genes in a cell-context-dependent manner.[49] Therefore, TGF-β signalling promotes or suppresses tumour phenotypes.[50]

TGF-β signalling induces the EMT, and SMADs directly upregulate transcription factors that mediate the EMT.[51,52] ZEB1 is a crucial activator of the EMT in cancer and inhibits miR-200c and miR-141, which inhibit ZEB1 to reduce the expression of E-cadherin, leading to the induction of the EMT.[53] The cell membrane protein MUC1, which regulates the expression of at least 103 microRNAs, including miR-200c and miR-141, directly interacts with ZEB1 at the promoter of miR-200c/141 to inhibit the expression of these miRNAs.[54] Further, miR-15b targets the mRNA encoding SMURF2, which is a negative regulator of SMADs, and overexpression induces the EMT in PDAC cells.[55] Moreover, the expression of miR-15b is associated with the metastatic phenotype of PDAC.[55]

CELL CYCLE

The progression of the cell cycle is driven by the periodic oscillation of Cdk/cyclin activities, which is tightly regulated by numerous mechanisms in normal cells. In cancer cells, cell cycle signalling is hyperactivated, leading to uncontrolled DNA replication and cell proliferation.[56] miR-107 functions by targeting *CDK6* mRNA that encodes a cyclin D1-dependent kinase to facilitate cell cycle progression.[56,57] Interestingly, in PDAC, miR-107 is silenced by the methylation of CpG islands in its 5′ promoter region.[57] miR-26a is a tumour suppressor in several cancers as well.

miR-26a regulates cyclin E2, leading to the arrest of the G1-to-S-phase transition during the cell cycle.[58] Cyclin E2 is indirectly targeted by miR-223, and miR-223, in turn, targets FBXW7 that is associated with the degradation of cyclin E2 through ubiquitination.[59,60] Further, cyclin E2 is inhibited by P27 and P57, which are critical negative regulators of G1/S progression, and the former is regulated by miR-21 and the latter is regulated by miR-222.[30,61–63] miR-148b functions as a tumour suppressor by targeting AMPKα1, and AMPKα1 functions in normal cells as a central regulator of lipid and glucose metabolism.[64] AMPKα1 is overexpressed and contributes to tumorigenesis by altering the cell cycle, apoptosis and the invasive phenotype of PDAC cells.[65] CDC25A, CDC25B and CDC25C control the specific activation of distinct CDK/cyclin complexes.[66] For example, CDC25B is the target of miR-148a, and an enforced expression of miR-148a inhibits the malignant phenotypes of PDAC cells.[67]

APOPTOSIS

Apoptosis is a central regulator of homeostasis, and the internal (mitochondrial) pathway or external (death-receptor) pathway initiates apoptosis.[68] Defects in these programs lead to primary or acquired resistance of PDAC to therapies that target cell death or cytotoxic agents.[69] Apoptosis involves stimulatory and inhibitory factors and is influenced by numerous miRNAs. miR-21 is an oncogenic miRNA in many cancers and regulates genes that are required for apoptosis. For example, BCL2 is a key regulator of the mitochondrial pathway of apoptosis and exerts tumorigenic effects in numerous cancers.[68,69] In PDAC, BCL2 is overexpressed through the effects of miR-21, which leads to an enhanced anti-apoptotic effect.[70,71] BCL2 is targeted by miR-181b, and the inhibition of BCL2 expression following miR-181b transfection reduces gemcitabine resistance.[72]

Programmed cell death 4 (PDCD4) is a tumour suppressor that regulates multiple proteins involved in tumour progression, cell cycle control and differentiation and may be regulated by miR-21 in PDAC,

potentially leading to cell death and poor prognosis.[14,73] miR-155 mediates multiple signalling pathways and functions as an oncogene by binding to the 3′-UTR of *TP53INP1* mRNA, which is functionally associated with TP73 and regulates cell cycle progression and apoptosis independent of TP53 to reduce the expression and promote tumour growth. Further, the restoration of TP53INP1 inhibits tumour growth.[74,75] The tissue-specific expression of miR-23a is upregulated in certain haematological malignancies and bladder cancer, although it is downregulated in oral squamous cell carcinoma.[76–79]

miR-23a targets APAF1, which activates caspase-9 in association with cytochrome *c*, promotes apoptosis, and acts as an oncogenic regulator.[80–82] TP53 is an important factor in apoptosis and functions in conjunction with other proteins.[83] For example, members of the inhibitor of growth (ING) family promote processes such as cell cycle arrest, cellular senescence and apoptosis.[84] ING4 and ING5 interact with TP53, and the former and latter are targets of miR-214 and miR-196a, respectively.[85,86] In particular, the inhibition of miR-196a leads to enhanced apoptosis and reduces invasion and proliferation.[86] BIM contains a single BCL2 homology-3 domain and interacts with all anti-apoptotic proteins of the BCL2 superfamily, making it an efficient killer that promotes apoptosis.[87] In PDAC, BIM expression is significantly reduced by the direct regulation of miR-24 and its restoration by miR-24 inhibition promotes apoptosis and inhibits cell cycle.[88]

TRANSCRIPTION FACTORS AND DNA METHYLATION

Genes, other than those discussed above, interact with miRNAs in PDAC. Forkhead box (FOX) proteins are subgroup of the Forkhead family of transcription factors, and FOXO1 transcription factors regulate various cellular functions such as apoptosis and the cell cycle.[89] *FOXO1* mRNA is the direct target of miR-21, and the intraductal infusion of a miR-21antisense molecule inhibits the growth of PDAC growth *in vivo*.[90] FOXO3a is regulated by miR-155 in PDAC, and KRAS activation stimulates miR-155 expression through NF-κB and MAPK signalling.[91] miR-155 negatively regulates FOXO3 expression, leading to cell proliferation and malignant transformation via the accumulation of reactive oxygen species.[91]

Recent studies show that DNA methylation induces the transcriptional silencing of tumour suppressor genes, which may have an important role during oncogenesis.[92] DNA methyltransferase (DNMT), as its name indicates, methylates DNA, and DNMT-1 is overexpressed in cancers.[93,94] miR-148b and miR-152 are significantly downregulated and directly target DNMT-1 in PDAC. Thus, DNMT-1 can act as a silencer of tumour suppressor genes in PDAC.[95] Yes-associated protein (YAP) is the major downstream effector of the HIPPO pathway, which regulates tissue homeostasis, organ size, regeneration and tumorigenesis.[96] In PDAC, miR-141, which targets *YAP1* mRNA directly, is significantly downregulated and leads to the increase of YAP1 expression. Re-expressing miR-141 repressed the malignant phenotype of PDAC cells.[97] Sirtuins (SIRTs) are NAD-dependent deacetylases that regulate target-gene expression and protein activities that control proliferation, differentiation, apoptosis, metabolism, DNA damage, stress responses, genome stability and cell survival.[98] Downregulation of miR-217 upregulates the expression of SIRT1, and *SIRT1* mRNA is the direct target of miR-217.[99] Further, upregulation of SIRT1 might facilitate the EMT in patients with chronic pancreatitis and PDAC.[99]

CONCLUSION

miRNAs that are aberrantly expressed have critical roles in the development and progression of PDAC by influencing cellular functions such as proliferation, apoptosis, metastasis and chemoresistance. Investigations of the relationship between miRNAs and the development and progression of PDAC provide a better understanding of the molecular mechanisms responsible for the pathogenesis of PDAC, although they raise new questions. The present review indicates that these questions may be answered by analysing miRNA expression profiles.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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