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Noncoding RNAs: an emerging modulator of drug resistance in pancreatic cancer

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Pancreatic cancer is the eighth leading cause of cancer-related deaths worldwide. Chemotherapy including gemcitabine, 5-fluorouracil, adriamycin and cisplatin, immunotherapy with immune checkpoint inhibitors and targeted therapy have been demonstrated to significantly improve prognosis of pancreatic cancer patients with advanced diseases. However, most patients developed drug resistance to these therapeutic agents, which leading to shortened patient survival. The detailed molecular mechanisms contributing to pancreatic cancer drug resistance remain largely unclear. The growing evidences have shown that noncoding RNAs (ncRNAs), including microRNAs (miRNAs), long noncoding RNAs (lncRNAs) and circular RNAs (circRNAs), are involved in pancreatic cancer pathogenesis and development of drug resistance. In the present review, we systematically summarized the new insight on of various miRNAs, lncRNAs and circRNAs on drug resistance of pancreatic cancer. These results demonstrated that targeting the tumor-specific ncRNA may provide novel options for pancreatic cancer treatments.

KEYWORDS

pancreatic cancer, drug resistance, microRNA, long non-coding RNA, circular RNA

Introduction

Pancreatic cancer (PC), a highly lethal human malignancy, ranks the fourth leading cause of cancer-related death in the United States and the eighth worldwide. PC patients had only 5% overall survival rate at 5-years after diagnosis (Von Hoff et al., 2009). A total of 458,918PC cases were diagnosed all around the world and 432,242 deaths were reported in 2018 (Bray et al., 2018). Pancreatic ductal adenocarcinoma (PDAC) is the most common pathological type, accounting for 85%–90% of all PC patients. Due to lack of the effectively early diagnosis methods, the vast majority of PC patients are diagnosed at advanced disease stages and tumors are unresectable. Systematical therapy with chemotherapy, immunotherapy and targeted therapy drugs with or without radiation therapy is only viable alternative for advanced PC patients. Currently, chemotherapeutic agents applied in PC treatments include gemcitabine (GEM), 5-fluorouracil (5-FU), adriamycin (ADM), cisplatin (DDP), oxaliplatin, nab-paclitaxel, irinotecan and

capecitabine (Springfeld et al., 2019). Targeted therapy drugs for PC include small molecule tyrosine kinase inhibitor (TKI) erlotinib targeting epidermal growth factor receptor (EGFR), oral mammalian target of rapamycin (mTOR) inhibitor everolimus and small molecule multi-target receptor TKI sunitinib which targets RTK. GEM combined with erlotinib is commonly used to treat locally advanced PC or metastatic PC (Irigoyen et al., 2017; Halfdanarson et al., 2019). Everolimus and sunitinib were applied in PC patients with progressive neuroendocrine tumors that cannot be resected or have metastatic spread (Angelousi et al., 2017; Nunez et al., 2019). In the aspect of immunotherapy, there are several monoclonal antibodies of immune checkpoint inhibitors (ICIs), such as ICIs of cytotoxic T lymphocyte antigen-4 (CTLA-4) (ipilimumab and trimetamumab), as well as ICIs of programmed cell death protein 1(PD-1) (pidilizumab, nivolumab and pembrolizumab) (Weiss et al., 2018; Kamath et al., 2020). Unfortunately, intrinsic drug resistance or acquired drug resistance severely limits the applications of these therapeutic agents. The deregulations of cell cycle control, apoptosis, DNA damage repair, autophagy, epithelial-mesenchymal transition (EMT), ABC transporters and cancer stem cells (CSCs), have been reported to be associated with drug resistance in PC (Modi et al., 2016; Kuwada et al., 2018; Liu Q G et al., 2018; Ma T et al., 2018; Knudsen et al., 2019; Qian et al., 2019; Yang Z et al., 2020). Up to now, the molecular mechanisms for development of drug resistance in PC still remain largely unclear.

Noncoding RNAs (ncRNAs) transcripts, a series of RNA molecules lacking of proteins coding potentials, constitute about 70% of human genome and modulate most signaling pathways, physiological and pathological processes (Jadeja et al., 2020; Song et al., 2020; Su et al., 2020; Wang et al., 2020; Wei et al., 2020). Multiple types of ncRNAs have been identified, such as microRNAs (miRNAs), long ncRNAs (lncRNAs), circular RNAs (circRNAs), small nucleolar RNAs (snoRNAs) and PIWI-interacting RNAs (piRNAs) (Huang et al., 2020; Pammer et al., 2020; Qin et al., 2020; Xu W et al., 2020; Zhang Y et al., 2020; Zhao et al., 2020). A number of miRNAs, lncRNAs and circRNAs have been shown to be related to various cell behaviors, such as cell growth, apoptosis, cell cycle progression, EMT and autophagy (Luo et al., 2023; Xu, 2023). It has been demonstrated that many dysregulated ncRNAs in PC not only might serve as biomarkers of diagnosis and prognosis, but also contribute to resistance development to therapeutic agents and irradiation (Hao et al., 2019; Xu et al., 2019; Li et al., 2020b; Franses et al., 2020; Nguyen et al., 2020; Ye et al., 2020; Yu et al., 2020). Although a large number of ncRNAs have been found to be involved in PC chemoresistance, only a few ncRNAs were reported to confer resistance to targeted therapy in PC. miR-142-5p has been shown to modulate the expression of PD-L1 in PC cells and promote anti-tumor immunity (Jia et al., 2017), nevertheless, no studies have reported the impacts of ncRNAs on immunotherapy resistance of PC cells.

Considering the critical and complicated roles of ncRNAs in PC drug resistance development, herein, we systematically summarized the underlying molecular mechanisms how miRNAs, lncRNAs and circRNAs confer drug resistance in PC.

miRNAs and drug resistance

miRNAs, a subclass of sncRNAs, negatively regulate target gene expression through binding to the 3′-untranslated region (3′-UTR) of the target mRNA and are involved in multiple cellular process, such as cell difference, proliferation, apoptosis, cell cycle progression, angiogenesis, EMT and CSC formation. Several dysregulated miRNAs, functioning as oncogenes or tumor suppressors, have been identified to be involved in resistance development to therapeutic agents in PC (Li et al., 2020a; An and Zheng, 2020; Guo et al., 2020; Jiang et al., 2020; Wu et al., 2020). Compared with naive cells, some abnormally expressed miRNAs have been reported in various drug-resistant PC cells (Dhayat et al., 2015; Shen et al., 2015; Tian et al., 2016). The involvement of miRNAs in PC resistance to GEM, 5-FU and other drugs are summarized below.

MiRNAs and GEM resistance

GEM, a kind of cytosine nucleoside derivative, is currently the first-line standard chemotherapeutic agent to treat PC patients. However, only a few PC patients can maintain sensitivity to GEM chemotherapy and subsequently, inevitable drug resistance often leads to low response rate and poor treatment efficacy. A variety of miRNAs have been found to be associated with GEM resistance in PC. Multiple mechanisms, such as diminished apoptosis, increased DNA repair, disordered cell cycle, decreased intracellular drug accumulation due to increased expression of drug efflux transporters, EMT, as well as CSCs, play crucial roles in miRNAs-mediated development of GEM resistance in PC. Oncogenic and tumor suppressor miRNAs involved in GEM resistance are summarized in details (Table 1; Table 2).

Oncogenic miRNAs and GEM resistance

Several miRNAs, such as miR-17-5p, miR-21, miR-29a, miR-365, miR-155 and miR-181, have been found to confer GEM resistance through promoting proliferation and reducing apoptosis of PC cells. For example, silencing of oncogenic miR-17-5p, which targeting *Bim*, could potentiate GEM sensitivities, activate caspase-3 and promote apoptosis in human PANC-1 and BxPC3 PC cell lines (Yan et al., 2012). Similarly, inhibition of miR-29a could increase apoptotic cells, upregulate S phase fraction, and reverse GEM resistance via elevating expression of *Dikkopf-1* (*Dkk1*), *Kremen2*, *secreted frizzled related protein 2* (*sFRP2*) and activating the Wnt/β-catenin signaling in human MIAPaCa-2 and PSN-1 PC cells (Nagano et al., 2013). miR-21, which has been found to be upregulated in several cancers, could confer GEM resistance in PC by affecting expression of multiple target genes, including *phosphatase and tensin homologue deleted on chromosome ten* (*PTEN*)/*RECK*, *programmed cell death 4* (*PDCD4*), *Bcl-2*, *FasL*, *matrix metalloproteinase-2* (*MMP-2*), *MMP-9* and *VEGF* (Park et al., 2009; Giovannetti et al., 2010; Bhatti et al., 2011; Dong et al., 2011; Wang et al., 2013). Interestingly, patients with GEM-resistance PDAC demonstrated highly activated cancer-associated fibroblasts (CAFs) and elevated miR-21 expression. Overexpression

TABLE 1 Oncogenic miRNAs modulating gemcitabine resistance in pancreatic cancer.

miRNAs	Expression[a]	Genes and pathways	References
miR-17-5p	upregulated	Bim	Yan et al. (2012)
miR-29a	upregulated	Dkk1/Kremen2/sFRP2/Wnt/β-catenin	Nagano et al. (2013)
miR-21	upregulated	PTEN/RECK	Park et al. (2009)
		PDCD4	Bhatti et al. (2011)
		Bcl-2	Dong et al. (2011)
		FasL	Wang et al. (2013)
		MMP-2/MMP-9/VEGF	Giovannetti et al. (2010)
		MMP-3/MMP-9/PDGF/CCL-7/PDCD4	Zhang L et al. (2018)
miR-365	upregulated	SHC1/BAX	Hamada et al. (2014)
		cytidine deaminase	Binenbaum et al. (2018)
miR-181b	upregulated	Bcl-2	Cai et al. (2013)
		NF-κB/CYLD	Takiuchi et al. (2013)
miR-181c	upregulated	Hippo signaling	Chen et al. (2015)
miR-155	upregulated	-	Mikamori et al. (2017)
		CAT, DCK	Patel et al. (2017)
miR-106b	upregulated	TP53INP1	Fang et al. (2019)
miR-210	upregulated	mTOR	Yang Q et al. (2020)
miR-301	upregulated	CDH1	Funamizu et al. (2019)
miR-301a-3p	upregulated	PTEN	Xia et al. (2017)
miR-301a	upregulated	TAp63	Luo et al. (2018)
miR-296-5p	upregulated	BOK/vimentin/N-cadherin	Okazaki et al. (2020)
miR-1246	upregulated	CCNG2/CSC	Hasegawa et al. (2014)
miR-125a	upregulated	A20	Yao et al. (2016)
miR-10a-5p	upregulated	TFAP2C	Xiong et al. (2018)
miR-342-3p	upregulated	KLF6	Ma et al. (2019)
miR-744	upregulated	-	Miyamae et al. (2015)
miR-135b	upregulated	BMAL1/YY1	Jiang et al. (2018)
miR-320c	upregulated	SMARCC1	Iwagami et al. (2013)
miR-93-5p	upregulated	PTEN/PI3K/Akt	Wu et al. (2021)
miR-331-3p	upregulated	Wnt/β-Catenin, ST7L	Zhan et al. (2020)
miR-3178	upregulated	RhoB/PI3K/Akt, ABC transporters	Gu et al. (2022)

[a]miRNAs, upregulated in gemcitabine resistant pancreatic cancer cells. This table shows 23 miRNAs, whose expression levels and potential targets in gemcitabine resistance of pancreatic cancer.

of miR-21 in CAFs could significantly promote GEM resistance in PDAC. On the contrary, silencing of miR-21 in CAFs diminished GEM resistance. Meanwhile, CAFs with high miR-21 level also displayed increased expression of *platelet-derived growth factor* (*PDGF*), *MMP-3*, *MMP-9* and *chemokine (C-C motif) ligand 7* (*CCL7*) (Zhang L et al., 2018). Through directly suppressing expression of the apoptosis-promoting protein *BAX* and adaptor protein *Src Homology 2 Domain Containing 1* (*SHC1*), miR-365 has been shown to potentiate the resistance against GEM in PC cells (Hamada et al., 2014). Moreover, overexpressed miR-365 in macrophage-derived exosomes (MDE) could also contribute to GEM resistance through increasing the triphospho-nucleotide pool and enzyme cytidine deaminase in PDAC cells (Binenbaum et al., 2018). In addition, oncogenic miR-181 has also been shown to promote GEM resistance of PC cells via modulating expression of *Bcl-2*, *nuclear factor kappa B (NF-κB)* and *cylindromatosis* (*CYLD*) as well as activation of the Hippo signaling (Cai et al., 2013; Takiuchi et al., 2013; Chen et al., 2015). Interestingly, accumulating data has

TABLE 2 Tumor suppressive miRNAs modulating gemcitabine resistance in pancreatic cancer.

miRNAs	Expression[a]	Genes and pathways	References
miR-33a	downregulated	Pim-3/Akt/GSK-3β/β-catenin	Liang et al. (2015b)
		β-catenin	Liang et al. (2015a)
miR-497	downregulated	FGF2/FGFR1	Xu et al. (2014)
miR-210	downregulated	ABCC5	Amponsah et al. (2017)
miR-1285	downregulated	YAP1/EGFR/β-catenin	Huang et al. (2017)
miR-608	downregulated	RRM1/CDA	Rajabpour et al. (2017)
miR-506	downregulated	SPHK1/Akt/NF-κB	Li et al. (2016)
miR-30a-5p	downregulated	FOXD1/ERK	Zhou et al. (2019)
miR-146a-5p	downregulated	TRAF6/NF-kBp65/P-gp	Meng et al. (2020)
miR-34a	downregulated	Bcl-2/Notch1/Notch2	Ji et al. (2009)
miR-34	downregulated	Slug/PUMA	Zhang Q A et al. (2018)
miR-494	downregulated	c-Myc/SIRT1	Liu et al. (2015)
miR-373-3p	downregulated	CCND2	Hu et al. (2018)
miR-101	downregulated	DNA-dependent protein kinase catalytic subunit (DNA-PKcs)	Hu et al. (2017)
miR-101-3p	downregulated	RRM1	Fan et al. (2016)
miR-153	downregulated	Snail	Liu et al. (2017)
miR-374b-5p	downregulated	bcl-2	Sun et al. (2018)
miR-410-3p	downregulated	HMGB1	Xiong et al. (2017)
miR-29c	downregulated	USP22	Huang et al. (2018)
miR-127	downregulated	CCNE1, CDKN1A, CDKN1B, CCND1, CDK2	Panebianco et al. (2021)
miR-509-5p	downregulated	E-cadherin/ZO-1/ZEB1/Snail	Hiramoto et al. (2017)
miR-1243	downregulated	E-cadherin/ZO-1/ZEB1/Snail	Hiramoto et al. (2017)
miR-200c	downregulated	CSCs	Ma et al. (2015)
miR-200b	downregulated	ZEB1/ZEB2/CDH1	Funamizu et al. (2019)
miR-125a-3p	downregulated	Fyn	Liu B et al. (2018)
miR-3656	downregulated	RHOF	Yang R M et al. (2017)
miR-17-92cluster	downregulated	NODAL/ACTIVIN/TGF-β1/p21/p57/TBX3	Cioffi et al. (2015)
miR-205	downregulated	TUBB3/RRM1/ZEB1	Chaudhary et al. (2017)
miR-497	downregulated	NF-κB1	Yu Y et al. (2022)
miR-142-5p	downregulated	-	Ohuchida et al. (2011)
miR-145	downregulated	p70S6K1	Lin et al. (2016)
miR-429	downregulated	PDCD4	Yu et al. (2017)
miR-30a	downregulated	SNAI1/IRS1/ERK/AKT	Wang T et al. (2019)
miR-760	downregulated	MOV10/ITGB1	Yang et al. (2019)
let-7	downregulated	RRM2	Bhutia et al. (2013)
miR-211	downregulated	RRM2	Maftouh et al. (2014)
miR-20a-5p	downregulated	RRM2	Lu et al. (2019)
miR-7	downregulated	PARP1/NF-κB	Ye et al. (2021)

(Continued on following page)

TABLE 2 (*Continued*) Tumor suppressive miRNAs modulating gemcitabine resistance in pancreatic cancer.

miRNAs	Expression[a]	Genes and pathways	References
miR-136-5p	downregulated	ZNF32	Xu Y et al. (2020)
miR-3662	downregulated	HIF-1α, glycolysis	Liu S L et al. (2021)

[a]miRNAs, downregulated in gemcitabine resistant pancreatic cancer cells. This table shows 39 miRNAs, whose expression levels and potential targets in gemcitabine resistance of pancreatic cancer.

shown that exosomes play a role in the development of chemoresistance. Mikamori et al. found that miR-155, an over-expressed miRNA in GEM-resistant PANC-1-GR PDAC cells, could potentiate exosome secretion and confer GEM resistance in PDAC via anti-apoptosis effects. On the contrary, blocking exosome delivery could alleviate miR-155 induced GEM resistance (Mikamori et al., 2017). In addition, through inhibiting the expression of deoxycytidine kinase (DCK), an important enzyme involved in GEM metabolism, miR-155 could promote exosome-mediated acquired resistance to GEM in PC cells (Patel et al., 2017). Recently, it has been found that exosomal miR-106b deriving from CAFs, could confer GEM resistance through targeting *TP53INP1* in PC (Fang et al., 2019). By contrast, exosomes deriving from pancreatic CSCs with GEM resistance could deliver miR-210 and transform GEM-sensitive cells to drug-resistance cells via activating the *mTOR* signaling pathway (Yang Q et al., 2020).

EMT and CSCs also play crucial roles in development of drug resistance. It has been shown that several miRNAs conferred GEM resistance of PC via modulating EMT and CSCs. miR-301, a highly expressed miRNA in GEM-resistant Capan-2 and PANC-1 cells, could trigger EMT and potentiate GEM resistance through inhibiting *cadherin 1* (*CDH1*) expression (Funamizu et al., 2019). miR-301a-3p has also been shown to confer GEM resistance via suppression of *PTEN* expression (Xia et al., 2017). Hypoxia, a prevalent phenomenon during tumorigenesis, has been found to promote resistance of chemotherapy and radiotherapy in PC. miR-301a, a hypoxia-sensitive miRNA, has been shown to be involved in hypoxia-induced GEM resistance via targeting P63 family member *TAp63* in PC (Luo et al., 2018). In addition, through suppressing a pro-apoptotic gene of *Bcl2-related ovarian killer* (*BOK*) and EMT marker *vimentin* and *N-cadherin*, exogenous expression of miR-296-5p has been found to weaken the apoptosis induced by GEM, indicating that targeting miR-296-5p may have therapeutic potential to overcome GEM resistance of PC patients (Okazaki et al., 2020). Ectopic expression of miR-1246 could promote CSC-like properties and GEM resistance via inhibiting expression of *CCNG2*. Moreover, high expression levels of miR-1246 in PC tissues predicted poor prognosis of patients (Hasegawa et al., 2014).

In addition, oncogenic miR-125a, miR-10a-5p and miR-342-3p have also been found to enhance GEM resistance of PC cells through targeting A20, transcription factor activating protein 2 gamma (TFAP2C) and Krüppel-like factor 6 (KLF6), respectively (Yao et al., 2016; Xiong et al., 2018; Ma et al., 2019). Plasma miR-744 might be a valuable marker to predict poor prognosis and GEM resistance through PC patients' plasma miRNA profiling analyses (Miyamae et al., 2015). Interestingly, a novel miR-135b-BMAL1-YY1 signaling, which could promote tumorigenesis and GEM resistance in pancreas, has been identified (Jiang et al., 2018). In addition, miR-320c could confer GEM resistance via modulating expression of SMARCC1, a core subunit of chromatin remodeling complex of switch/sucrose nonfermentable (SWI/SNF) in PC cells (Iwagami et al., 2013). Also, miR-93-5p could promote GEM resistance in PC cells through silencing expression of its target gene *PTEN* and, thus activating the PI3K/Akt pathway. miR-331-3p could confer GEM resistance in PC cells through targeting ST7L and activating the Wnt/β-Catenin signaling (Zhan et al., 2020; Wu et al., 2021). miR-3178 has also been found to promote GEM resistance via activating the RhoB/PI3K/Akt signaling and upregulation ABC transporters (Gu et al., 2022).

Tumor suppressive miRNAs and GEM resistance

Multiple tumor suppressive miRNAs also participate in regulating GEM resistance of PC cells through different mechanisms, such as apoptosis, cell proliferation, cell cycle, EMT, CSCs, autophagy and glycolysis. miR-33a, for example, could suppress GEM resistance and cell proliferation in PC via targeting Pim-3 and inhibiting the Akt/GSK-3β/β-catenin signaling pathway (Liang et al., 2015b). Similarly, miR-33a could enhance the sensitivity to GEM in human PC cells through inhibiting β-catenin nuclear translocation, suppressing *survivin*, *cyclin D1* (*CCND1*) and *multi-drug resistance 1* (*MDR-1*) transcription, as well as reducing protein expression of N-cadherin, slug and vimentin (Liang et al., 2015a). miR-497, a downregulated miRNA in GEM-resistant PC cells, could reverse GEM resistance through silencing expression of its target genes *FGF2* and *FGFR1* (Xu et al., 2014). It has been shown that over-expression of miR-210 could also potentiate GEM sensitivity via suppressing expression of its target gene *ABCC5* (Amponsah et al., 2017). In addition, tumor suppressors miR-1285, miR-608, miR-506, miR-30a-5p and miR-146a-5p have been demonstrated to impair GEM resistance of PC by silencing expression of YAP1/EGFR/β-catenin, ribonucleotide reductase M1 (RRM1)/CDA, sphingosine kinase 1 (SPHK1)/Akt/NF-κB, FOXD1/ERK and the tumor necrosis factor receptor-associated factor 6 (TRAF6)/NF-kB p65/P-gp signaling, respectively (Li et al., 2016; Huang et al., 2017; Rajabpour et al., 2017; Zhou et al., 2019; Meng et al., 2020). miR-34 has been found to induce apoptosis, cell cycle arrest in G1 and G2/M phase and sensitize PC cells to GEM via suppressing expression of its target genes *Bcl-2* and *Notch1/2*. Moreover, miR-34 could inhibit growth of CSCs and tumor spheres *in vitro* and tumorigenesis *in vivo* (Ji et al., 2009). Additionally, miR-34 has also been shown to potentiate GEM-induced apoptosis of PC cells through inhibiting expression of *Slug* and elevating expression of *p53 upregulated modulator of apoptosis* (*PUMA*) (Zhang Q A et al., 2018). miR-494, a miRNA with decreased levels in PC tissues and cells, could

lead to apoptosis, senescence, G1 phase accumulation and the impaired GEM resistance, through directly silencing the c-myc/sirtuin1(SIRT1) signaling (Liu et al., 2015). In addition, tumor suppressors miR-373-3p, miR-101, miR-101-3p, miR-153 and miR-374b-5p have also been found to reverse GEM resistance in PC via promoting apoptosis (Fan et al., 2016; Hu et al., 2017; Liu et al., 2017; Hu et al., 2018; Sun et al., 2018). It has been found that tumor suppressor miR-410-3p and miR-29c could attenuate the resistance to GEM in PC through inhibiting expression of *High mobility group box 1* (*HMGB1*) and *ubiquitin specific peptidase-22* (*USP22*) and, thus, reducing autophagy, respectively (Xiong et al., 2017; Huang et al., 2018). Similarly, miR-127 could confer GEM sensitivity of PC cells through down-regulating expression of *CCNE1*, *CDKN1A*, *CDKN1B*, *CCND1* and *CDK2*, and promoting cell cycle arrested in S phase (Panebianco et al., 2021).

Tumor suppressive miRNAs are also involved in regulating the EMT process and/or CSC formation which have been associated with development of GEM resistance in PC. For instance, tumor suppressors miR-509-5p and miR-1243 have been found to enhance GEM sensitivity through modulating expression of EMT markers *E-cadherin*, *Z O -1*, *Zinc finger E-box binding homeobox transcription factor 1* (*ZEB1*) and *Snail* in PC (Hiramoto et al., 2017). In addition, miR-200c, a miRNA with significantly reduced levels in human CSCs of PC (PCSCs), could effectively overcome GEM resistance and diminish colony formation of PCSCs (Ma et al., 2015). Similarly, in Capan-1, Capan-2, PANC-1, MIAPaCa-2, BxPC-3 and PL45 PC cell lines, miR-200b levels have been found to be negatively correlated with GEM resistance. Moreover, miR-200b overexpression could enhance GEM sensitivity by modulating expression of EMT markers *ZEB* and *CDH1* (Funamizu et al., 2019). In addition, miR-125a-3p and miR-3656 could also potentiate GEM sensitivity of PC cells through silencing *Fyn* and *RHOF* and interfering EMT process, respectively (Yang S Z et al., 2017; Liu B et al., 2018). The miR-17-92 cluster miRNAs, which were downregulated in chemoresistant PCSCs, could reverses GEM resistance and quiescence through the NODAL/ACTIVIN/TGF-β1 signaling (Cioffi et al., 2015). Moreover, miR-205 has been shown to suppress the PCSCs proliferation and reduce GEM resistance via silencing expression of *tubulin beta 3 class III* (*TUBB3*), *RRM1* and *ZEB1* (Chaudhary et al., 2017). Similarly, tumor suppressor miR-497, downregulated in CSCs from BxPC-3 and ASPC-1 PC cells and PC tissues, has also been found to inhibit GEM resistance and metastasis via directly targeting *NF-κB1*. On the contrary, suppression of miR-497 could dramatically contribute to GEM resistance, migration and invasion of PC CSCs (Yu Q et al., 2022).

Additionally, levels of tumor suppressor miR-142-5p in surgically resected PC tissues have been found to be as a prospective marker to predict GEM response (Ohuchida et al., 2011). Multiple tumor suppressor miRNAs, such as miR-145, miR-429, miR-30a and miR-760, could also reverse GEM resistance of PC through inhibiting expression of *p70S6K1*, *PDCD4*, *SNAI1/IRS1/ERK/AKT, moloney leukemia virus 10 (MOV10) and Integrin β1 (ITGB1),* respectively (Lin et al., 2016; Yu et al., 2017; Wang T et al., 2019; Yang et al., 2019). Interestingly, let-7, miR-211 and miR-20a-5p have also been shown to improve the sensitivity to GEM in PC cells via silencing expression of *RRM2* (Bhutia et al., 2013; Maftouh et al., 2014; Lu et al., 2019). Tumor suppressor miR-7 could reverse GEM resistance of PC cells via modulating poly (ADP-ribose) polymerase 1 (PARP1)/NF-κB axis and cellular senescence (Ye et al., 2021). miR-136-5p has been shown to reduce GEM resistance through silencing expression of *ZNF32* (Xu Y et al., 2020). Tumor suppressor miR-3662 could also reduce GEM resistance and aerobic glycolysis in PDAC cells via suppressing levels of *hypoxia-inducible factor 1*α (*HIF-1*α) (Liu A et al., 2021).

miRNAs and 5-FU resistance

As a thymidylate synthase inhibitor, 5-FU is commonly used for PC treatments in clinic. 5-FU leads to apoptosis and cell cycle arrest through interfering DNA replication, RNA function and protein synthesis. It has been demonstrated that several oncogenic or tumor suppressor miRNAs contribute to the resistance to 5-FU in PC (Table 3).

Multiple oncogenic miRNAs, such as miR-21, miR-221, miR-296-5p, miR-320a and miR-499a-5p, have been found to be involved in 5-FU resistance in PC. For example, miR-21 could confer 5-FU resistance in human PATU8988 and PANC-1 PC cells via inhibiting the expression of tumor suppressor genes *PTEN* and *PDCD4* (Wei et al., 2016). In tumor-initiating stem-like PC cells (L3.6 pL), suppression of miR-21 and miR-221 have been shown to reduce side population (SP) cell fraction and reverse 5-FU resistance (Zhao et al., 2015). Moreover, low expression of miR-21 not only was associated with good prognosis of PDAC cases treated with 5-FU-based adjuvant regimens in two independent cohorts, but also could potentiate the sensitivity to 5-FU in PL45 and HPAF-II PC cells (Hwang et al., 2010). miR-221-3p could promote cell proliferation, EMT and 5-FU resistance via targeting the *RB1* 3′-UTR region in PC (Zhao et al., 2016). In addition, oncogenic miR-296-5p and miR-320a contribute to 5-FU resistance of PC cells by modulating *BOK*, *vimentin*, *N-cadherin* and *PDCD4* expression levels, respectively (Wang et al., 2016; Okazaki et al., 2020). miR-499a-5p could promote cell proliferation, migration and 5-FU resistance in PC cells through targeting *PTEN* and activating the PI3K/Akt pathway. Moreover, miR-499a-5p has been shown to influence the expression of MDR-related genes, including *adenosine triphosphate* (*ATP*) *binding cassette subfamily B member 1* (*P-gp*), *ATP binding cassette subfamily C member 1* (*MRP1*), and *ATP binding cassette subfamily G member 2* (*BCRP*) (Ouyang et al., 2021).

By contrast, several tumor suppressor miRNAs can reverse 5-FU resistance of PC. MiR-137, for instance, has been found to be markedly downregulated in PC cell lines and tissues. Over-expression of miR-137 could sensitize cells to 5-FU through inhibiting *pleiotropic growth factor* (*PTN*) expression (Xiao et al., 2014). In addition, miR-138-5p and miR-494, which were both downregulated in PC tissues and cell lines, have been shown to increase 5-FU sensitivity through targeting *vimentin*, *SIRT1* and *c-myc* expression, respectively (Liu et al., 2015; Yu et al., 2015).

miRNAs and resistance to other drugs

ADM, DDP, oxaliplatin and FOLFIRINOX (a combination regimen of folinicacid, 5-FU, irinotecan and oxaliplatin), targeted

TABLE 3 miRNAs modulating 5-FU resistance in pancreatic cancer.

miRNAs	Expression[a]	Genes and pathways	References
miR-21	upregulated	PTEN/PDCD4	Wei et al. (2016)
		-	Zhao et al. (2015)
		-	Hwang et al. (2010)
miR-221	upregulated	-	Zhao et al. (2015)
miR-221-3p	upregulated	RB1	Zhao et al. (2016)
miR-296-5p	upregulated	BOK/vimentin/N-cadherin	Okazaki et al. (2020)
miR-320a	upregulated	PDCD4	Wang et al. (2016)
miR-499a-5p	upregulated	PI3K/Akt, PTEN, P-gp,MRP1, BCRP	Ouyang et al. (2021)
miR-137	downregulated	PTN	Xiao et al. (2014)
miR-138-5p	downregulated	vimentin	Yu et al. (2015)
miR-494	downregulated	SIRT1/c-myc	Liu et al. (2015)

[a]miRNAs, either upregulated or downregulated in 5-FU, resistant pancreatic cancer cells. This table shows 9 miRNAs, whose expression levels and potential targets in 5-FU, resistance of pancreatic cancer.

therapy drugs and immunotherapy agents are also used during PC clinical treatments. It has been found that several tumor suppressor miRNAs, including miR-137, miR-142 and miR-212, could weaken ADM resistance of PC. For example, through targeting *ATG5* and improving autophagy, exogenous expression of miR-137 could enhance ADM sensitivity and promote apoptosis in PC cells (Wang Z C et al., 2019). Interestingly, the plectin-1(PL-1)/miR-212 nanoparticles could significantly promote ADM-induced apoptosis and autophagy by silencing the expression of *ubiquitin specific peptidase 9 X-linked* (*USP9X*) in PC cells (Chen Y et al., 2019). Oncogenic miR-223 has been shown to promote proliferation and DDP resistance via targeting *forkhead transcription factor O subfamily 3a* (*FoxO3a*) in PC cells (Huang et al., 2019). In human MiaPaCa2 and BxPC3 PC cells harboring *P53* mutations, exogenous expression of tumor suppressor miR-34 could not only result in cell cycle arrest, apoptosis, the reduced tumor-initiating cell population and tumor sphere growth, but also sensitize the cells to DDP through down-regulating *Notch1/2* and *Bcl-2* expression (Ji et al., 2009). miR-100, a downregulated miRNA in PC tissues and cell lines, could increase DDP sensitivity and suppress tumor growth *in vivo* via targeting *fibroblast growth factor receptor 3* (*FGFR3*) (Li et al., 2014). In addition, it has been found that miR-374b, a downregulated miRNA in DDP-resistant PC cell line BxPC3-R, contributed to the acquired DDP resistance, at least partly by targeting *ATP7A* (*ATPase, Cu^{2+} Transporting, Alpha Polypeptide*) and *clusterin* (*CLU*) (Schreiber et al., 2016). Tumor suppressor miR-1291-5p could act as a metabolism regulator and potentiate the sensitivity to DDP via diminishing *glucose transporter protein type 1* (*GLUT1*) expression and GLUT1-mediated glycolysis in ASPC-1 and PANC-1 PC cells (Tu et al., 2020). Laura and colleagues showed that inhibition of miR-181a-5p could potentiate oxaliplatin sensitivity of PC cells via suppressing expression of *ATM*. Moreover, PC patients with better response to FOLFIRINOX displayed lower levels of miR-181a-5p both in cancerous tissues and plasma specimens (Meijer et al., 2020). Interestingly, through regulation of DNA damage, miR-1307 has been shown to modulate FOLFIRINOX sensitivity in PDAC cells (Carotenuto et al., 2021).

In addition to be involved in chemoresistance, a few miRNAs have been shown to confer resistance to targeted therapy and immunotherapy in PC. For instance, silencing oncogeneic miR-21 could potentiate the sensitivity to sunitinib in PDAC (Passadouro et al., 2014). Izumchenko and colleagues showed that silencing of tumor suppressor miR-200 could upregulate the expression of negative EGFR regulator of *mitogen-inducible gene 6* (*MIG6*) in the process of transforming growth factor β (TGFβ)-mediated EMT. Moreover, the ratio of *MIG6* mRNA to miR-200 (*MIG6* mRNA/miR-200) was negatively correlated with erlotinib response not only in cancer cell lines with diverse tissue origins *in vitro*, but also in xenografts derived from PC patients carrying wild-type EGFR *in vivo* (Izumchenko et al., 2014). Similarly, tumor suppressor miR-497 could impact erlotinib resistance via modulating expression levels of *fibroblast growth factor 2* (*FGF2*) and *fibroblast growth factor receptor 1* (*FGFR1*) (Xu et al., 2014). Through inhibiting the expression of *erythropoietin-producing hepatocellular receptor 2* (*EphA2*), tumor suppressor miR-124 has also been found to improve erlotinib sensitivity in Capan-1 PC cells with *K-RAS* mutations (Du et al., 2019). Table 4.

lncRNAs and drug resistance

LncRNAs could be divided into four types according to their location in the genome: intronic lncRNAs, intergenic lncRNAs, divergent lncRNAs and antisense lncRNAs (Lee, 2012). Accumulating evidences demonstrated that multiple lncRNAs, functioning as oncogenes or tumor suppressors, contribute to tumorigenesis, disease progression and therapy response by regulating specific target genes or signaling pathways (Johnsson et al., 1991; Feng et al., 2020; Gong et al., 2020; He et al., 2020; Zhu

TABLE 4 miRNAs modulating resistance to other drugs in pancreatic cancer.

miRNAs	Expression[a]	Genes and pathways	Drugs	References
miR-137	downregulated	ATG5	ADM	Wang Z C et al. (2019)
miR-212	downregulated	USP9X	ADM	Chen Y et al. (2019)
miR-223	upregulated	FoxO3a	DDP	Huang et al. (2019)
miR-34	downregulated	Bcl-2/Notch1/Notch2	DDP	Ji et al. (2009)
miR-100	downregulated	FGFR3	DDP	Li et al. (2014)
miR-374b	downregulated	ATP7A/CLU	DDP	Schreiber et al. (2016)
miR-1291-5p	downregulated	GLUT1	DDP	Tu et al. (2020)
miR-181a-5p	upregulated	ATM	Oxaliplatin, FOLFIRINOX	Meijer et al. (2020)
miR-1307	upregulated	CLIC5	FOLFIRINOX	Carotenuto et al. (2021)
miR-21	upregulated	-	Sunitinib	Passadouro et al. (2014)
miR-200	downregulated	MIG6	Erlotinib	Izumchenko et al. (2014)
miR-497	downregulated	FGF2/FGFR1	Erlotinib	Lin et al. (2020)
miR-124	downregulated	EphA2	Erlotinib	Du et al. (2019)

[a]miRNAs, either upregulated or downregulated in other drugs resistant pancreatic cancer cells. This table shows 12 miRNAs, whose expression levels and potential targets in other drugs resistance of pancreatic cancer.

et al., 2020; Qu et al., 2021). In PC, lncRNAs have been found to be involved in development of drug resistance (Table 5; Table 6).

lncRNAs and GEM resistance

Similar with miRNAs, several lncRNAs have been shown to participate in GEM resistance in PC, including oncogenic lncRNAs and tumor suppressive lncRNAs molecules (Table 5).

Oncogenic lncRNAs and GEM resistance

Multiple oncogenic lncRNAs have been shown to contribute to GEM resistance in PC, such as *HOXA transcript at the distal tip* (*HOTTIP*), *glutathione S-transferase mu 3, transcript variant 2* (*GSTM3TV2*), *metastasis-associated lung adenocarcinoma transcript 1* (*MALAT1*), *plasmacytoma variant translocation 1* (*PVT1*) and *DiGeorge syndrome critical region gene 5* (*DGCR5*).

HOTTIP, an overexpressed lncRNA in PDAC tissues and cells, has been found to promote GEM resistance by modulating levels of *HOXA13* in PDAC cells. In contrast, silencing HOTTIP could lead to enhanced sensitivity of PC cells to GEM (Li et al., 2015). LncRNA GSTM3TV2, which was significantly upregulated in GEM-resistant PC cells, could confer GEM resistance by competitively sponging let-7 and subsequently up-regulating expression of *L-type amino acid transporter 2* (*LAT2*) and *oxidized low-density lipoprotein receptor 1* (*OLR1*). Moreover, the increased levels of GSTM3TV2 in PC tissues have been significantly associated with worse prognosis, indicating that GSTM3TV2 may be a novel prognostic marker and therapeutic target in PC (Xiong et al., 2019). LncRNA MALAT-1, initially identified as a prognostic marker for lung cancer patients, was involved in PC chemoresistance. It has been demonstrated that MALAT-1 could not only reduce GEM sensitivity, but also potentiate the proportion and self-renewal ability of PCSCs, by up-regulating expression of self-renewal related factor *Sox2* (Jiao et al., 2015). Interestingly, over-expression of lncRNA PVT1 could promote GEM resistance in naïve ASPC-1 PC cells (You et al., 2011). Moreover, PVT1 could confer the resistance to GEM in PC via regulating the miR-619-5p/Pygo2 and miR-619-5p/ATG14 axes, which lead to dysregulated autophagic activities and the Wnt/β-catenin signaling (Zhou et al., 2020). Similarly, silencing of PVT1 could suppress autophagy and promote GEM sensitivity through modulating the miR-143/HIF-1α/VMP1 axis in PC (Liu S L et al., 2021). In addition, oncogenic lncRNA TUG1 has also been shown to contribute to GEM resistance of PDAC cells via inducing expression of SCH772984 which is an ERK pathway suppressor (Yang et al., 2018). LncRNA *DiGeorge syndrome critical region gene 5* (*DGCR5*) could enhance GEM resistance via functioning as a ceRNA through sponging miR-3163 to inhibit the Wnt/β-catenin signaling and modulate expression of *DNA topoisomerase 2-alpha* (*TOP2A*) (Liu Y F et al., 2021). LncRNA *HIF1A-AS1* (*antisense RNA1 of HIF-1α*) has been found to prevent GEM sensitivity of PC cells through activating the AKT/YB1/HIF-1α signaling and promoting glycolysis (Xu F et al., 2021a). Interestingly, lncRNA u*rothelial carcinoma-associated 1* (*UCA1*), which was delivered by hypoxic pancreatic stellate cells (PSCs)-derived exosomes (HPSC-EXO), has also been shown to enhance GEM resistance in PC (Chi et al., 2021). Through enhancer of zeste homolog 2 (EZH2) -mediated epigenetic modification, lncRNA *small nucleolar RNA host gene 16 (SNHG16)* has been found to confer GEM resistance via diminishing *SMAD family member (Smad4)* expression in PC (Yu Y et al., 2022). Via sponging miR-139-5p and activating Wnt pathway, and subsequently increasing the expression of *ezh2,* lncRNA *SH3BP5-AS1* has been demonstrated to contribute to GEM resistance of PC cells (Lin et al., 2022).

TABLE 5 LncRNAs modulating gemcitabine resistance in pancreatic cancer.

LncRNAs	Expression[a]	Genes and pathways	References
HOTTIP	upregulated	HOXA13	Li et al. (2015)
GSTM3TV2	upregulated	let-7/LAT2/OLR1	Xiong et al. (2019)
MALAT-1	upregulated	Sox2	Jiao et al. (2015)
PVT1	upregulated	-	You et al. (2011)
		miR-619-5p/Pygo2/ATG14	Zhou et al. (2020)
		miR-143/HIF-1α/VMP1	Liu Y F et al. (2021)
TUG1	upregulated	ERK	Yang et al. (2018)
DGCR5	upregulated	miR-3163/TOP2A,Wnt/β-catenin	Liu S L et al. (2021)
HIF1A-AS1	upregulated	AKT/YB1/HIF-1α	Xu F et al. (2021a)
UCA1	upregulated	SOCS3/EZH2	Chi et al. (2021)
SNHG16	upregulated	Smad4	Yu Q et al. (2022)
SH3BP5-AS1	upregulated	miR-139-5p/Wnt/CTBP1	Lin et al. (2022)
LINC00460	upregulated	PDAP1/PDGFA/PDGFR	Zhu et al. (2022)
linc-DYNC2H1-4	upregulated	miR-145/ZEB1/Lin28/Nanog/Sox2/Oct4	Gao et al. (2017)
SLC7A11-AS1	upregulated	NRF2, ROS	Yang Q et al. (2020)
SBF2-AS1	upregulated	miR-142-3p/TWF1	Hua et al. (2019)
HCP5	upregulated	miR-214-3p/HDGF	Liu et al. (2019)
SNHG14	upregulated	miR-101/RAB5A/ATG4D	Zhang et al. (2019)
LINC01559	upregulated	P62, LC3, caspase3, PARP	Deng et al. (2020)
LINC00346	upregulated	miR-188-3p/BRD4	Shi et al. (2019)
SNHG8	upregulated	caspase-3/PARP	Song et al. (2018)
HOST2	upregulated	apoptosis	An and Cheng (2020)
ANRIL	upregulated	miR-181a, HMGB1	Wang et al. (2021)
NEAT1	upregulated	miR-491-5p/Snail/SOCS3	Wu et al. (2023)
GAS5	downregulated	miR-221/SOCS3	Liu B et al. (2018)
		miR-181c-5p/Hippo	Gao et al. (2018)
AB209630	downregulated	PI3K/Akt	Wang et al. (2018)
MEG3	downregulated	snail	Ma T et al. (2018)
DLEU2L	downregulated	miR-210-3p, BRCA2	Xu F et al. (2021b)
DBH-AS1	downregulated	miR-3163/USP44	Ye et al. (2022)
DSCR9	downregulated	miR-21-5p/BTG2	Huang et al. (2022)

[a]lncRNAs, either upregulated or downregulated in gemcitabine resistant pancreatic cancer cells. This table shows 28 lncRNAs, whose expression levels and potential targets in gemcitabine resistance of pancreatic cancer.

Accumulating evidences demonstrated that CAFs are critically involved in chemoresistance (Qin et al., 2019; Zhang H et al., 2020; Yang et al., 2022). LINC00460, a lncRNA molecule mainly located in the cytoplasm, has been shown not only to correlate with GEM response in PDAC patients, but also to regulate GEM resistance of CAFs through mediating the cellular communication of PDAC cancer cells and CAFs by platelet derived growth factor subunit A (PDGFA) associated protein 1 (PDAP1)/PDGFA/PDGFR signaling pathway (Zhu et al., 2022).

Additionally, EMT and CSCs have also been shown to promote lncRNAs-mediated chemotherapy resistance. Linc-DYNC2H1-4, an upregulated intergenic lncRNA in GEM-resistant BxPC-3-GEM PC cells, could promote EMT and stemness of the parental sensitive cells. In cells, Linc-DYNC2H1-4 could sponge miR-145 and elevate levels of several EMT key players including *ZEB1* and CSC markers including *Lin28*, *Nanog*, *Sox2* and *Oct4* (Gao et al., 2017). LncRNA *SLC7A11-AS1*, which was over-expressed in PDAC tissues and

TABLE 6 LncRNAs modulating resistance to other drugs in pancreatic cancer.

LncRNAs	Expression[a]	Genes and pathways	Drugs	References
TUG1	upregulated	miR-376b-3p/DPD	5-FU	Tasaki et al. (2021)
HOTTIP	upregulated	miR-137	DDP	Yin et al. (2020)
UPK1A-AS1	upregulated	IL8, Ku70, Ku80	Oxaliplatin	Zhang et al. (2022)
HOTAIR	upregulated	EZH2/DR5	TRAIL	Yang R M et al. (2017)
SNHG7	upregulated	Notch1/Jagged1/Hes-1, MSCs	FOLFIRINOX	Cheng et al. (2021)
LINC02432	upregulated	miR-98-5p/HK2	EGFR, MEK and ERK inhibitors	Tan et al. (2022)
GAS5	downregulated	miR-181c-5p/Hippo	5-FU	Gao et al. (2018)

[a]lncRNAs, either upregulated or downregulated in other drugs resistant pancreatic cancer cells. This table shows 7 lncRNAs, whose expression levels and potential targets in other drugs resistance of pancreatic cancer.

GEM-resistant cell lines, has also been found to potentiate PDAC stemness and GEM resistance through stabilizing nuclear factor erythroid-2-related factor 2 (NRF2) and stimulating intracellular reactive oxygen species (ROS) (Yang Z et al., 2020). In addition, oncogenic lncRNA *SBF2-AS1* could promote EMT and GEM resistance in PC via sponging miR-142-3p and up-regulating expression of *twinfilin 1* (*TWF1*) (Hua et al., 2019).

Autophagy also contributes to drug resistance and cancer progression (Kim and Lee, 2014; Levy et al., 2017; Wu and Zhang, 2020). It has been found that lncRNAs *HLA complex P5* (*HCP5*) and *SNHG14* could confer GEM resistance of PC through sponging miR-214-3p and miR-101 and activating autophagy (Liu et al., 2019; Zhang et al., 2019). LncRNA LINC01559 has also been found to confer GEM resistance by promoting autophagy and inhibiting apoptosis (Deng et al., 2020). In addition, oncogenic lncRNAs LINC00346, small nucleolar RNA host gene 8 (SNHG8) and HOST2, have also been shown to confer GEM resistance of PC via regulating the miR-188-3p/BRD4 axis, the caspase-3/PARP axis and apoptosis (Song et al., 2018; Shi et al., 2019; An and Cheng, 2020). Additionally, lncRNA ANRIL could enhance GEM resistance of PC cells through inhibiting miR-181a expression and modulating autophagy induced by HMGB1 (Wang et al., 2021).

Mesenchymal stem cells (MSCs), a crucial cell type in tumor micro-environment, may contribute to drug resistance in multiple neoplasms via producing protective cytokines or influencing gene expression (Houthuijzen et al., 2012; Liu C et al., 2021). It has been found that extracellular vesicle -loaded oncogenic lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1) from adipose-derived MSCs could promote GEM resistance in PC by regulating the miR-491-5p/snail/suppressor of cytokine signaling 3 (SOCS3) signaling pathway (Wu et al., 2023).

Tumor suppressor lncRNAs and GEM resistance

Several tumor suppressor lncRNAs have also been found to be associated with the resistance to therapeutic agents in PC. For instance, lncRNA *growth arrest-specific 5* (*GAS5*) has been demonstrated to suppress GEM resistance of PC cells through inhibiting miR-221 expression and increasing *SOCS3* expression (Liu G et al., 2018). Interestingly, GAS5 has also been found to antagonize GEM resistance in PC cells via negatively regulating miR-181c-5p expression and subsequently activating the Hippo signaling (Gao et al., 2018). AB209630, an evidently downregulated lncRNA in PDAC tissues, could improve GEM sensitivity of PDAC cells by modulating the PI3K/Akt pathway. Moreover, high levels of lncRNA *AB209630* were associated with good prognosis of PDAC patients (Wang et al., 2018). MEG3, which is a downregulated lncRNA in PC tissues and cells, has been found to sensitize GEM in PC cells. On the contrary, silencing MEG3 led to inhibited GEM sensitivities. Moreover, low expression of MEG3 in PC patients were associated with GEM resistance and poor outcomes (Ma L et al., 2018). LncRNA DLEU2L (deleted in lymphocytic leukemia 2-like), which was downregulated in PC tissues, has been shown to lessen GEM resistance of PC cells via modulating expression of *BRCA2* (Xu F et al., 2021b). Through modulating the miR-3163/USP44 axis in PC cells, tumor suppressive lncRNA DBH-AS1 has been found to reverse GEM resistance and inhibit cell growth (Ye et al., 2022). Most recently, down syndrome critical region 9 (DSCR9), a downregulated lncRNA in PC cells and tissues, has also been shown to suppress the proliferation, invasion and GEM resistance by miR-21-5p/BTG anti-proliferation factor 2 (BTG2) axis (Huang et al., 2022).

lncRNAs and resistance to other drugs

In addition to participate in GEM resistance, lncRNAs have also been shown to promote other drugs resistance, such as 5-FU, DDP, oxaliplatin, FOLFIRINOX and targeted therapy agents (Table 6).

Oncogenic lncRNAs and resistance to other drugs

LncRNA TUG1 could promote 5-FU resistance in PC cells via inhibiting expression of miR-376b-3p and elevating *dihydropyrimidine dehydrogenase* (*DPD*) expression (Tasaki et al., 2021). HOTTIP has been found to promote DDP resistance of PC cells through silencing miR-137 (Yin et al., 2020). Similarly, oncogenic lncRNA UPK1A-AS1 could confer oxaliplatin resistance induced by paracrine IL8 derived from CAFs via activating Ku70 and Ku80 interaction and, thus, promoting

TABLE 7 CircRNAs modulating drug resistance in pancreatic cancer.

CircRNAs	Expression[a]	Genes and pathways	Drugs	References
circHIPK3	upregulated	miR-330-5p, RASSF1	GEM	Liu et al. (2020)
circZNF91	upregulated	miR-23b-3p	GEM	Zeng et al. (2021)
circ-MTHFD1L	upregulated	miR-615-3p/RPN6	GEM	Chen et al. (2022)
circ_0074298	upregulated	miR-519, SMOC	GEM	Hong et al. (2022)
circFARP1	upregulated	LIF/STAT3	GEM	Hu et al. (2022)
circLMTK2	upregulated	miR-485-5p/PAK1	GEM	Lu et al. (2022)
circ_0092367	downregulated	miR-1206/ESRP1	GEM	Yu et al. (2021)
circ_0013587	downregulated	miR-1227/E-cadherin	Erlotinib	Xu H et al. (2021)

[a]circRNAs, either upregulated or downregulated in resistant pancreatic cancer cells. This table shows 8 circRNAs, whose expression levels and potential targets in drugs resistance of pancreatic cancer.

nonhomologous end joining (NHEJ) and DNA double-strand break (DSB) repair. On the contrary, silencing UPK1A-AS1 could reverse oxaliplatin resistance of PC cells (Zhang et al., 2022). Interestingly, oncogenic lncRNA *HOX transcript antisense gene RNA* (*HOTAIR*) has been demonstrated to confer resistance to TNF-related apoptosis-inducing ligand (TRAIL) via interacting with the epigenetic regulator EZH2 and inhibiting *TRAIL receptor death receptor 5* (*DR5*) expression. Silencing HOTAIR could enhance TRAIL-induced apoptosis in TRAIL-resistant PC cells. On the contrary, HOTAIR over-expression could inhibit apoptosis induced by TRAIL in TRAIL-sensitive cells, indicating that HOTAIR may act as a potential therapeutic target to conquer TRAIL-resistance in PC (Yang R M et al., 2017). In addition, it has been shown that lncRNA small nucleolar RNA host gene 7 (SNHG7) could modulate activities of MSCs and confer FOLFIRINOX resistance in PC through the Notch1/Jagged1/Hes-1 signaling pathway (Cheng et al., 2021). Aerobic glycolysis, a hallmark of PC, has been shown to promote tumorigenesis and progression via multiple mechanisms. Glycolysis-related lncRNA LINC02432 could inhibit ferroptosis and predict drug sensitivity to EGFR inhibitors (afatinib and sapitinib), MEK inhibitors (trametinib, PD0325901 and selumetinib) and ERK inhibitors (VX-11e, Ulicocitinib, SCH772984, and ERK_6604) in PC by regulating miR-98-5p/hexokinase 2 (HK2) axis (Tan et al., 2022).

Tumor suppressive lncRNAs and resistance to other drugs

Unlike tumor suppressive miRNA, few tumor suppressor lncRNA has been found to be associated with other drugs resistance. Until now, only tumor suppressive lncRNA GAS5 could prevent 5-FU resistance in PC cells by sponging miR-181c-5p and subsequently activating the Hippo signaling (Gao et al., 2018).

circRNAs and drug resistance

CircRNAs, a special class of ncRNAs with covalently closed-loop structure, have been shown to function as important regulator in various tumors, including PC (Kristensen et al., 2019; Wong et al., 2020). Amounting data indicated that circRNAs function in carcinogenesis and progression of PC (Shao et al., 2018; Chen W et al., 2019). Importantly, several circRNAs have been associated with development of drug resistance in PC (Table 7).

circRNAs and GEM resistance

Through circRNA-sequencing analyses of GEM-resistant PANC-1-GR PC cells and wide-type PANC-1 cells, it has been found that 68 upregulated circRNAs and 58 downregulated ones in PANC-1-GR cells. Seven upregulated circRNAs (hsa_circ_0000522, hsa_circ_0000943, chr4:174305802-174325101+, chr1:169947226-170001116-, chr14:101402109-101464448+, chr4:52729603-52780244+, chr6:29901995-29911250+) and three downregulated circRNAs (hsa_circ_0070033, hsa_circ_0008161, hsa_circ_0006355) were successfully verified by the qRT-PCR assay. Among which, chr14:101402109-101464448 + and chr4:52729603-52780244+ have been found to be highly expressed in plasma of PC patients, who showed no response to GEM treatment. Silencing these two circRNAs could restore GEM sensitivity of PANC-1-GR cells (Shao et al., 2018). Similarly, Xu et al. found that the top 10 upregulated circRNAs in SW1990/GZ PC cells were circ_101672, circ_004077, circ_003251, circ_102,402, circ_074298, circ_089762, circ_003596, circ_089761, circ_002178 and circ_102,403. In contrast, the top 10 downregulated circRNAs were circRNA_101,543, circRNA_102,747, circRNA_000926, circRNA_059665, circRNA_103827, circRNA_406521, circRNA_103128, circRNA_104490, circRNA_103829 and circRNA_070037 (Xu et al., 2018).

CircHIPK3, an upregulated circRNA in PC tissues and GEM-resistant PC cells, has also been found to confer GEM resistance through regulating *RASSF1* expression (Liu et al., 2020). Through depriving the suppression of miR-23b-3p on expression level of deacetylase SIRT1 and leading to increased glycolysis, circZNF91 has been shown to confer GEM resistance in PC cells (Zeng et al., 2021). Oncogenic circ-MTHFD1L could induce DNA damage repair and confer GEM resistance in PDAC through the miR-615-3p/RPN6 axis. On the contrary, inhibition of circ-MTHFD1L combined with olaparib could reverse GEM resistance (Chen et al., 2022). Similarly, circ_

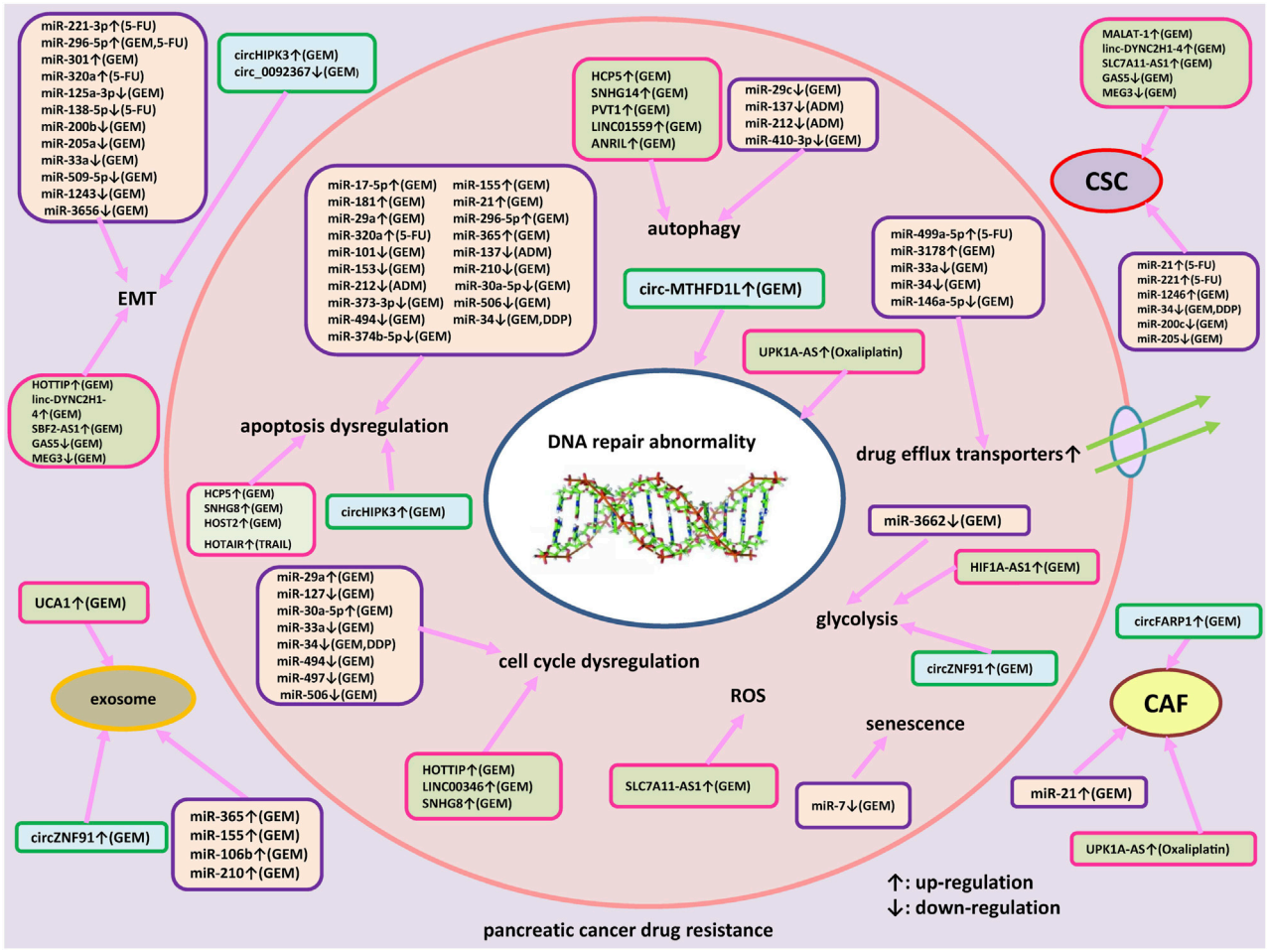

FIGURE 1
An outlined diagram of miRNAs, lncRNAs and circRNAs participated in the resistance to therapeutic agents in pancreatic cancer. Several miRNAs, lncRNAs, and circRNAs have been shown to be associated with pancreatic cancer drug resistance via regulating apoptosis, cell cycle arrest, DNA damage repair, cell proliferation, autophagy, epithelial-mesenchymal transition (EMT), drug efflux transporter, reactive oxygen species, glycolysis and cancer stem cells (CSC) through regulating specific signaling pathways and target genes.

0074298 has also been found to promote GEM resistance and PC progression through sponging miR-519 and regulating *SMOC* expression (Hong et al., 2022). Interestingly, circFARP1 could enable CAFs to promote GEM resistance in PC via the leukemia inhibitory factor (LIF)/STAT3 axis (Hu et al., 2022). CircLMTK2, an over-expressed circRNA in GEM-resistant PC cells and PC tissues, could contribute to GEM resistance via modulating p21 (RAC1) activated kinase 1 (PAK1) by sponging miR-485-5p (Lu et al., 2022).

Similarly, tumor suppressive circRNA has also been demonstrated to participate in the resistance to GEM. For example, tumor suppressor circ_0092367 could inhibit EMT and enhance GEM sensitivity in PC cells through regulating the miR-1206/epithelial splicing regulatory protein 1 (ESRP1) axis (Yu et al., 2021).

circRNAs and resistance to other drugs

To date, no report has shown that oncogenic circRNAs could involve in the resistance to other drugs. In the aspect of tumor suppressor circRNAs, only circ_0013587 has been found to reverse erlotinib resistance through modulating the miR-1227/E-cadherin signaling in PC cells (Xu H et al., 2021).

Conclusion

Many ncRNAs have been shown to be involved in the pathogenesis and progression of PC, indicating the potential roles of ncRNAs as biomarkers for early diagnosis, as promising prognostic and predictive markers for the identification of candidates amenable to adjuvant treatment, enabling a personalized clinical approach. Interestingly, a number of studies attempted to investigate the diagnostic value of circulating miRNAs in PC (Previdi et al., 2017). Recently, a pilot study has proposed that an exosomal four miRNA biomarker panel, consisting of miR-93-5p, miR-339-3p, miR-425-5p, and miR-425-3p, may provide a promising avenue for PC screening (Makler and Asghar, 2023). Although the diagnostic and prognostic potential of ncRNAs have shown the promising results, large and

prospective validation studies should be implemented before they can enter clinical practice. Also, ncRNAs can be used as targets for novel therapeutics of PC patients. Accumulating evidences indicated that different kinds of ncRNAs have been reported to be involved in drug resistance of PC. As shown in Figure 1, we summarized how miRNAs, lncRNAs and circRNAs contribute to resistance development to therapeutic agents and the underlying molecular mechanisms in PC. Interestingly, drug resistance may be reversed through targeting specific endogenous miRNAs, lncRNAs and/or circRNAs. Several approaches could be employed to inhibit expression of dysregulated ncRNAs, such as small interfering RNAs (siRNAs), short hairpin RNAs (shRNAs), antagomirs, anti-oligonucleotides (ASOs), clustered regulatory interspaced short palindromic repeats-associated endonuclease 9 (CRISPR/Cas9)-based genome editing, small molecule inhibitors of ncRNAs, and artificial miRNA sponges (Lin et al., 2020; Pandya et al., 2020). The strategies which could restore the normal levels of tumor suppressor ncRNAs involved in drug resistance of PC include to replace or substitute these ncRNAs through synthetic ncRNA-like molecules, for example, miRNA mimics. However, multiple challenges for therapeutic targeting ncRNAs remain to be faced, such as off-target effects, lack of efficient carrier systems, immune related toxicities, tolerability and other side effects. Progresses in ncRNAs delivery vector systems help to increase the potential for ncRNA-based treatment. Due to the improved circulation time and diminished recognition by the immune system of host, nanoparticles have been shown to function as efficient vectors for various gene therapies in PC patients, including siRNAs and miRNAs (Kurtanich et al., 2019). Through searching the database of http://clinicaltrials.gov, no clinical trials based on ncRNAs therapeutics in PC were found currently. The combined therapeutic modalities based on the manipulation of ncRNAs' levels and traditional treatments, i.e. chemotherapy, molecular targeted therapy or immunotherapy, may be a promising approach to overcome drug resistance and help to improve prognosis of advanced PC patients. Nevertheless, a serious issue is how to select the appropriate target molecules from a huge number of ncRNA candidates. More importantly, clinical studies and translational studies are also needed for conquering drug resistance in PC.

Author contributions

MY conceived and designed this study. LW and MY collected data, conceived this review, provided project funding, and wrote the manuscript. JS, XW, YiH, LHan, LHuang, YZ, YX, and NZ performed the initial work. NZ critically revised the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Glossary

PC	Pancreatic cancer
PDAC	Pancreatic ductal adenocarcinoma
GEM	Gemcitabine
ADM	Adriamycin
DDP	Cisplatin
5-FU	5-fluorouracil
TKI	Tyrosine kinase inhibitor
EGFR	Epidermal growth factor receptor
mTOR	Mammalian target of rapamycin
CTLA-4	Cytotoxic T lymphocyte antigen-4
PD-1	Programmed cell death protein 1
EMT	Epithelial-mesenchymal transition
CSCs	Cancer stem cells
ncRNAs	Noncoding RNA
lncRNA	Long noncoding RNA
Nt	Nucleotide
sncRNA	Short ncRNAs
miRNA/miR	MicroRNA
circRNA	Circular RNA
snoRNA	Small nucleolar RNA
piRNA	PIWI interacting RNA
MIG6	Mitogen-inducible gene 6
TGF	Transforming growth factor
FGF2	Fibroblast growth factor 2
FGFR1	Fibroblast growth factor receptor 1
EphA2	Erythropoietin-producing hepatocellular receptor 2
3′-UTR	3′-Untranslated region
Dkk1	Dikkopf-1
sFRP2	Secreted frizzled related protein 2
PTEN	Phosphatase and tensin homologue
PDCD4	Programmed cell death 4
CAFs	Cancer-associated fibroblasts
PDGF	Platelet-derived growth factor
MMP-3	Matrix metalloproteinase-3
CCL7	Chemokine (C-C motif) ligand 7
SHC1	Src Homology 2 Domain Containing 1
MDE	Macrophage-derived exosomes
CYLD	Cylindromatosis
DCK	Deoxycytidine kinase
CDH1	Cadherin 1

BOK	Bcl2-related ovarian killer
TFAP2C	Transcription factor activating protein 2 gamma
KLF6	Krüppel-like factor 6
SNF	Sucrose nonfermentable
MDR-1	Multi-drug resistance 1
RRM1	Ribonucleotide reductase M1
SPHK1	Sphingosine kinase 1
TRAF6	Tumor necrosis factor receptor-associated factor 6
PUMA	P53 upregulated modulator of apoptosis
HMGB1	High mobility group box 1
USP	Ubiquitin specific peptidase
CCND1	Cyclin D1
ZEB1	Zinc finger E-box binding homeobox transcription factor 1
PCSCs	CSCs of PC
TUBB3	Tubulin beta 3 class III
MOV10	Moloney leukemia virus 10
ITGB1	Integrin β1
PARP1	Poly (ADP-ribose) polymerase 1
HIF-1α	Hypoxia-inducible factor 1α
DNA-PKcs	DNA-dependent protein kinase catalytic subunit
SP	Side population
PL-1	Plectin-1
USP9X	Ubiquitin specific peptidase 9, X-linked
FoxO3a	Forkhead transcription factor O subfamily 3a
FGFR3	Fibroblast growth factor receptor 3
ATP7A	ATPase, Cu++ Transporting, Alpha Polypeptide
CLU	Clusterin
GLUT1	Glucose transporter protein type 1
HOTTIP	HOXA transcript at the distal tip
GSTM3TV2	Glutathione S-transferase mu 3, transcript variant 2
MALAT1	Metastasis-associated lung adenocarcinoma transcript 1
PVT1	Plasmacytoma variant translocation 1
HOTAIR	HOX transcript antisense gene RNA
LAT2	L-type amino acid transporter 2
OLR1	Oxidized low-density lipoprotein receptor 1
TOP2A	Topoisomerase 2-alpha
DGCR5	DiGeorge syndrome critical region gene 5
UCA1	Urothelial carcinoma-associated 1
PSC	Pancreatic stellate cell
HPSC-EXO	Hypoxic pancreatic stellate cells derived exosome
NHEJ	Nonhomologous end joining
DSB	DNA double-strand break

ROS	Reactive oxygen species
NRF2	Nuclear factor erythroid-2-related factor 2
TWF1	Twinfilin 1
HCP5	HLA complex P5
SNHG8	Small nucleolar RNA host gene 8
TRAIL	Tumor necrosis factor-related apoptosis inducing ligand
DR5	Death receptor 5
EZH2	Epigenetic regulator enhancer of zeste homolog 2
CTBP1	C-terminal binding protein 1
NEAT1	Nuclear paraspeckle assembly transcript 1
PAK1	P21 activated kinase 1
MSC	Mesenchymal stem cell
SNHG7	Small nucleolar RNA host gene 7
SOCS3	Suppressor of cytokine signaling 3
GAS5	Growth arrest-specific 5
DLEU2L	Deleted in lymphocytic leukemia 2-like
SIRT1	Sirtuin1
LIF	Leukemia inhibitory factor
ESRP1	Epithelial splicing regulatory protein 1
siRNA	Small interfering RNA
shRNA	Short hairpin RNA
ASOs	Anti-oligonucleotides
CRISPR/Cas9	Clustered regulatory interspaced short palindromic repeats-associated endonuclease 9