Molecular Therapy
Nucleic Acids
Review

The role of non-coding RNAs in chemotherapy for gastrointestinal cancers

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Gastrointestinal (GI) cancers, including colorectal, gastric, hepatic, esophageal, and pancreatic tumors, are responsible for large numbers of deaths around the world. Chemotherapy is the most common approach used to treat advanced GI cancer. However, chemoresistance has emerged as a critical challenge that prevents successful tumor elimination, leading to metastasis and recurrence. Chemoresistance mechanisms are complex, and many factors and pathways are involved. Among these factors, non-coding RNAs (ncRNAs) are critical regulators of GI tumor development and subsequently can induce resistance to chemotherapy. This occurs because ncRNAs can target multiple signaling pathways, affect downstream genes, and modulate proliferation, apoptosis, tumor cell migration, and autophagy. ncRNAs can also induce cancer stem cell features and affect the epithelial-mesenchymal transition. Thus, ncRNAs could possibly act as new targets in chemotherapy combinations to treat GI cancer and to predict treatment response.

INTRODUCTION

Gastrointestinal (GI) cancers are a major cause of death worldwide, and they impose a tremendous financial burden on many countries. Some therapeutic approaches for inoperable GI cancer, such as radiotherapy and chemotherapy, have been slowly developed along with advances in technology, and they have been shown to be partly effective in patients. Today, chemotherapy is the first-line standard procedure for most patients with cancer, particularly where surgery is impractical. There are already hundreds of chemotherapy drugs that have been approved to treat cancer, along with more new drugs being developed. The mechanisms of these anti-cancer drugs are different; while many aim to inhibit elements of the basic cellular function, others aim to kill the proliferating cells. They include compounds such as DNA-modifying agents (cisplatin [DDP]), molecular drugs targeting hormones such as estrogen receptor (ER) blockers (tamoxifen [TAM]), drugs that interfere with microtubules (taxol), and drugs that interfere with metabolic activity (methotrexate [MTX]).[1] Radiotherapy is often used as an adjuvant therapy and is used in the treatment of nearly 50% of patients with cancer around the world. The treatment principles can be divided into two broad groups: (1) tumor cells have a restricted capability to repair damaged DNA; and (2) cancer cells are usually rapidly dividing and show higher sensitivity to chemotherapy and radiation compared to slower dividing normal cells.[2] Radiotherapy and chemotherapy have both been shown to improve the overall survival (OS) and/or progression-free survival of patients. However, a problem is very likely to gradually appear; that is, cancer cells usually develop resistance to cytotoxic drugs or radiation. Both acquired and intrinsic resistance can dramatically reduce the therapeutic efficacy, leading to poor prognosis, recurrence, and eventual tumor metastasis.[3] Nowadays, the discovery of approaches to overcome these challenges is an urgent need.

It has been reported that non-coding DNAs account for 95% of the DNA sequences within the human genome. A majority of the non-coding DNAs have been shown to be transcribed into more than 10,000 different functional non-coding RNAs (ncRNAs), including microRNAs (miRNAs), small interfering RNAs (siRNAs), antisense RNAs (asRNAs), and long non-coding RNAs (lncRNAs).[4–7] Recent

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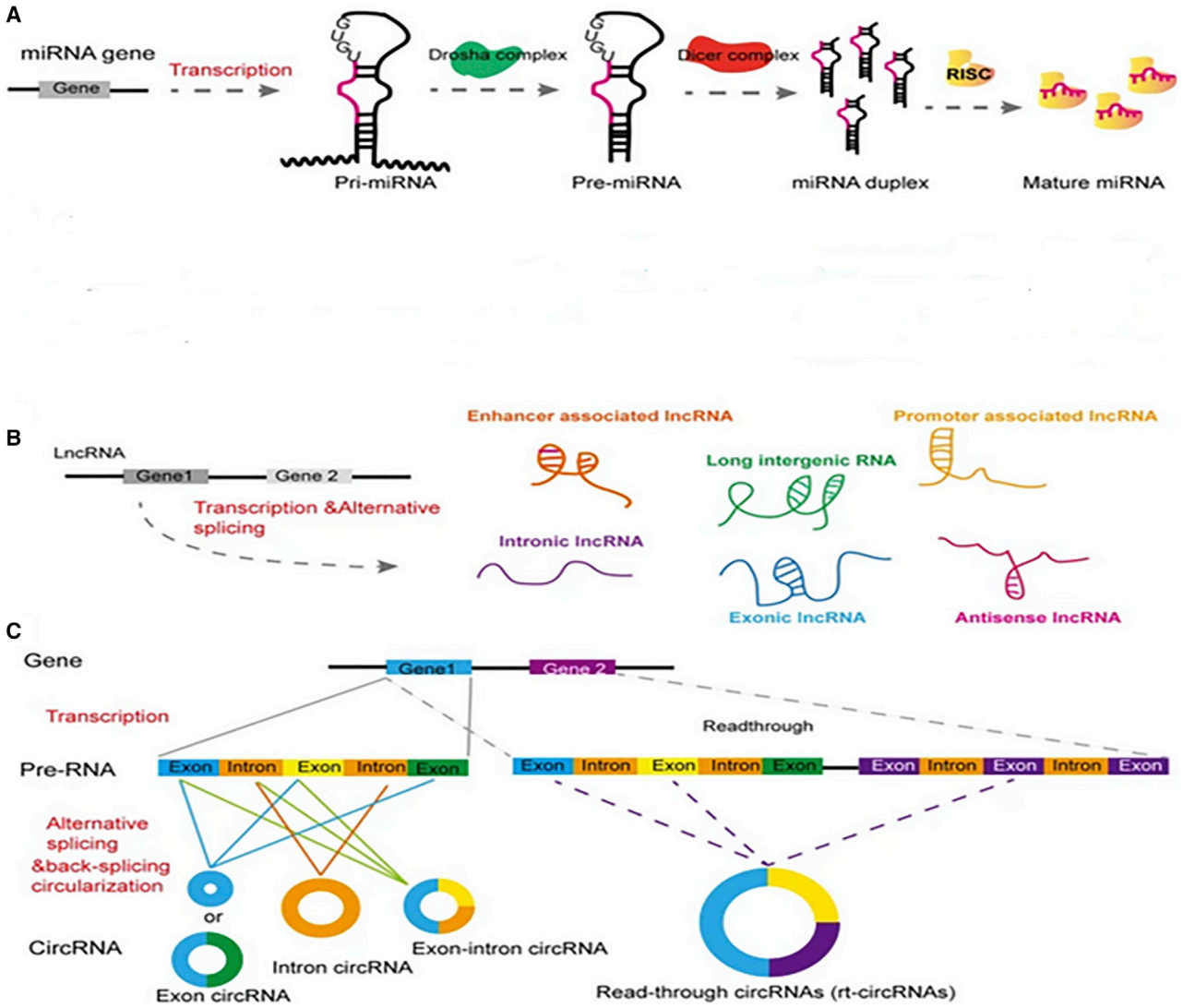

Figure 1. The biogenesis process of different types of ncRNAs

(A) RNA polymerase II (RNA Pol II) transcribes most miRNA genes and generates pre-miRNAs longer than 200 nt, composed of a hairpin structure containing the miRNA sequence. The pre-miRNAs are cleaved in the nucleus by RNase III enzyme Drosha into nearly 70-nt-long pre-miRNAs with a stem-loop motif. The pre-miRNAs are exported to the cytoplasm and are then cleaved by another RNase III enzyme called Dicer. Eventually, the ~22 miRNA duplex is loaded into the RNA-induced silencing complex (RISC) where the mature single-stranded miRNA binds to complementary mRNA targets. (B) lncRNAs have been shown to be transcribed from genomic sequences. lncRNAs are classified into various categories, including promoter-related lncRNAs, enhancer-related lncRNAs, intronic and exonic lncRNAs, antisense lncRNAs, and long intergenic lncRNAs. (C) Numerous circRNAs are obtained from the pre-mRNAs, depending on the spliceosomes. circRNAs are classified into different types, including intron circRNAs, exon circRNAs, and extron-intron circRNAs. Read-through circRNA (rt-circRNA) is a new type of circRNA (dotted line).

studies have identified a new type of ncRNA, termed circular RNA (circRNA).[8–10] Many circRNAs have been shown to be produced from the exons of coding genes, and several of them do not translate to proteins.[8,10,11] Figure 1 summarizes the biogenesis of various ncRNAs, including miRNAs,[5,12,13] siRNAs, lncRNAs,[4] and circRNAs.[8,10,11] Another class of ncRNAs that are produced to act as active enhancers are called enhancer RNAs (eRNAs).[14] eRNAs are transcribed from genomic enhancer regions, which are generally considered as transcription factor binding sites distal to gene transcription start sites.[15] The role of most eRNAs has remained enigmatic. Some studies have suggested that eRNAs carry out crucial tasks in regulating the chromatin conformation or transcription activation.[16]

Many studies have shown that several ncRNAs are deregulated (higher or lower) in cancer, where they are involved in cancer-associated processes, such as promotion of cancer stem cells (CSCs), drug resistance, and metastasis, underlining the role of ncRNAs as possible new targets in cancer.[5,6,8,10,11,17–21] Some miRNAs have entered

clinical trials.[21–23] Moreover, circRNAs and lncRNAs have both been shown to be involved in cancer growth and treatment response by several different mechanisms.[6,8] Some successful preclinical studies of nucleic acid-based therapeutics have suggested that ncRNAs could be used to treat cancer.[5,21–23]

miRNAs AND RESPONSE TO CHEMOTHERAPY IN GI CANCER

miRNAs and response to chemotherapy in colorectal cancer (CRC)

miR-135b is involved in various cancer cell processes, such as proliferation, apoptosis, and invasion in CRC.[24] Moreover, miR-135b has been shown to inhibit phosphatase and tensin homolog (PTEN) signaling in CRC.[25] miR-182 can promote drug resistance, cell proliferation, and metastasis in several malignancies.[26,27] Knockdown of miR-182 could inhibit cell proliferation in triple-negative breast cancer.[28] Some miRNAs were overexpressed in 5-fluorouracil (5-FU)-resistant CRC cell-line and tumor tissues.[24]

The levels of α-*N*-acetylgalactosaminide-α-2,6-sialyltransferase (ST6GALNAC2) were reduced by forced expression of miR-135b and miR-182. Moreover, ST6GALNAC2 was found to be a direct target of miR-135b and miR-182, and its expression showed an opposite pattern compared to miR-135b and miR-182 in CRC cell lines and tissues. Proliferation was increased by upregulation of miR-182 and miR-135b, and their upregulation resulted in reduced apoptosis in 5-FU-resistant CRC cell lines. Repression of these miRs by miR-135b/miR-182 inhibitors showed an opposite effect by increasing ST6GALNAC2 expression and promoting CRC progression. miR-135b and miR-182 were shown to modulate the activity of the AKT/ phosphatidylinositol 3-kinase (PI3K) pathway. Inhibition of the AKT/PI3K pathway increased the effects of 5-FU in LoVo and HCT-8 cells. Hence, miR-135b and miR-182 could be targets for CRC treatment.[24]

miR-138-5p has been found to act as an inhibitor in several different cancers.[29–31] In pancreatic cancer (PC), for example, miR-138-5p played a tumor suppressor role.[32] A study by Gao et al.[33] showed that miR-138-5p improved the effect of radiotherapy on nasopharyngeal cancer through targeting EIF4EBP1. Roberto et al.[34] showed that the expression of miR-138-5p changed the prognosis in osteosarcoma. Zhao et al.[35] showed that RHBDD1 (rhomboid domain containing 1) was a direct target of miR-138-5p, and the reduction of RHBDD1 could inhibit breast cancer progression. Zhu et al.[36] showed that the reduction of RHBDD1 by miR-138-5p suppressed lung cancer development.

Xu et al.[37] showed that the expression of miR-138-5p was downregulated in CRC cells. miR-138-5p inhibited the migration of CRC cells and may also overcome chemoresistance. miR-138-5p controlled the expression of Snail1 by targeting NFIB, which is involved in the chemoresistance and migration of CRC cells. Their research showed that miR-138-5p could inhibit migration and reduce chemoresistance by affecting the NFIB/Snail axis, and could be a target in CRC treatment.[37]

miR-133b functions as a tumor repressor in CRC. For example, miR-133b reduced metastasis and proliferation of CRC cells *in vitro* and *in vivo*.[38,39] Additionally, the miR-133b expression level was correlated with the risk of metastasis and survival in CRC patients[40] and could be used as a prognostic indicator.[41] Lv et al.[42] reported that miR-133b was underexpressed in CRC spheroids enriched with CSCs, which also showed increased chemoresistance. Also, overexpression of miR-133b resulted in overcoming chemoresistance to oxaliplatin (OXP) and 5-5-FU and reducing CRC stemness. It was shown that miR-133b inhibited CRC chemoresistance and stemness by downregulating telomeric silencing disruptor 1-like (DOT1L) and a specific H3K79 methyl transferase.[43]

DOT1L replacement abrogated the inhibitory effects of miR-133b on CRC chemoresistance and stemness. These findings suggest that miR-133b may be a new target for overcoming CRC stemness and chemoresistance.[42]

miR-375 is a tumor suppressor that targets crucial oncogenes in several cancer types, such as hepatocellular carcinoma (HCC), CRC, gastric cancer (GC), and cervical cancer. In addition, miR-375 can be used as a therapeutic target because it can suppress tumor cell growth *in vivo* and *in vitro*.[44] miR-375 is correlated with the susceptibility to chemotherapy in prostate cancer, breast cancer, and HCC.[45–47] miR-375 also plays a key role in determining which patients should receive preoperative chemoradiation therapy for CRC.[48,49] To date, more studies are required to prove a connection between drug resistance and miR-375 in CRC.[50]

Xu et al.[51] reported that miR-375 was remarkably underexpressed in CRC cell lines and tissues, and that low expression of miR-375 was correlated with poor prognosis in CRC patients. *In vivo* and *in vitro* overexpression of miR-375 rendered the CRC cells more sensitive to a wide range of chemotherapy drugs. Further mechanistic analysis showed that, by directly targeting SP1 and YAP1, miR-375 improved the chemosensitivity of CRC to 5-FU. miR-375 negatively regulated YAP1, leading to a decrease in the expression of the downstream genes of Hippo-YAP1 (also known as survivin), such as CTGF, cyclin D1, and the BIRC55 pathway. Overall, miR-375 could be a potential molecular biomarker for chemoresistance in CRC patients, and also could have a role in the treatment of CRC patients, particularly those with chemoresistant tumors.[51]

Most studies about the role of miR-552 in tumor biology have concentrated on CRC.[29–32] In addition, measuring the miR-552 expression profile improved the prediction of lung metastasis in CRC patients.[52] The involvement of aberrant miR-552 expression in the undifferentiated and highly proliferating tumors characteristic of DNA mismatch repair-deficient (dMMR) CRC was recently reported.[53] Also, miR-552 can enhance the progression of HCC by stimulating the epithelial-mesenchymal transition (EMT).[54]

Zhao et al.[55] found significantly downregulated miR-552 expression in 5-FU-resistant CRC cells and tissues, as well in dMMR tumors

with poor prognosis after chemotherapy. Overexpression of miR-552 increased apoptosis and reduced 5-FU resistance, while inhibiting miR-552 expression increased 5-FU resistance in CRC cells. From a mechanistic point of view, miR-552 directly targeted the 3′ UTR of SMAD2. Overall, they demonstrated that the miR-552/SMAD2 pathway governed the response to 5-FU chemotherapy in dMMR CRC tumors.[55]

Previous studies have shown that miR-106a was overexpressed in CRC tumor tissues, fecal samples, and in plasma.[56–58] A lower level of miR-106a was correlated with decreased overall survival as well as disease-free survival (DFS) in CRC patients.[59] It was shown that miR-106a is involved in the regulation of CRC oxaliplatin sensitivity.[60] miR-106a transfection mildly suppressed the growth of CRC cells and rendered them more sensitive to oxaliplatin. Furthermore, miR-106a overexpression decreased the FOXQ1 level in CRC cells at both mRNA and protein levels. Increased miR-106a expression also increased the expression of Wnt target genes, including matrix metallopeptidase 2 and vascular endothelial growth factor-A, which are known to be modulated by FOXQ1. It was predicted that miR-106a could directly bind to the 3′ UTR of FOXQ1, and this was confirmed by the finding of higher miR-106a and lower FOXQ1 levels in tumor tissues from oxaliplatin-sensitive CRC patients, compared to oxaliplatin-resistant CRC patients. They concluded that miR-106a increased CRC sensitivity to oxaliplatin through direct suppression of FOXQ1 expression.[60]

miR-744 was upregulated in head and neck tumors compared to normal tissues.[61] High plasma levels of miR-744 correlated with chemoresistance and poor prognosis in patients with PC undergoing gemcitabine-based chemotherapy.[62,63] Moreover, there were higher levels of serum miR-744 in GC patients compared to controls.[64] Zhou et al.[65] reported that miR-744 levels were substantially higher in CRC tissues from patients receiving oxaliplatin prior to surgery, and in oxaliplatin-resistant HCT116 cells. Oxaliplatin chemoresistance was increased by miR-744 overexpression, while miR-744 inhibition in HCT116 and T84 cells increased oxaliplatin sensitivity. In addition, the level of BIN1 protein was reduced by miR-744, and the oxaliplatin chemoresistance caused by miR-744 was reversed by BIN1 overexpression. In addition, a luciferase reporter assay demonstrated that BIN1 was a direct target of miR-744. Taken together, these results showed that by suppressing BIN1 expression in CRC cells, miR-744 could increase oxaliplatin drug resistance and could be a strategy to reverse oxaliplatin resistance in CRC therapy.[65]

miR-214 plays a role in several cancer types and has been implicated in many cellular pathways.[66,67] miR-214 has been found to act as a tumor suppressor in CRC[68,69] and can bind to the 3′ UTR of ARL2 (ADP ribosylation factor like GTPase 2). Also, miR-214 can control the signaling of the ErbB2/ErbB3 pathway and target the cellular adhesion molecule Necl-2.[70] A study by Yang et al.[71] showed that miR-214 was downregulated in 5-FU-resistant CRC cells in comparison with normal cells. 5-FU-sensitive and 5-FU-resistant CRC cells could both be sensitized to 5-FU by increasing the expression of miR-214. In terms of function, miR-214 suppressed cell growth and colony formation and increased 5-FU-mediated caspase-3 activity and apoptosis levels. Western blotting and dual-luciferase reporter assays showed that miR-214 could target heat shock protein 27 (Hsp27). Hsp27 makes LoVo and HT-29 cells sensitive to 5-FU by increasing apoptosis. Hsp27 overexpression blocked the action of miR-214, and the 5-FU sensitivity was affected. In summary, miR-214 targeted Hsp27 and sensitized CRC cells to 5-FU, suggesting a possible role in chemotherapy.[71]

miR-34a has received some interest in CRC because p53, which is a major transcriptional regulator of apoptosis, is regulated upstream.[72] In CRC biopsies, miR-34a expression was significantly lower as compared to healthy colon tissue.[73] It was proposed that miR-34a could control the asymmetric division of stem cells,[74] inhibit the EMT, and reduce proliferation, tumorigenicity, and metastasis in CRC.[75] The mechanism of miR-34a as a tumor suppressor miRNA works by controlling Notch,[76] affecting multiple oncogenes, as well as PDGFRA signaling.[77]

Li et al.[78] also found that miR-34a expression was significantly downregulated in clinical CRC specimens from oxaliplatin-resistant patients and could be experimentally used to develop multidrug-resistant CRC cells. Multidrug-resistant HCT-8/OR cells could be resensitized to oxaliplatin by exogenous expression of miR-34a, while miR-34a inhibition increased oxaliplatin resistance in chemosensitive HCT-8 cells. Mechanistically, miR-34a positively increased the stability of ornithine decarboxylase antizyme 2 (OAZ2) mRNA by directly targeting its 3′ UTR. Inhibition of miR-34a/OAZ2 signaling increased chemoresistance by activating anti-apoptotic pathways and multidrug resistance (MDR) ATP-binding cassette (ABC) drug efflux pumps, contributing to MDR development in CRC cells.[78]

Table 1 lists some miRNAs that affect the response to chemotherapy agents in CRC.

miRNAs and response to chemotherapy in PC

miR-1291-5p (or miR-1291) is underexpressed in samples from patients with PC, compared to adjacent normal tissues.[136] Moreover, miR-1291 has been shown to act as a tumor inhibitor by affecting the cell metabolome, inducing apoptosis and cell cycle arrest.[136,137] Arginine succinate synthase 1 (ASS1) is extensively downregulated in PC samples, and it might be a target of miR-1291.[136] miR-1291 has been reported to suppress renal carcinoma cell viability by direct targeting of GLUT11.[138]

A new approach to develop recombinant miR-1291 agents (different from standard synthetic miRNA mimics) was reported by Tu et al.[139] First, they showed that when the bioengineered miR-1291 agent was expressed in human PC cells it was processed into functional miR-1291-5p at high levels. miR-1291 disturbed arginine homeostasis by repressing ASS1 protein levels and rendered ASS1-abundant L3.3 cells sensitive to arginine deprivation treatment. In contrast, treatment with miR-1291 decreased the level of GLUT1 protein in both

Table 1. Various microRNAs that affect the chemotherapy response in colorectal cancer

MicroRNA	Expression in CRC	Target	Drug	Model	Type of cell line	Ref.
miR-224	up	KRAS	5-FU	*in vitro*	HCT116	79
miR-31	up		oxaliplatin	human		80
miR-135b, miR-182	up	ST6GALNAC2	5-FU	*in vitro*	HCT-8, 5-FU-resistant HCT-8 cells (HCT-8/5-FU), LoVo	24
miR-1914, miR-1915	down	NFIX	5-FU, oxaliplatin	*in vitro*	HCT116	81
miR-107, miR-99a-3p	up	CCND1, DICER1, DROSHA, NFKB1	fluoropyrimidine	human		82
miR-5323p	down	ETS1, TGM2	cisplatin, 5-FU	*in vitro*	RKO, SW480, SW620, HCT116, CaCo2, HT29, LoVo, colorectal mucosal cell line FHC, kidney cell 293FT	83
miR-587	up	PPP2R1B	5-FU	*in vitro*	RKO, HCT116, FET, GEO	84
miRNA-17-5p	up	PTEN	oxaliplatin, irinotecan, 5-FU	human	human CRC cell lines COLO205 (CCL-222), SW480 (CCL-228)	85
miR-143	down	IGF-IR	oxaliplatin	*in vitro*	SW1116	86
miR-138-5p	down	NFIB, Snail1	5-FU, doxorubicin, cisplatin	*in vitro*	LOVO, HCT116, HT29, SW620, SW480	37
miR-195-5p	down	GDPD5	5-FU	*in vitro*	Caco-2, HCT8, HCT116, SW480	87
miR-93-5p	up	cyclin-dependent kinase inhibitor 1A (CDKN1A)	multiple drugs	*in vitro*	HCT-8	88
miR-143	down	FXYD3	fluoropyrimidine	human		89
miR-199b	down	SET	oxaliplatin	*in vitro*	W480 (ATCC CCL-228), WiDr (ATCC CCL-218), DLD-1 (ATCC CCL-221), HT-29 (ATCC HTB-38), SW620 (ATCC CCL-227)	90
miR-133b	down	DOT1L	oxaliplatin, 5-FU	*in vitro*	HT29, HCT116, SW620, HEK293	42
miR-375-3p	down	YAP1, SP1	5-FU	*in vitro*	HCT116	51
miR-204-5p	down	RAB22A	oxaliplatin	*in vitro*	Caco2, DLD1, HCT8, HCT116, HT29, LoVo, SW480, SW620	91
miR-503-5p	up	PUMA	oxaliplatin	*in vitro*, *in vivo*, human	HCT116, HT29	92
miR-214	up	AEBP1	oxaliplatin	*in vitro*, human	HT29	93
miR-761	Down	FOXM1	5-FU	*in vitro*	HT29, SW480, SW620, DLD-1, FHC	94
miR-940	down	MACC1	anlotinib	*in vitro*, *in vivo*	SW620, Lovo	95
miR-330	down	thymidylate synthase (TYMS)	5-FU	*in vitro*	HCT116, HT29, SW480, SW620, FHC, HEK293T	96
miR-218	down	BIRC5, TS	5-FU	*in vitro*	HT29, HCT116	97
miR-197	up	TYMS	5-FU	*in vitro*	HCT8, HCT116, SW480	98
miR-520 g	up	p21	5-FU	*in vitro*	RKO, HCT116, FET, GEO	99
miR-153	up	FOXO3a	cisplatin	*in vitro*	SW480	100
miR-552	down	SMAD2	5-FU	*in vitro*	SW-480, SW-620, HT-116, CCD-18Co	55
miR200c	down	JNK2	multiple drugs	human	HCT8, HCT116, SGC7901, Bel7402	101
miR-20a	up	ASK1	cisplatin	*in vitro*	FHC,HT29, SW480, LoVo	102
miR-106a	up	FOXQ1	oxaliplatin	*in vitro*	293T, HCT116, HT-29	60
miR-149	down	FOXM1	5-FU	*in vitro*	HCT-8, LoVo	103
miR-1271	down	mTOR	cisplatin	*in vitro*	SW480	104
miR-143	up	ERK5, NF-κB, Bcl-2	5-FU	*in vitro*	HCT116	105
miR-744	up	BIN1	oxaliplatin	*in vitro*	HCT116	65

(*Continued on next page*)

Table 1. *Continued*

MicroRNA	Expression in CRC	Target	Drug	Model	Type of cell line	Ref.
miR-199a/b	up	β-catenin, Gsk3β, ABCG2	cisplatin	*in vitro*	ALDHA1^{+} cells, ALDHA1^{-} cells	106
miR-214	down	Hsp27	5-FU	*in vitro*	HT-29, LoVo	71
miR-129	down	BCL2	5-FU	human	HCT116, RKO, SW480	107
miR-21	up	RECK	5-FU, oxaliplatin	human	?	108
miR-106a	up	DUSP2	5-FU	human	HCT116/SW620	109
miR-361	up	FOXM1	5-FU	*in vitro*	HCT116, HT29	110
miR-139-5p	down	NOTCH-1	5-FU	*in vitro*	HCT-116, LoVo, HCT-8	111
miR-195	down	G2 checkpoint kinase WEE1, CHK1	5-FU	*in vitro*	HCT-116	112
miRNA-497	down	Smurf1	5-FU	*in vitro*	SW480	113
miR-519c	down	ABCG2, HuR	5-FU	*in vitro*	S1, S1M1 80	114
miR-543	up	PTEN	5-FU	*in vitro*	HCT8, HCT8/FU	115
miR-34a	down	TGF-β, Smad4	oxaliplatin	*in vitro*	HT29	116
miRNA-126	up		capecitabine, oxaliplatin	human	N/A	117
miR-1290	up	hMSH2	5-FU	*in vitro*	RKO, SW480, HCT116, LoVo	118
miR-770-5p		HIPK1	methotrexate	*in vitro*	HT-29	119
miR-200c	down	PTEN,E-cadherin	5-FU	*in vitro*	HCT-116	120
miR-20a	down, up	BNIP2	5-FU, L-OHP, VM-26	*in vitro*	SW620, SW480	121
miR-101	down		5-FU, cisplatin	human	HT-29, RKO	122
miR-203	down	SIK2	paclitaxel (Taxol)	*in vitro*	CCD-18Co, CCD-33Co, LoVo, CaCo2, T-84, SW480, DLD-1 NCIN87, SKBR3, LNCaP	123
miR-196b-5p	up	SOCS1, SOCS3	5-FU	*in vitro*	Caco-2, COLO 205, COLO 320DM, CW-2, DLD-1, HCT15, HCT116, HT-29, NCI-H716, LS 174T, LoVo, RKO, SW480, SW620, SW948, SW1116	124
miR-409-3p	down	Beclin-1	oxaliplatin	*in vitro*	LoVo, HCT 116, DLD-1, SW480, HT-29, RKO, FHC, CCD-18Co	125
miR-338-3p	down	mTOR	5-FU	*in vitro*	HCT116, HT29	126
miR-107		CAB39	DCA, oxaliplatin (L-OHP)	*in vitro*	HCT-8, LoVo, HEK293T	127
miR-210-3p	up	succinate dehydrogenase subunits D	5-FU	*in vitro*	HT29	128
miR-145	down	RAD18	5-FU	*in vitro*	SW620	129
miR-874-3p	down	YAP, TAZ	5-FU	*in vitro*	HCT116, SW480	130
miR-34a	down	LDHA	5-FU	*in vitro*	DLD-1	131
miR-203	up	ATM kinase	oxaliplatin	*in vitro*	HT29, RKO, HCT116	132
miR-34a	down	OAZ2	multiple drugs	*in vitro*	HCT-8, HCT-116, SW-480	78
miR-492	down	CD147	oxaliplatin	*in vitro*	LS174T	133
miR-21	up	hMSH2	5-FU	*in vitro*	HT-29, HT-29/5-FU	134
miR-222	down	ADAM-17	multiple drugs	*in vitro*	HCT-8, HCT-116	135

PANC-1 and AsPC-1 cells, thereby lowering glucose uptake and reducing glycolysis. As a result, miR-1291 greatly increased the ability of cisplatin to inhibit PC cell viability. The findings showed that miR-1291 could sensitize PC cells to arginine deprivation therapy and chemotherapy by targeting GLUT1-mediated glycolysis and ASS1 arginolysis, and it may help in a treatment for lethal PC.[139]

miR-301-3p was downregulated in PANC-1 cells *in vitro* by treatment with luteolin, and the knockdown of miR-301-3p showed antiproliferative effects, suggesting that miR-301-3p was an oncogenic lncRNA. miR-301-3p specifically targeted caspase-8, which is required for apoptosis, and miR-301-3p knockdown sensitized PANC-1 cells to the effects of TRAIL. TRAIL is considered to be a potent anticancer agent due to its ability to selectively kill malignant cells. However, resistance to TRAIL is the main factor that limits its application.[140] Inhibition of various cell survival pathways, such as PI3K/AKT, inhibitory nuclear factor κB (NF-κB) (IκB) kinase (IKK), and protein kinase C (PKC) have been suggested to combat TRAIL resistance.[141] Upregulation of caspase-8 makes cancer cells more susceptible to TRAIL, while downregulation of capsase-8 makes them more resistant.[142,143] Epigenetic modifications can potentiate TRAIL cytotoxicity by controlling death receptor expression, inducing cell cycle arrest and increasing caspase-8 levels.[140,142] Multiple genes have been identified as targets for miR-301-3p. In PC cells, miR-301-3p directly targeted PTEN and activated PI3K/AKT signaling.[144] Inhibition of miR-301-3p could potentiate the cytotoxicity of gemcitabine. The NF-κB-repressing factor (NKRF) is another confirmed target of miR-301-3p. Thus, miR-301-3p overexpression can stimulate NF-κB signaling by repressing NKRF in PC cells.[145]

Moeng et al.[146] studied the role of miR-301-3p in controlling cell proliferation, target gene expression, and TRAIL sensitivity. PANC-1 cells exposed to luteolin, a small molecule that suppresses PANC1 cell growth and sensitizes the cells to TRAIL, showed lower expression of miR-301-3p. The knockdown of miR-301-3p suppressed the proliferation and increased the TRAIL cytotoxicity. Additionally, caspase-8 was specifically targeted by miR-301-3p. The interaction between caspase-8 and miR-301-3p could also explain the function of miR-301-3p in different types of cancer.[146]

miR-137 has been shown to possess tumor-suppressor properties in several different types of human cancer.[147] Moreover, it has been shown that miR-137 reduces tumor development and increases the chemosensitvity in lung cancer[148] and in neuroblastoma cells.[149] More specifically, miR-137 has been shown to inhibit mitophagy by controlling two mitophagy receptors, NIX and FUNDC1.[150] In glioma cells, miR-137 upregulation inhibited autophagy, while treatment with a miR-137 antagomir promoted autophagy.[151] Previous studies have shown that miR-137 expression inhibits tumor formation and invasion and increases the effects of chemotherapy in human PC cells.[152,153]

Wang et al.[154] hypothesized that miR-137 could control autophagy and thereby sensitize PC cells to chemotherapy. The findings revealed that doxorubicin (DOX) caused autophagy in PC cells, but it decreased the expression level of miR-137. In contrast, overexpression of miR-137 increased the effects of DOX to reduce viability, trigger apoptosis, and inhibit autophagy by affecting the PC cell autophagic flux. ATG5 was a direct target of miR-137. In contrast, ATG5 overexpression significantly inhibited apoptosis and prevented autophagy induced by overexpression of miR-137. miR-137 made PANC-1 tumor xenografts more sensitive to DOX by inhibiting autophagy and ATG5 *in vivo*.[154]

The effects of glucocorticoids (GCs) on the differential control of miRNAs has been examined in only a small number of studies. Smith et al.[155] reported that the inhibition of Dicer in response to treatment with glucocorticoids led to the decreased expression of several specific miRNAs. There was a high-density CpG island in the promoter region of miR-132, which showed a 2-fold increase in DNA methylation after treatment with dexamethasone (DEX), leading to the extensive silencing of many genes.[156] Hypermethylation after DEX treatment was identified by a detailed examination of the promoter region of miR-132. Treatment with a demethylating agent could restore the expression of miR-132. Another investigation in prostate cancer found that hypermethylation regulated the miR-132 promoter region, resulting in its decreased expression.[157]

Abukiwan et al.[158] analyzed 35 PC tissue samples from patients who received or did not receive glucocorticoids before surgery, as well as one primary and two established PC cell lines. They detected 268 miRNAs differentially expressed between DEX-treated and untreated cells by miRNA microarray analysis, qRT-PCR, and *in silico* analysis. They selected miR-132 and its target gene, transforming growth factor β2 (TGF-β2), as the lead candidates that could be involved in cancer progression. As shown by the enhanced luciferase activity, miR-132 mimics bound directly to the 3′ UTR of TGF-β2 luciferase and enhanced its expression. In comparison, DEX inhibited miR-132 expression via promoter methylation. The DEX-induced migration, expression, and clonogenicity PC cells, and the expression of E-cadherin and vimentin were decreased by miR-132 mimics. The growth of PC xenografts was also reduced. Glucocorticoid admininstration to patients post-surgery increased the overall hypermethylation of the miR-132 promoter and TGF-β2 expression in tissues; miR-132 expression was observed but could not be quantitatively measured. DEX-mediated suppression of miR-132 as a component of PC treatment could provide a basis for miRNA-based treatment.[158]

Several assorted diseases, including calcified aortic stenosis, obesity, infertility, ischemic stroke, and immunoglobulin (Ig)A nephropathy, are all characterized by the dysregulation of miR-374b-5p.[159–163] Some studies have shown the overexpression of miR-374b-5p in prostate, breast, head and neck, and GC, and also in melanoma.[164–169] Alternatively, the downregulation of miR-374b-5p was observed in CRC and T cell lymphoblastic lymphoma.[170,171] The findings suggest that miR-374b-5p could have different functions in different tumor types. A report by Schreiber et al.[172] revealed a correlation between miR-374b-5p downregulation and the development of the cisplatin-resistant phenotype after stepwise treatment with an increasing dose of cisplatin across >20 passages. This suggested that in PC, the reduced expression of miR-374b-5p was correlated to chemoresistance. Nonetheless, the clinical relevance and the main mechanism behind the effect of miR-374b-5p in PC has yet to be elucidated. In PC tissues, miR-374b-5p was downregulated and was correlated with chemoresistance and low progression-free and overall survival rates. miR-374b-5p upregulation leads to the downregulation of anti-apoptotic proteins, such as baculoviral IAP repeat-containing 3 (BIRC3), X-linked apoptosis inhibitor (XIAP), and B cell lymphoma 2 (BCL2), which

Table 2. Various microRNAs that affect chemotherapy response in pancreatic cancer

MicroRNA	Expression in pancreatic cancer	Target	Drug	Model	Type of cell line	Ref.
miR-1291-5p	up	GLUT1, ASS1	cisplatin	*in vitro*	AsPC-1, PANC-1, L3.3	174
miR-138-5p	up	vimentin	5-FU	*in vivo*, human	AsPC-1, BxPc-3, Capan-1, Capan-2, CFPAC-1, PANC-1, MIA PaCa-2, SW1990	32
miR-100	up	FGFR3	cisplatin	*in vitro*, *in vivo*	AsPC1, BxPc-3, Capan-1, Capan-2, CFPAC-1, PANC-1, MIA PaCa-2, SW1990	175
miR-137	up	pleiotropic growth factor (PTN)	5-FU	*in vivo*, *in vitro*	AsPC-1, BxPc-3, Capan-1, Capan-2, CFPAC-1, PANC-1, MIA PaCa-2, SW1990	153
miR-137	down	ATG5	doxorubicin	*in vivo*	PANC-1-Dox, PANC-1	176
miR-20a-5p	down	ribonucleotide reductase subunit M2 (*RRM2*)	gemcitabine	*in vivo*	MIA-PaCa2, HEK293	177
miR-21	up	p85α	gemcitabine	*in vivo*	MIA-PaCa2, PANC-1, Hs766T	178
miR-21	up	PDCD4	5-FU	*in vivo*	PATU8988, PANC-1	179
miR-429	down	PDCD4	gemcitabine	*in vivo*	SW1990	180
miR-374b-5p	down		gemcitabine	*in vivo*, *in vitro*	BxPC-3, PANC-1, AsPC-1, SW1990, Capan-1, Capan-2, CFPAC-1, MIA PaCa-2	173
miR-132	down	TGF-β2	dexamethasone	*in vitro*	AsPC-1, PANC-1	158
miR-30a	down	SNAI1-IRS1-AKT (snal1)	gemcitabine	*in vitro*, *in vivo*	SW1990, SW1990-R	181
miR-221-3p	up	RB1	5-FU	*in vivo*	PANC-1, PATU8988	182
miR-320a	up	PDCD4	5-FU	*in vivo*	PANC-1, PATU8988	183
miR-21	down	FasL	gemcitabine	human, *in vivo*	PANC-1 BxPC3	184
miR-1285	down	YAP1	gemcitabine	*in vivo*	AsPC-1, BxPC-3, MIA PaCa-2, PANC-1, SU86.86 T3M4	185
miR-3656	Down	RHOF	gemcitabine	*in vitro*, *in vivo*	GR PANC-1 (PANC-1-GR)	186
miR-663a	up (gem), down (OSI-027)		gemcitabine	*in vivo*	Panc-1, BxPC-3, T3-M4, MIA PaCa-2	187
miR-320c	up	SMARCC1	gemcitabine	*in vitro*, human	MIA PaCa2, PSN1	188
miR-21	down	RRM2	gemcitabine	*in vivo*	SUIT2-028, SUIT2, SUIT2-007	189
miR-101-3p	down	RRM1	gemcitabine	*in vitro*, human	PANC-1, AsPC-1, MIA-PaCa2, AsanPaCa, BxPC-3	190
miR-410-3p	down	3′ UTR of HMGB1	gemcitabine	*in vivo*, *in vitro*	MIA PaCa-2, PANC-1	191
miR-21	down	PDCD4	gemcitabine	*in vivo*	PANC-1	192
miR-301-3p	down	caspase-8	luteolin	*in vitro*	PANC-1	146

reduces the response of PC cells to gemcitabine. This confirms that miR-374b-5p has a tumor-suppressor function and governs PC resistance to chemotherapy.[172]

miR-374b-5p has been proposed to be a diagnostic biomarker in multiple cancer types. Hanniford et al.[166] reported that miR-374-b-5p could provide a diagnostic signature in brain metastasis of melanoma. The Cancer Genome Atlas (TCGA) data analysis has also shown that miR-374b-5p could predict the progression of breast cancer. In PC tissues, miR-374b-5p expression was significantly lower, and the down-regulation of miR-374b-5p predicted poor progression-free and overall survival in PC patients.[165] Moreover, Summerer et al.[167] reported that higher plasma miR-374b-5p levels predicted poor outcomes in head and neck cancer patients. They suggested that miR-374b-5p could be used as a minimally invasive diagnostic marker in cancer patients.

Sun et al.[173] quantified the expression of miR-374b-5p in PC patient samples using qRT-PCR. They then assessed whether the levels of miR-374b-5p were correlated with clinicopathological features and progression-free or overall survival in PC patients. They used loss- or gain-of-function experiments *in vivo* and *in vitro* to test the effects of miR-374b-5p expression on chemoresistance and characterized the possible targets of miR-374b-5p using western blotting, bioinformatics analysis, qRT-PCR, RNA immunoprecipitation (RIP) assays, and luciferase reporter RIP assays. They showed that reduced expression of miR-374b-5p increased the tolerance of PC cells to gemcitabine chemotherapy, by increasing several anti-apoptotic proteins, such as XIAP, BCL2, and BIRC3. The findings indicated that miR-374b-5p may be considered a new therapeutic strategy for treating patients with chemoresistant PC.[173] Table 2 lists some miRNAs that may affect the response of PC to chemotherapy.

miRNAs and response to chemotherapy in GC

Zheng et al.[193] investigated the effects of miR-34c (and its upstream transcription factor E2F1) on the susceptibility of GC cells to paclitaxel in combination with cisplatin. They compared paired samples of GC tissue and adjacent normal tissue from 74 GC patients. Western blotting was used for E2F1 and real-time qPCR for miR-34c. Steadily increasing drug concentrations induced cisplatin and paclitaxel resistance in GC cells. They found that E2F1 inhibited miR-34c to promote proliferation of the GC cells and increase the resistance to cisplatin plus paclitaxel. Alternatively, silencing of E2F1 led to an increase in the effectiveness of paclitaxel plus cisplatin in GC cells.[193]

The roles of miR-567 in targeting FGF5 and inhibiting cell proliferation, invasion, and migration were previously reported in osteosarcoma.[194] Other studies showed that miR-567 served as a tumor suppressor and an inhibitor of tumorigenesis in breast cancer.[195–198] Zhang et al.[199] investigated the biological effects of miR-567 on gastric tumorigenesis and chemoresistance and the potential mechanism thereof. *In vitro* and loss- and gain-of-function assays demonstrated that miR-567 decreased proliferation and sensitized the GC cells to oxaliplatin and 5-FU. The tumorigenesis of GC cells in vivo was significantly inhibited by overexpression of miR-567. The mechanistic investigation revealed that PIK3AP1 triggered AKT phosphorylation in GC cells. miR-567 directly targeted PIK3AP1 to inhibit the PI3K/AKT/c-Myc pathway, and c-Myc negatively modulated miR-567 expression in a miR-567-PIK3AP1-PI3K/AKT-c-Myc feedback loop. They concluded that miR-567 was a tumor suppressor and inhibited GC carcinogenesis and chemoresistance via a miR-567-PI3K/AKT-PIK3AP1-c-Myc feedback loop. miR-567 may serve as a possible biomarker for GC prognosis and response to therapy.[199]

miR-4766-5p was recently identified as a possible tumor suppressor in breast cancer.[200] Liang et al.[200] discovered that knockdown of miR-4766-5p could increase proliferation, metastasis, and chemoresistance.

NKAP is a notch signaling transcriptional repressor that is critically required for T cell development.[201,202] In 2011, Hsu et al.[202] observed that NKAP was engaged in T cell maturation and was required for T cell functional competence. Only a few researchers have studied the role of NKAP in GC. Juan et al.[203] suggested in 2010 that NKAP could be causally involved in GC because it was overexpressed during GC development. NKAP was found to be a nuclear speckle protein with roles in RNA splicing and processing. Knockdown of NKAP resulted in an increased proportion of chromosome misalignment, more unprocessed precursor (pre-)mRNAs, and cell cycle arrest.[204,205]

A study conducted by Wei et al.[206] examined the expression of miR-4766-5pin GC cells and tissues using qRT-PCR. RNA interference (RNAi) was used to alter miR-4766-5p expression in the GC cell lines MKN45 and AGS. Cell proliferation was assessed by colony formation and Cell Counting Kit-8 (CCK-8) assays. Cell cycle and apoptosis were examined by flow cytometry. A dual-luciferase reporter assay was used to demonstrate the association between miR-4766-5p and NKAP. Western blotting was used to measure the protein expression in various signaling pathways. Their results showed that miR-4766-5p was downregulated in GC cell and tissue samples. miR-4766-5p decreased the proliferation of GC cell lines and also inhibited invasion and migration. miR-4766-5p triggered apoptosis in cells. The NKAP gene was directly targeted by miR-4766-5p, and the Akt/mTOR pathway was inhibited. They concluded that miR-4766-5p inhibited cell metastasis and proliferation by attacking NKAP and could have applications as a diagnostic and prognostic biomarker in GC.[206]

miR-31 has been shown to be involved in many pathways associated with cancer cells. For example, low miR-31 expression was correlated with poor prognosis and accelerated tumor progression in patients with bladder cancer.[207] miR-31 was found to be responsible for higher chemosensitivity and lower infiltration of colon cancer cells.[208] In GC samples, miR-31 expression was found to be lower, which was related to poor prognosis, and therefore was clinically important.[209,210] miR-31 can target the enhancer of zeste homolog 2 (EZH2), a polycomb protein that has been implicated in the tumorigenesis, progression, and metastasis of various types of cancer. Higher expression of EZH2 in liver cancer increased metastasis via downregulation of tumor suppressor miRNAs.[211] Likewise, EZH2 was overexpressed in prostate cancer and was correlated with metastasis.[212] EZH2 was also upregulated in CRC and could serve as a biomarker.[213]

Sun et al.[214] studied the tumor-repressor function of miR-31 in GC by regulation of EZH2. They observed significant downregulation of miR-31 in GC cell lines. Upregulation of miR-31 decreased the viability and colony formation by induction of G_2/M cell cycle arrest in AGS GC cells. In addition, overexpression of miR-31 increased the response to 5-FU. EZH2 was suggested to be the target of miR-31 in AGS cells by using *in silico* analysis and a dual-luciferase reporter assay.

The expression of EZH2 was upregulated in GC cell lines, while miR-31 overexpression in AGS cells led to EZH2 suppression. In addition, silencing of EZH2 in AGS cells reduced colony formation and proliferation and caused G_2/M cell cycle arrest. In addition, overexpression of EZH2 could at least partly abrogate the tumor-suppressor effects of miR-31. It was suggested that EZH2 was directly involved in the miR-31-mediated inhibition of proliferation in AGS cells. Overexpression of miR-31 inhibited AGS invasion and migration and downregulated the mesenchymal markers (vimentin and N-cadherin) as well as upregulation of the epithelial marker (E-cadherin) in AGS cells. It was concluded that miR-31 is a tumor suppressor gene and may have a role in GC treatment.[214]

miR-200c is a member of the miR-200 family, which is underexpressed in GC.[215] Studies have also suggested that miR-200c could reduce chemoresistance.[216–218] Many studies have shown the key contribution of miR-200c to cancer cell apoptosis and metastasis affecting various genes such as E-cadherin, FN1, FAP1, ZEB1, and ZEB2, among others. Furthermore, miR-200c downregulation was strongly associated with cancer cell metastasis and proliferation.[120,215,219] Other studies

demonstrated that miR-200c plays a significant role in chemoresistance, and that the response to chemotherapy could be enhanced by the upregulation of miR-200c in cancer cells.[120,218,220]

The possible mechanism and role of miR-200c in improving the activity of cisplatin to inhibit migration and induce apoptosis in GC cells were investigated by Ghasabi et al.[221] First, miR-200c and locked nucleic acid (LNA)-anti-miR-200c mimics were transfected into KATOIII cells. In addition, the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay showed that cisplatin and increased miR-200c expression could further inhibit KATOIII cell proliferation. The migration of KATOIII cells in a wound-healing assay was inhibited by miR-200c overexpression. The combination of miR-200 and cisplatin could suppress colony formation in KATOIII cells. In order to determine the possible targets of miR-200c, they measured its effects on RhoE, VEGFR, MMP9, and PTEN expression levels. A decrease in the mRNA and protein levels of MMP9 and VEGFR was produced by increased miR-200c expression, suggesting that MMP9 and VEGFR were miR-200c targets. Furthermore, RT-PCR revealed that the target gene of miR-200c was RhoE, and PTEN expression was reduced by LNA-anti-miR-200c. DAPI staining and flow cytometry showed increased cisplatin-mediated apoptosis by miR-200c expression that could be related to the inhibition of RhoE in KATOIII cells. Moreover, cell cycle analysis showed arrest at the G_2 stage. They concluded that miR-200c acts in KATOIII cells as a tumor suppressor gene and could be a therapeutic strategy to overcome cisplatin resistance in GC treatment.[221]

miR-362-5p also plays a role in different cancer types. Ying et al.[177] used miRNA expression profiling datasets from seven widely accessible renal cell carcinomas (RCCs) to show that hsa-miR-362-5p was downregulated in RCC. Ni et al.[222] showed that miR-362-5p could target the tumor suppressor gene for cylindromatosis (CYLD), thus promoting proliferation and metastasis of HCC. It has also been shown that upregulation of miR-362-5p increases proliferation, migration, and invasion of MCF7 human breast cancer cells.[177]

Wei et al.[223] examined the functional miRNAs that can modulate the cisplatin sensitivity of human GC cells. miRNA microarray analysis revealed differentially expressed miRNAs between SGC7901 (a human cisplatin-sensitive GC cell line) and SGC7901/DDP (the cisplatin-resistant counterpart). miR-362-5p was found to be downregulated in SGC7901/DDP cells compared to SGC7901 cells using qRT-PCR. Overexpression of miR-362-5p enhanced cisplatin susceptibility and apoptosis, whereas downregulation of miR-362-5p showed the opposite results. Database prediction suggested that the suppressor of zeste 12 protein (SUZ12) could be a miR-362-5p target. Moreover, relative to SGC7901 cells, the mRNA and protein levels of SUZ12 were substantially higher in SGC7901/DDP cells and were negatively correlated with the expression of miR-362-5p. Furthermore, in SGC7901/DDP cells, western blotting and MTT assays showed that knockdown of SUZ12 increased cisplatin sensitivity and also reduced the protein levels of NF-κB/p65. Furthermore, overexpression of miR-362-5p in SGC7901/DDP cells lowered the expression level of SUZ12 protein, while downregulation of miR-362-5p increased its levels. Deregulation of miR-362-5p could target SUZ12 to increase cisplatin resistance and reduce cisplatin-induced apoptosis. miR-362-5p could be a potential clinical approach for cisplatin-resistant GC patients.[223]

Table 3 lists some miRNAs that could affect the response to chemotherapy drugs in GC.

miRNAs and response to chemotherapy in hepatocellular cancer

It has been observed that the expression of miR-144-3p is altered in thyroid cancer, where it can target ZEB1 and ZEB2 to reduce the invasion and migration capability of thyroid cancer cells.[255] Additionally, since miR-144-3p plays a direct regulatory role in the expression of ZFX (zinc finger protein X-linked), it could not only prevent the growth of NSCLC tumor cells, but also induce apoptosis.[256] miR-144-3p was underexpressed in HCC samples.[257] Although numerous investigations have suggested that miR-144-3p could inhibit HCC proliferation via targeting E2F3 and AKT3,[258,259] the role of miR-144-3p in tumor angiogenesis is still unclear.[260,261]

Wu et al.[262] showed that miR-144-3p was downregulated in HCC. Restoring the expression of miR-144-3p in HCC cells could reduce proliferation, migration, and angiogenic potential both *in vitro* and *in vivo*. In addition, a clinical review demonstrated an association between low expression of miR-144-3p and shorter disease-free survival in HCC patients. From a mechanistic point of view, the TargetScan database[263] predicted the target of miR-144-3p to be glucocorticoid kinase 3 (SGK3). When SGK3 was inhibited by miR-144-3p, a PI3K-independent pathway was activated to suppress the activation of mTOR-VEGF downstream signaling. Therefore, miR-144-3p, which is often downregulated in HCC, can suppress migration, proliferation, and angiogenesis by modulating SGK3 activation by a PI3K-independent signaling pathway, and could act as a prognostic marker for HCC patients.[262]

Researchers have also shown the underexpression of the liver-specific miR-122 in primary HCC samples.[264,265] Downregulation of miR-122 may be a poor prognostic factor for liver cancer and its risk of metastasis.[266–268] Restoration of miR-122 expression in HCC using an adenoviral vector (Ad-miR122) led to cell cycle arrest and increased apoptosis.[269] Restoration of miR-122 in HCC cells could increase the response to DOX and vincristine (VCR). Moreover, overexpression of miR-122 in HCC cells using the adenovirus could increase the sensitivity to VCR or DOX. Cell cycle analysis showed that the anti-proliferative role of miR-122 was related to a higher number of cells in the G_2/M phase. Ad-miR122 led to increased HCC cell sensitivity to DOX or VCR by downregulation of MDR efflux pumps, as well as other genes, such as GST-π, cell cycle-associated gene cyclin B1, and the anti-apoptotic gene BCL-w. Ad-miR122 combined with chemotherapy drugs inhibited HCC cells via G_2/M arrest and downregulation of cyclin B1 and MDR-associated genes (at least in part).[265]

Table 3. Various microRNAs that can affect chemotherapy response in gastric cancer

MicroRNA	Expression in gastric cancers	Target	Drug	Model	Type of cell line	Ref.
miR-214	down		cisplatin	*in vitro*, *in vivo*	SGC7901, SGC7901/DDP	224
miR-31	up	RhoA	5-FU	*in vivo*	MKN-45, HEK293T	225
miR-125b	down	HER2	cisplatin	*in vivo*	HGC-27, MGC-803	226
miR-204	down	Bcl-2	5-FU	*in vitro*, *in vivo*	GTL-16, N87 GC	227
mir-204	down	TGFBR2	5-FU	*in vitro*, *in vivo*	GES-1, AGS, SGC-7901, MKN-45, MGC-803, BGC-823	228
miR-128	down	MAPK signaling	cisplatin	*in vivo*	GES-1, BGC823, SGC7901	229
miR-567	down	PIK3AP1	5-FU, oxaliplatin	*in vivo*	GES-1, MKN45, BGC823, AGS, MGC803, BGC803, MKN28	199
miR-647	down	NK2, FAK, MMP2, MMP12, CD44, SNAIL1	vincristine	*in vitro*, *in vivo*	SGC7901/VCR	230
miRNA-29	down	catenin-δ (CTNND1)	cisplatin, docetaxel	*in vitro*, *in vivo*	GES-1 HGC27, MGC803, BGC823, MKN45	231
miR-200c	down	ZEB1/ZEB2	trastuzumab	*in vivo*	SGC7901, BGC803, MKN28, NCI-N87	232
miR-let-7	down	AURKB	cisplatin	*in vivo*	SGC7901/DDP	233
miR-135a	up	DAPK2, E2F	oxaliplatin	*in vitro*, *in vivo*	SNU-5 NCI-N87 SGC7901/OXA, MGC-803/OXA, SGC7901, MGC-803	234
miR-181a	up	ATG5	cisplatin	*in vitro*, *in vivo*	SGC7901/CDDP	235
miR-200c	up	VEGFR, MMP9, RhoE	cisplatin	*in vitro*, *in vivo*	KATOIII	221
miR-31	down	EZH2	5-FU	*in vivo*	GES-1 (AGS, SNU-1, SNU-5, SNU16	214
miR-21-5p	down	PTEN, TIMP3	doxorubicin	*in vivo*	SGC7901/DOX	236
miR-26a	down	NRAS, E2F2	cisplatin	*in vivo*	SGC-7901, SGC7901/DDP	237
miRNA-200c	down	RhoE	cisplatin	*in vivo*	SGC7901, SGC7901/DDP	217
miR-15a-5p	down	PHLPP2	cisplatin, oxaliplatin	*in vivo*		238
miR-524-5p	up	SOX9	cisplatin	*in vivo*	SC-M1, AZ521	239
miR-34a	up	met	cisplatin	*in vivo*	SGC7901/DDP	240
miR-218	up	survivin	cisplatin	*in vivo*	SGC7901, SGC7901/DDP	241
miR-375	down	ERBB2	cisplatin	*in vivo*	SGC7901/DDP	242
miR-362-5p	down	SUZ12	cisplatin	*in vivo*	SGC7901, SGC7901/DDP	223
miR-126	down	EZH2	vincristine, doxorubicin	*in vivo*	SGC7901/VCR, SGC7901/ADR	243
miR-495	up	mTOR, ERBB2	cisplatin, 5-FU	human		244
miR-20a	up	NFKBIB	cisplatin	*in vivo*	SGC7901/DDP, SGC7901	245
miR-185	down	ARC	cisplatin, doxorubicin	*in vivo*, human	SGC-7901, NCI-N87, MGC-803, BGC-823, AGS	246
miR-429	down	Bcl-2	5-FU	*in vivo*	AGS	247
miR-20a	down	CYLD	cisplatin	*in vivo*, human	SGC7901/DDP, SGC7901	248
miR-16-1	up	FUBP1	doxorubicin	*in vitro*, *in vivo*, human	SGC790	249
miR-21	up	PTEN/PI3K/Akt pathway	cisplatin	*in vivo*	SGC7901/DDP, SGC7901	250
miR-223	up	FBXW7	cisplatin	*in vivo*	SGC-7901, BGC-823	251
miR-129	down	P-gp	cisplatin	*in vivo*	BGC823, MKN45	252
miR-21	up	PTEN pathway	trastuzumab	*in vitro*, *in vivo*	MKN45, NUGC4, NCI-N87	253
miR-4290	down	PDK1 (pyruvate dehydrogenase kinase 1)	cisplatin	*in vitro*, *in vivo*	GES-1 SGC7901, MKN45, HGC27, HEK293	254

miR-122 has a crucial function in modulating normal hepatocyte growth, differentiation, and cholesterol metabolism.[270] As mentioned above, miR-122 downregulation was associated with HCC growth and progression,[267,271] as well as HCC cell chemoresistance. miR-122 downregulation is also associated with the EMT and HCC metastasis. Ectopic expression of miR-122 could increase the cell sensitivity to sorafenib (SOR) and DOX in HepG2 and Hep3B cells.[266,272] Earlier work suggested that miR-122 may directly target the Wnt/β-catenin pathway,[273] which has a critical role in tumor growth and the modulation of MDR1 expression.[274,275]

Cao and Yin[276] confirmed the underexpression of miR-122 in HCC cells. Overexpression of miR-122 or inhibition of Wnt/β-catenin signaling increased HCC cell apoptosis and enhanced the sensitivity of HCC cells to oxaliplatin. miR-122 inhibited the Wnt/β-catenin pathway, as well as reduced the expression of MDR1 and increased the sensitivity of HCC cells to oxaliplatin. miR-122 may be a new therapeutic target for HCC treatment.[276]

miR-182 acts as an oncogenic miRNA in many cancers, including HCC, ovarian carcinoma, and breast cancer.[27,277,278] miR-182 is overexpressed in HCC and could stimulate HCC metastasis by suppressing MTSS11 (metastasis suppressor 11) protein.[27] Moreover, miR-182 may be involved in chemoresistance. Husted et al.[279] used a microarray-based approach to survey drug resistance-related miRNAs and discovered that miR-182 was overexpressed in MDR Ehrlich ascites tumor cells. Suppression of miR-182 is a possible therapeutic approach because it is involved in glucocorticoid resistance via targeting FOXO3A in lymphoblastic malignancies.[280]

Qin et al.[281] found that the level of miR-182 was higher in cisplatin-resistant HepG2cells compared to parental HepG2 cells. miR-182 overexpression increased cell viability while miR-182 suppression decreased cell viability during cisplatin therapy. This was more pronounced in HepG2-R cells. Upregulation of miR-182 decreased the expression of tumor protein 53-induced nuclear protein 1 (TP53INP1; tumor suppressor gene) *in vitro*. miR-182 overexpression decreased the tumor response to cisplatin *in vivo*, partly by targeting TP53INP1.

Human miR-204 has been shown to be underexpressed in multiple types of cancer, such as CRC[282] and acute myeloid leukemia (AML).[283] miR-204 expression was remarkably reduced in HCC samples compared to adjacent normal liver tissue.[284] miR-204 targeted S1RT1 to inhibit the development of HCC.[285] miR-204 has also been shown to be associated with venous metastasis of HCC.[286]

Yu et al.[287] reported that miR-204 could enhance drug sensitivity in HCC by reducing the expression of NUAK1 (novel nua kinase family 1). miR-204 was identified as a tumor suppressor by reducing NUAK1 in HCC. This suggested that both NUAK1 and miR-204 could be promising targets for liver cancer treatment.[287]

miR-223 often shows lower expression in HCC cells, and it has been shown to be involved in many critical pathological and physiological processes, such as HCC proliferation, maintenance of stemness, and metastasis. miR-223 is also involved in MDR in HCC cells.[288,289] Targeted therapy with miR-223 may be clinically relevant.[290–293] Moreover, miR-223 inhibited uncontrolled autophagy in cardiomyocytes.[294]

One study by Zhou et al.[295] found lower levels of miR-223 expression in DOX-treated HCC cells. They suggested that overexpression of miR-223 suppressed DOX-mediated autophagy that participates in chemoresistance. Inhibition of autophagic flux by chloroquine abrogated the ability of miR-223 overexpression to reverse the resistance of HCC cells to DOX. FOXO3a has been characterized as a direct downstream target of miR-223, and it could be a central intermediate of the activity of miR-223 on DOX-mediated autophagy and chemoresistance in HCC cells.[295]

miR-125b is downregulated in many types of cancer, such as HCC. Ectopic expression of miR-125b suppressed the proliferation, invasion, and tumorigenic properties of HCC cells, suggesting that it can act as a liver cancer suppressor.[296–299] Although the function of miR-125b in drug resistance remains unknown, it has been suggested as a prognostic biomarker in HCC patients.[300]

Comparison of oxaliplatin-resistant and oxaliplatin-sensitive HCC cell lines showed that miR-125b was underexpressed in the resistant cells. Therefore, miR-125b was proposed to increase the ability of oxaliplatin to suppress proliferation, cell migration, and EMT.[301] In addition, higher expression of EVA1A was demonstrated in tissue specimens from oxaliplatin-resistant HCC patients. Ectopic expression of EVA1A increased autophagy and abrogated the effects of miR-125b on inhibiting oxaliplatin-resistant cell lines and xenograft tumors. A pathway involving the downregulation of EVA1A-mediated autophagy and miR-125b may play a role in HCC cell chemoresistance.[301]

Researchers have also revealed a critical contribution of miR-222 to tumor cell proliferation, oncogenesis, migration, invasion, and drug resistance.[302,303] They also detected the overexpression of miR-222 in many different kinds of cancer, such as CRC, HCC, glioblastoma, and breast cancer.[135,304–307] Several studies have shown that miR-222 is involved in chemoresistance. Miller et al.[305] reported that miR-221/222 increased tamoxifen resistance in breast cancer. Zhong et al.[308] showed that miR-222 was implicated in PTEN-mediated resistance to DOX and docetaxel. Garofalo et al.[309] found that miR-221/222 induced TRAIL resistance via targeting the tumor inhibitors TIMP3 and PTEN and increased cell migration.

It has been shown that miRNA inhibitors designed to specifically target miR-222 could suppress cell migration, proliferation, and invasion, cause G_1/S cell cycle arrest, and induce apoptosis in HepG2 cells.[310] Furthermore, miR-222 could increase resistance to SOR in HepG2 cells. They found that miR-222 inhibitors could increase susceptibility to the antitumor activity of SOR in HepG2 cells. The phosphorylation of PI3K and AKT was regulated by miR-222, explaining the induction of SOR resistance. Therefore, miR-222 can enhance

Table 4. Various microRNAs that can affect chemotherapy response in hepatocellular cancer

MicroRNA	Expression in GI cancers	Target	Drug	Model	Type of cell line	Ref.
miR-21	up	AP-1	5-fluorouracil, pirarubicin	*in vitro*	Hep3b, SMMC7721	311
miR133a, miR326	down	Bcl-xl	5-FU, cisplatin	*in vitro*	HepG2 HCC	312
miR-133b	up	PP2A-B55δ	cisplatin	*in vitro*	L02, HCC cell lines HepG2, MHCC97H, MHCC97L, Hep3B, amd Huh7, human embryonic kidney 293T cells (HEK293T	313
miR-215	up	P53, P21	adriamycin	human	HepG2 (cat. no. HB-8065), Hep3B (cat. no. HB-8064), 786-O (cat. no. CRL1932), and ACHN (cat. no. CRL-1611), RCC cell lines, and A549 (cat. no. CRM-CCL-185), H1299 (cat. no. CRL-5803)	314
miR-223	down	FOXO3a	doxorubicin	*in vitro*	HepG2, Huh7, SNU387, and SNU449, and human embryonic kidney cell line (HEK293T)	315
miR-122	down	cyclin B1	adriamycin (ADM), vincristine (VCR)	*in vitro*	Hep3B, HepG2, Huh7, and PLC/PRF/5	265
miR-33a-5p	down	HSPA8?	cisplatin	*in vitro*	Hep3B and 97L	316
miR-590-5p	up	YAP1	adriamycin	human	HepG2 and Huh7	317
miR-125b	down	EVA1A	oxaliplatin	human	HepG2, Huh6, Mahlavu, and SK-Hep1	301
miR-122	down	MDR1	oxaliplatin	*in vitro*	HepG2, Bel-7402, SMMC-7721, Huh7, and normal liver cell line (WRL-68)	276
miR-26	down	ULK1?	doxorubicin	*in vitro*	HepG2, Huh7, 293T	318
miR-34a	down	MDR1/P-gp, AXL	doxorubicin	*in vitro*	HepG2	319
miR-16	down	IKBKB	paclitaxel	*in vitro*	SMMC-7721, PLC, BEL-7402, BEL-7404, HepG2, HCCLM3, and the normal liver cell line LO2	320
miR-1258	down	CKS1B	doxorubicin	*In vitro*	HuH7, HCCLM3	320
miR122	down	PCDH20	5-FU	*In vitro*	SNU-449, MHCC97, HepG2, and SMMC-7721	321
miR-367-3p	down	MDM2	sorafenib	human	SKhep1, HepG2, Huh7, SNU398, HA22T, SNU423	322
miR-589-5p	up	SOCS members SOCS2 and SOCS5, and tyrosine phosphatases members PTPN1, PTPN5, PTPN7, PTPN11, PTPN13, PTPN18, and PTPN20	doxorubicin	*in vitro*		323
miR-125b	down	HK II	5-FU	*in vitro*	SMMC-7221, Huh7, MHCC-97L, HepG2, HepG3, and BEL-7402 human HCC cell lines, THLE-2 and THLE-3 normal human liver cell lines	324
miR-124	down	SIRT1/ROS/JNK pathway	cisplatin	*in vitro*	HepG2, Huh7	325
miR-222	up	PI3K/AKT signaling pathway	sorafenib	*in vitro*	HepG2, normal human hepatocyte cell line HL-7702	310
miR-520c-3p	down	Mcl-1	doxorubicin	*in vitro*	HepG2?	326
miR-101	down	Mcl-1	doxorubicin	*in vitro*	HepG2, Hep3B, Huh7, PLC human HCC cell lines, and the L-O2 normal liver cell line	327
miR-182	up	TP53INP1	cisplatin	*in vitro*	HEK293, HepG2	281
miR-340	down	Nrf2	cisplatin	*in vitro*	HepG2	328
miR-193b	down	Mcl-1	cisplatin	*in vitro*	normal hepatic cell line L02, and HCC cell lines Huh7, HepG2, and PLC	329

(*Continued on next page*)

Table 4. *Continued*

MicroRNA	Expression in GI cancers	Target	Drug	Model	Type of cell line	Ref.
miR-363	down	Mcl-1	cisplatin	human	HepG2	330
miR-130a	up	RUNX3?	cisplatin	human	Huh7, HEK293	331
miR-3163		ADAM-17		*in vitro*	L-02 (a non-tumor hepatic cell line), MHCC97-H, or LM-3 (two highly metastatic cell lines of HCC), HepG2, Hu7, BEL-7402, or SMMC-7721, and MHCC97-L (a lowly metastatic cell line of HCC)	332
microRNA-122	down	ADAM10, SRF, and Igf1R	sorafenib	*in vitro*	HepG2, Hep3B, and SK-Hep-1	272
miR-122	down	IGF-1R	sorafenib	*in vitro*	Huh7, Huh7-DR3	333
miR-221	up	caspase-3	sorafenib	human	Huh-7	334
miR-137	down	ANT2	sorafenib	human	Huh7	335
miR-23a	up	TOP1	etoposide	*in vitro*	HepG2 and embryonic kidney cell line HEK293T	336
miR-27b	down	p53, CYP1B1		*in vitro*	HepG2	337
miR-372-3p	down	Mcl-1?	doxorubicin	*in vitro*	HepG2	338
miR-223	down	ABCB1	doxorubicin and paclitaxel	*in vitro*	HCC3, LM-6, SMMC7721, Huh-7, SK-Hep-1, HepG2, BEL-7402, Hep3B	289

proliferation, migration, and invasion. They concluded that miR-222 could trigger the PI3K/AKT signaling pathway and increase HCC cell resistance to SOR.[310]

Table 4 lists some miRNAs that can affect the response to chemotherapy agents in HCC .

miRNAs and response to chemotherapy in esophageal cancer

miR-133b has been identified as an important miRNA in muscle that modulates myoblast differentiation and is involved in some myogenic disorders.[339] miR-133b functions as a tumor suppressor and is downregulated in many cancers, including bladder cancer,[340] prostate cancer,[339] lung cancer,[341] and GC.[342] miR-133b was also downregulated in cells and tissues from esophageal squamous cell carcinoma (ESCC).[343] However, the functional molecular mechanism of miR-133b in ESCC is still uncertain. The epidermal growth factor receptor (EGFR) is a 170 kDa transmembrane protein that binds to its cognate ligands, to trigger its tyrosine kinase activity.[344] EGFR has a critical contribution to tumor growth by binding to EGF. EGFR is known to positively affect proliferation, migration, invasion, and apoptosis. EGFR expression is significantly higher in ESCC tissues where it is associated with poor prognosis, clinical stage, and invasion.[345,346] ESCC patients who had a low copy number of EGFR genes were shown to have a higher survival rate than cases with a higher copy number.[347,348] However, the association between miR-133b and EGFR in ESCC and the respective mechanism should be clarified. It was reported that in prostate cancer, miR-133b inhibited migration, growth, and invasion of PC3 and DU145 cell lines via EGFR targeting.[339,349]

Lower levels of miR-133b expression and higher expression of EGFR were found to occur together in ESCC specimens.[343] Cell proliferation, invasion, and migration in ESCC cells were inhibited either by miR-133b overexpression or by EGFR knockdown, and the percentage of cells in the G_1 stage was increased. The overexpression of miR-133b and knockdown of EGFR both increased apoptosis in ESCC cells. Overexpression of miR-133b decreased the phosphorylation of AKT, extracellular signal-regulated kinase (ERK), and PI3K via direct reduction of EGFR. Higher levels of CK-18 and E-cadherin, and lower levels of N-cadherin and vimentin were observed following the transfection with miR-133b mimics or short hairpin RNA (shRNA) EGFR (shEGFR). They concluded that overexpression of miR-133b could block the PI3K/AKT and mitogen-activated protein kinase (MAPK)/ERK signaling pathways via EGFR targeting and inhibit ESCC cell proliferation, invasion, and migration, suggesting a role of miR-133b in ESCC treatment.[343]

miR-145 is a well-characterized tumor suppressor in different cancer types.[350–352] miR-145 was first reported to be downregulated in ESCC.[353] miR-145 inhibited proliferation, invasion, and the EMT and increased differentiation in ESCC.[354,355] Moreover, miR-145 increased the sensitivity of human colon cancer cells toward 5-FU.[356]

The downregulation of miR-145 in ESCC cells and tissues was correlated with the upregulation of REV3L (protein reversionless 3-like) in ESCC tumor specimens. In the KYSE150 ESCC cell line, miR-145 overexpression reduced the level of REV3L mRNA and protein. On the contrary, miR-145 decreased REV3L mRNA and protein in the normal esophageal epithelium cell line (HEEC).[357] Additionally, ESCC cell viability was decreased following transfection with a miR-145 mimic. Overexpression of miR-145 strongly suppressed viability and increased the apoptosis rate after application of 5-FU. Furthermore, transfection with miR-145 mimics altered the expression of

apoptosis-related genes (Bax, caspase-3, Bcl-2) in 5-FU-treated ESCC cells. Finally, Chen et al.[357] suggested that miR-145 could be a therapeutic agent to treat ESCC.

miR-193a-3p has previously been observed to reduce the invasion of cancer cells and prevent metastasis, while promoting apoptosis via ERBB44 downregulation in lung cancer cells.[358] Additionally, miR-193a-3p could increase apoptosis by affecting Mcl-1 in both U-251 and HeLa cells.[359] miR-193a suppressed the expression of c-kit and served as a methylation-silencing tumor suppressor in AML.[360]

Meng et al.[361] suggested a role of miR-193a-3p in the regulation of radioresistance and chemoresistance in ESCC cells (KYSE410 cells are moderately radiation resistant while KYSE150 cells are radiation sensitive). Upregulation of miR-193a-3p increased chemoresistance and radioresistance of the ESCC cells. Furthermore, miR-193a-3p downregulation decreased the radioresistance and chemoresistance of the ESCC cells. Additionally, miR-193a-3p was involved in DNA damage as shown by quantification of the γ-H2AX level in relationship to miR-193a-3p. Also, the siRNA-mediated suppression of the PSEN1 gene had similar effects as miR-193a-3p overexpression. They concluded that miR-193a-3p participated in radioresistance and chemoresistance in esophageal cancer via PSEN1 downregulation. Therefore, PSEN1 and miR-193a-3p might be biomarkers for resistance to chemotherapy and radiotherapy.[361]

miR-181a-5p is involved in cell apoptosis, proliferation, and migration, and it could be a new potential biomarker.[362,363] Although the precise molecular mechanism and function of miR-181a-5p in cisplatin resistance in ESCC are unclear, Hummel et al.[364] showed that miR-181a-5p was deregulated in samples from ESCC patients who were resistant to cisplatin.

Yang et al.[365] found strong expression of miR-181a-5p in OE19/CDDP-resistant cells, whereas CBLB (E3 ubiquitin-protein ligase) was underexpressed in the OE19 cell lines. The overexpression of miR-181a-5p or the knockdown CBLB inhibited cell viability and induced apoptosis in cisplatin-resistant CDDP/OE19 cells. In addition, miR-181a-5p suppression or CBLB upregulation increased cell viability and prevented apoptosis in the cisplatin-sensitive OE19 cells. CBLB was confirmed to be a miR-181a-5p target. Furthermore, a rescue assay demonstrated that CBLB upregulation abrogated the effects of miR-181a-5p on OE19/CDDP cell viability. Moreover, miR-181a-5p overexpression increased the effects of cisplatin on ESCC xenografts *in vivo*.[365]

miR-10b has been found to act as an oncogene in several cancer types, including breast cancer,[366] GC,[367] lung cancer,[368] and HCC.[369] Moreover, higher expression of miR-10b was associated with chemoresistance. For example, one study showed that miR-10b increased CRC cell resistance to 5-FU, likely by suppressing the pro-apoptotic BIM.[370] Zhang et al.[371] showed that miR-10b was overexpressed in cisplatin-resistant nasopharyngeal cancer cells. miR-10b deficiency reversed the EMT phenotype and reduced cisplatin resistance by regulating the Notch1/KLF4/E-cadherin pathway. Another study showed that miR-10b overexpression in ER-positive breast cancer resulted in enhanced tolerance to tamoxifen, partially by downregulating HDAC44.[372] An earlier investigation showed that miR-10b could increase invasion and migration in ESCC cells by targeting the KLF44 transcription factor.[373]

Wu et al.[374] found that overexpression of miR-10b and underexpression of the peroxisome proliferator-activated receptor-γ (PPARγ) were associated together in ESCC cells and tissues. PPARγ has been shown to be a target of miR-10b. Additionally, miR-10b inhibition increased the cisplatin chemosensitivity of ESCC cells *in vitro* and tumors *in vivo*. Furthermore, miR-10b overexpression abrogated the PPARγ-induced cisplatin sensitivity. Therefore, miR-10b targeted PPARγ and thereby activated the AKT/mTOR/p70S6K signaling pathway. AKT inhibitor (GSK690693) inactivated the AKT/mTOR/p70S6K signaling pathway and abrogated the miR-10b-mediated cisplatin resistance in the ESCC cells. Overall, miRNA-10b might be used to increase the response of esophageal cancer patients to DDP treatment.[374]

miR-96 expression has been found to be upregulated in non-small cell lung cancer,[375] breast cancer,[376] prostate cancer,[377] and bladder cancer.[378] Also, recent studies suggested that miR-96 could promote tumor growth by downregulating RECK expression in ESCC.[375–379]

Table 5 lists some miRNAs that could affect the response to chemotherapy agents in esophageal cancer.

lncRNAs AND RESPONSE TO CHEMOTHERAPY IN GI CANCER

lncRNAs and response to chemotherapy in GC

Some lncRNAs are critically involved in tumor development and are involved in various chemoresistance mechanisms, such as mutation of drug targets, increased drug efflux, inhibition of apoptosis, and DNA damage repair.[397] Furthermore, lncRNAs most often increase chemoresistance, whereas they hardly ever have the opposite effect. Figure 2 summarizes the respective pathways by which lncRNAs are involved in HCC, breast cancer, and lung cancer.

The lncRNA UCA1 increased metastasis and tumor growth in GC.[398,399] He et al.[400] reported that UCA1 expression could predict a poor prognosis in patients, and it could also modulate GC cell migration and proliferation *in vitro*. It was also reported that UCA1 could increase cisplatin resistance in ovarian cancer,[401] non-small cell lung cancer,[402] oral squamous cell carcinoma,[403] bladder cancer,[404] and GC.[405] UCA1 knockdown was reported to increase apoptosis by modulating the expression of Bax and cleaved caspase-3/9.[406] The activated protein Bax causes release of pro-apoptotic factors from the mitochondria into the cytoplasm to increase apoptosis.[407] EZH2 has a key role in modulating gene expression to increase cisplatin resistance in GC.[408,409] Overexpression of EZH2 promoted tumor development by activating the PI3K/AKT pathway.[398,410] The PI3K/AKT pathway also has a significant role in increasing chemoresistance.[411] Therefore, inhibition of the PI3K/AKT pathway will decrease drug resistance,

Table 5. Various microRNAs that affect chemotherapy response in esophageal cancer

MicroRNA	Expression in EC	Target	Drug	Model	Cell line	Ref.
miR-27b-3p, miR148a-3p	up	Sp1 and PPARy, DNMT-1, MSK-1, Bcl-2 and Bim	cisplatin	human	OE-19,OE-33, Flo-1, SKGT4, OACM5.1, OACP4C	380
miR-21	up	PDCD4	cisplatin	*in vitro*	Eca109/DDP	381
miR-143	up	lncRNA CCAT1	cisplatin	*in vitro*	ECA-109, TE-1, KYSE140, KYSE70, KYSE150, KYSE450	382
miR-142-5p	down	SREBP1	fatostatin	human	OE21, OE33	383
miR-141-3p	up	PTEN	5-FU, oxaliplatin	human	EC109, EC9706, TE-1, KYSE150	384
miR-224	up	DESC1	cisplatin, 5-FU + doxorubicin, doxorubicin + cisplatin, 5-FU + paclitaxel	*in vitro*	TE-13, KYSE140, EC9706, KYSE30	385
miR-130a, miR-148a-3p	up, down	Bcl-2	cisplatin, 5-FU	*In vitro*	KYSE70, KYSE140, KYSE270, KYSE410	380
miR-27	up	TGF–β	cisplatin	human	CAFs, NOFs	386
miR-196a	up	cyclin B1, ABCG2	cisplatin	*in vitro*	TE1, EC109	387
miR-145	down	REV3L	5-FU	*in vitro*	HEEC, TE-8, KYSE150, TE-1	357
miR-148a	down	MSK1, DNMT3B	cisplatin, 5-FU	*in vitro*	KYSE410	388
Let-7b	down	IL-6/STAT3 pathway	cisplatin	*in vitro*	TE1, TE5, TE8, TE9, TE10, TE11, TE13	389
miR-432-3p	up	KEAP1	cisplatin, 5-FU, actinomycin D	*in vitro*	KYSE170, KYSE770, KYSE2270	390
miR-499	down	polβ	cisplatin	*in vitro*	EC9706, KYSE30	391
miR-200c	up	PPP2R1B	cisplatin	*in vitro*	TE-1, TE-8, TE-10, TE-13, TE-15	392
miR-193a-3p	down	PSEN1	docetaxel, paclitaxel, vinorelbine, 5-FU	*in vitro*	KYSE150, KYSE410, KYSE450, KYSE510	361
miR-21	up		cisplatin, 5-FU	*in vitro*	KYSE170	393
miR-483-3p	up	E124	doxorubicin, cisplatin	*in vitro*	EC109, EC9706, TE-1	394
miR-181a-5p	up	CBLB	cisplatin	*in vitro*	OE19	365
miR-141	up	Yap1	cisplatin	*in vitro*	KYSE	28
miR-338-5p	down	Id-1	5-FU	*in vitro*	KYSE410, KYSE150, KYSE270	395
miR-10b	up	PPARγ	cisplatin	*in vitro*	EC109, TE10	374
miR-29c	down	FBXO31	5-FU	*in vitro*	KYSE150FR, KYSE410FR	396

thus restoring tumor sensitivity to chemotherapy drugs.[411] It has also been found that the PI3K/AKT pathway affects chemotherapy response by modulating anti-apoptotic proteins and drug efflux pumps.[412,413] It has been shown that the PI3K/AKT signaling pathway inhibits apoptosis by reducing the activity of caspase-9 and caspase-3.[412,413]

Dai et al.[414] investigated the role of UCA1 in the response of GC to cisplatin, as well as the underlying mechanism. Apoptosis assays and CCK-8 were employed to explore the effects of various doses of cisplatin on GC apoptosis and proliferation. They also investigated the association between EZH2 and UCA1 using western blotting and qRT-PCR. RNA pull-down and RIP assays were used to detect the relationship between EZH2 and UCA1. TCGA and the GEO database suggested that a higher expression of UCA1 in GC tissues was connected with worse patient prognosis. Moreover, UCA1 overexpression increased GC cell proliferation and prevented apoptosis caused by cisplatin. Knockdown of UCA1 produced the opposite results. UCA1 exerted its role by increasing EZH2 expression, while EZH2 knockdown lowered GC cell cisplatin resistance. Therefore, by increasing EZH2 and activating the PI3K/AKT pathway, UCA1 promoted GC cisplatin tolerance. Interventions directed at EZH2 or UCA1 could provide a therapeutic approach for cisplatin-resistant GC patients.[414]

The lncRNA FAM83H-AS1 is linked with poor prognosis in colon cancer, luminal subtype breast cancer, and cervical cancer.[415–417] Da et al.[418] found that FAM83H-AS1 was overexpressed in GC and may be a prognostic indicator in patients. However, they found that the expression level of FAM83H-AS1 was not linked to the clinical pathology, such as tumor-lymph node-metastasis (TNM) stage and tumor size.

Wang et al.[419] reported that FAM83H-AS1 was overexpressed in GC cell lines and tissues. It was correlated with invasion depth, poor

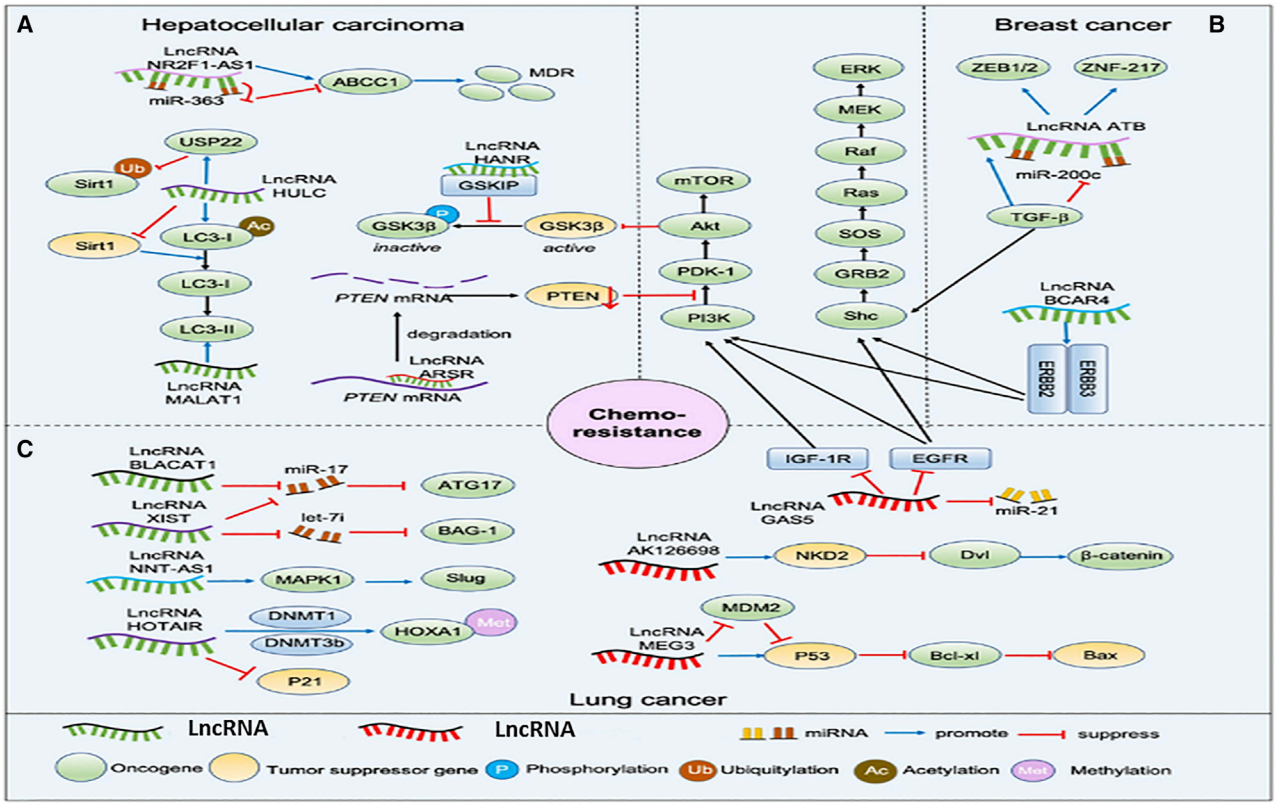

Figure 2. An overview of the role of lncRNAs in chemoresistance

(A) lncRNA-associated pathways in HCC. (B) lncRNA-associated pathways in breast cancer. (C) lncRNA-associated pathways in lung cancer.

differentiation, and chemoresistance in GC patients. FAM83H-AS1 was overexpressed in chemoresistant GC cell lines (SGC7901/R) and tissues. Furthermore, silencing of FAM83H-AS1 could sensitize SGC7901/R cells to 5-FU and cisplatin. Silencing of FAM83H-AS1 in SGC7901/R cells resulted in the inactivation of the Wnt/β-catenin signaling pathway. Activation of the Wnt/β-catenin signaling pathway reversed the effects of FAM83H-AS1 silencing on increasing chemosensitivity. They concluded that FAM83H-AS1 was involved in chemoresistance in GC patients by activating the Wnt/β-catenin signaling pathway.[419]

The relationship between miRNAs and lncRNAs has been widely investigated.[420] lncRNAs either stimulate or compete with certain specific miRNAs, which subsequently affect their target mRNAs, and some miRNAs may lower the longevity of certain lncRNAs.[420]

Cheng et al.[421] performed a study to explore the role and potential underlying mechanism of action of HOTAIR in modulating resistance to cisplatin in GC. Their study demonstrated that expression of HOTAIR was increased in GC tissues and cell lines, while miR-34a was downregulated. Using RIP assays and luciferase reporter assays, HOTAIR was found to have the potential to directly bind to miR-34a. miR-34a was remarkably upregulated in cells transfected with siRNA (si-)HOTAIR. In GC cells resistant to cisplatin, anti-miR-34a reduced the effect of si-HOTAIR on resistance to cisplatin and inhibited the Wnt/β-catenin and PI3K/Akt signaling pathways, as well as apoptosis-related genes, which suggests that the HOTAIR effects mainly depend on miR-34a. Additionally, HOTAIR suppression promoted the inhibitory effect of cisplatin on proliferation of tumors *in vivo*. Consequently, knockdown of HOTAIR suppressed resistance to cisplatin in GC cells through increasing expression of miR-34a. The HOTAIR/miR-34a axis may exert its effects on GC cells via the Wnt/β-catenin and PI3K/Akt signaling pathways. Their study suggested that HOTAIR may be a promising therapeutic target in patients with GC.[421]

Table 6 lists some lncRNAs that can affect the response to chemotherapy agents in GC.

lncRNAs and response to chemotherapy in PC

The lncRNA LINC00346 was upregulated in non-small cell lung and bladder cancer, and it was proposed to be a tumor promoter in these cancer types.[426,427] New research has shown overexpression of LINC00346 in PC, which could be a prognostic marker.[428] Overexpression of LINC00346 was correlated with shorter overall survival in PC patients.[428]

The function of LINC00346 in PC was investigated by Shi et al.[426] The effects of overexpression and knockdown of LINC00346 on

Table 6. Various lncRNAs that affect chemotherapy response in gastric cancer

lncRNA	Expression in GC	Target	Drug	Model	Type of cell line	Ref.
HOX transcript antisense RNA (HOTAIR)	down	miR-34a	cisplatin	*in vivo*	SGC7901, MGC803, GES1	421
lncR-D63785	down	miR-422a	doxorubicin	*in vitro*, *in vivo*	BGC823	422
LOC_006753	up	PI3K/AKT/mTOR	cisplatin, 5-FU	*in vivo*	SGC-7901/5-FU, SGC-7901/DDP	423
PVT-1	up		cisplatin	*in vivo*	BGC823, SGC7901	424
SNGH3	up	miR-3619-5p	cisplatin	*in vitro*	SGC7901 and BGC823	425
lncRNA UCA1	up	EZH2 and activation of PI3K/AKT pathway	cisplatin	human	HGC27, MKN45, MGC803, MKN28, AGS, SGC7901 GES-1	414
FAM83H-AS1	up	Wnt/β-catenin signaling	cisplatin, 5-FU	human	GES-1 SNU216, BGC823, SGC7901	419

proliferation, apoptosis, cell cycle, and resistance to gemcitabine were studied in PC cell lines. To explore the possible miRNAs that could be affected by LINC00346, a luciferase reporter assay, bioinformatics analysis, and RIP were employed. LINC00346 overexpression significantly increased PC cell proliferation, colony formation, and tumorigenesis. Conversely, LINC00346 knockdown suppressed the proliferation of PC cells and resulted in G_2/M cell cycle arrest. LINC00346 depletion increased the sensitivity of PC cells and xenograft tumors to gemcitabine. Mechanistic analysis showed that LINC00346 acted as a miR-188-3p sponge and blocked the downregulation of BRD4 (bromodomain-containing protein 4) caused by miR-188-3p in PC cells. A clinical study in PC tissue samples revealed a negative association between miR-188-3p and LINC00346. Rescue studies confirmed that LINC00346 attenuated the chemosensitizing and growth-inhibiting properties of miR-188-3p in PC. Silencing of BRD4 abrogated the increased colony formation and cell proliferation caused by LINC00346. They concluded that LINC00346 promoted PC resistance to gemcitabine by antagonizing miR-188-3p and increasing BRD4. LINC00346 targeting could boost the therapeutic effectiveness of gemcitabine in PC therapy.[426]

Table 7 lists some lncRNAs that could affect the response to chemotherapy agents in pancraatic cancer.

lncRNAs and response to chemotherapy in hepatic cancer

The lncRNA GAS5 (growth arrest-specific 5) was first identified to be involved in cell growth arrest.[430] Recent studies have demonstrated abnormal expression of GAS5 in a variety of human cancers. Researchers have shown downregulation of GAS5 in several cancer types, such as HCC, breast cancer, bladder cancer, and prostate cancer.[431,432] Decreased expression levels of GAS5 were detected in HCC cell lines and tissues compared to matched tissue samples. Low expression of GAS5 was associated with a shorter survival rate and lymph node metastasis in HCC patients. Cell cycle progression was inhibited by overexpression of GAS5, while proliferation and cell viability was enhanced by knockdown of GAS5 in several cancer cells, such as lung, gastric, and breast cancer.[433,434]

Wang et al.[435] investigated the role of lncRNA GAS5 and its molecular mechanism in HCC. They measured miR-21, GAS5, and PTEN levels using qRT-PCR. They used MTT and cell counting assays to measure proliferation *in vitro*, together with an *in vivo* xenograft mouse model. RIP and luciferase reporter assays were used to evaluate the correlation between GAS5 and miR-21. They demonstrated that GAS5 was underexpressed in tumor tissues as well as HCC cell lines. GAS5 knockdown was correlated with increased proliferation of HCC cells *in vitro* and in tumors *in vivo*. GAS5 knockdown also increased DOX resistance in HCC cells via acting as a sponge to silence miR-21, thereby resulting in PTEN overexpression. Their data revealed that GAS5 was a tumor suppressor in HCC via regulating the miR-21/PTEN signaling axis and indicated a possible role of GAS5 in HCC treatment.[435]

The lncRNA called cancer susceptibility candidate 2 (CASC2) is situated on chromosome 10q26 and has been found to act as a tumor suppressor in several human cancer types.[436] CASC2 has been found to be downregulated in HCC,[437] endometrial cancer,[438] and prostate cancer.[439] However, the role of CASC2 in HCC needs to be better understood. As mentioned above, many lncRNAs act by sponging certain specific miRNAs, and they thereby can affect the expression of the target genes of these miRNAs.[440,441] For instance, CASC2 was found to act as a competing endogenous RNA (ceRNA) to sponge miR-18a and therefore upregulate the target of miR-18a, which is PTEN. This could increase the chemosensitivity of cervical cancer cells to cisplatin.[441,442] By inhibiting autophagy and enhancing cell death, CASC2 was shown to function as a sponge of miR193a-5p and to increase glioma cell sensitivity to temozolomide. CASC2 could be a new therapeutic target for chemoresistant GC, since its overexpression increased the cisplatin sensitivity of GC cells by sponging miR-19a.[443]

The function and mechanism of CASC2 were investigated in a study by Liu et al. who looked at cisplatin-resistant HCC cells. The results showed that CASC2 was downregulated in HCC cells and tissues, particularly in those that were cisplatin resistant. Lower expression

Table 7. Various lncRNAs that affect the chemotherapy response in pancreatic cancer

lncRNA	Expression in pancreatic cancer	Target	Drug	Model	Type of cell line	Ref.
LINC00346	up	BRD4	gemcitabine	*in vitro*, *in vivo*	PANC-1, MIA PaCa-2, Capan-1, BxPC-3	[426]
SBF2-AS1	up	miR-142-3p	gemcitabine	*in vitro*, *in vivo*	AsPC-1/GEM, PANC-1/GEM	[429]

of CASC2 was correlated with shorter survival in HCC patients. CASC2 overexpression sensitized cisplatin-resistant HCC cell lines (SMMC-7721/cisplatin and Huh7/cisplatin) to cisplatin. Mechanistically, CASC2 increased the cisplatin sensitivity of HCC cells by sponging miR-222. These results showed that upregulation of CASC2 reduced cisplatin resistance in HCC by sponging miR-222, and could provide a route to overcome chemoresistance in HCC patients.[444]

The lncRNA celled TPTEP1 (transmembrane phosphatase with tensin homology pseudogene 1) has been found to have lower expression in kidney, liver, lung, and stomach cancer, because it is silenced by DNA methylation and has three transcript variants.[445] The expression of TPTEP1 could be restored by histone deacetylase inhibitors and by DNA demethylation.[445] Many studies have shown the effects of epigenetic alterations, such as DNA methylation, on the susceptibility of various cancers to chemotherapy,[446] including cisplatin sensitivity in cancer cells.[447,448]

A study by Ding et al.[449] explored the mechanism and differential expression of various lncRNAs using RNA sequencing (RNA-seq) in HCC cells during cisplatin therapy. They identified TPTEP1 as an important lncRNA in HCC cell lines (QYG-7703 and MHCC97H). Colony formation, qRT-PCR, cell invasion, cell proliferation, and flow cytometry assays were employed. Gain- and loss-of-function analysis, RNA pull-down, subcellular fractionation, western blotting, RIP, and dual-luciferase reporter assays were used to investigate the mechanism by which TPTEP1 could sensitize HCC cells to cisplatin. A subcutaneous xenograft animal model of HCC was used *in vivo*. qRT-PCR was used to detect TPTEP1 expression levels in clinical tumor specimens. The lncRNA TPTEP1 was found to be overexpressed in HCC cells treated with cisplatin and correlated with cisplatin-mediated apoptosis. TPTEP1 upregulation suppressed, whereas TPTEP1 knockdown increased, the proliferation, invasion, and tumorigenicity of HCC cells. TPTEP1 was found to exert its anti-tumor activity by interaction with signal transducer and transcription activator 3 (STAT3), where it inhibited STAT3 phosphorylation, homodimerization, nuclear translocation, and transcription of downstream genes. Furthermore, in an *in vivo* subcutaneous xenograft model of HCC, TPTEP1 upregulation clearly suppressed tumor growth *in vivo*. This agreed with the observation that TPTEP1 is often underexpressed in HCC tissues in comparison to normal liver samples. lncRNA TPTEP1 inhibited HCC development via altering interleukin (IL)-6/STAT3 signaling, and it could improve the response to chemotherapy.[449]

Table 8 lists some lncRNAs that could affect the response to chemotherapy agents in HCC.

lncRNAs and response to chemotherapy in CRC

BCYRN1 (brain cytoplasmic RNA 1) is a recently discovered lncRNA, which is activated by c-MYC.[457] BCYRN1 has been reported to be overexpressed in several cancer types,[458] such as HCC,[459] GC,[460] and lung cancer,[457] compared to healthy control tissues. Moreover, BCYRN1 also has a role in smooth muscle cell differentiation and vascularization within the cardiovascular system.[461,462]

Yang et al.[463] measured the expression levels of BCYRN1 in CRC tumor tissues and cell lines using RT-PCR. They used BCYRN1 knockdown in CRC cells to measure proliferation by 5-ethynyl-2′-deoxyuridine (EdU), CCK-8, and expression of proliferating cell nuclear antigen (PCNA) and Ki-67. Cell invasion and migration were assessed by a transwell assay and scratch wound healing. Flow cytometry analysis was used to determine whether BCYRN1 affected apoptosis. A dual-luciferase reporter assay was used to detect competitive binding of BCYRN1 to miR-204-3p, and *in vivo* experiments were conducted to assess the effects of BCYRN1 on tumor development. Rescue experiments confirmed that BCYRN1 could sponge miR-204-3p and thereby affect KRAS expression in CRC. Expression levels of BCYRN1 were higher in CRC cell lines and tumor tissues compared to normal intestinal epithelial cells and tissues. Knockdown of BCYRN1 inhibited proliferation, migration, and invasion and increased apoptosis. Furthermore, bioinformatics and a dual-luciferase reporter assay showed that BCYRN1 could competitively bind to miR-204-3p to promote CRC growth. Further experiments showed that miR-204-3p overexpression abrogated the effects of BCYRN1 on CRC. A dual-luciferase reporter assay and TargetScan suggested that KRAS was the miR-204-3p target gene. Tumorigenesis studies in a mouse model showed that tumor development was inhibited by BCYRN1 downregulation. Therefore, BCYRN1 modulates the KRAS/miR-204-3p axis and plays a tumor promoter function in CRC.[463]

Taurine upregulated gene 1 (TUG1) was initially characterized as a transcript that was overexpressed in the presence of taurine, and then found to be a lncRNA with a role in embryonic retinal growth.[464] Moreover, TUG1 overexpression was detected in gastric, bladder, and cervical cancer.[465–467] Alternatively, TUG1 was downregulated in non-small cell lung cancer,[468] suggesting contrasting functions in different types of cancer. Researchers recently observed that TUG1 could induce methotrexate resistance in CRC via affecting the CPEB2/miR-186 axis.[469]

Wang et al.[470] reported that the lncRNA TUG1 was associated with 5-FU resistance in CRC samples. TUG1 was substantially increased in samples from recurrent CRC patients. Kaplan-Meier survival analysis found that overexpression of TUG1 in CRC specimens was correlated with an increased risk of disease recurrence. In CRC cell lines, TUG1

Table 8. Various lncRNAs that can affect chemotherapy response in hepatic cancer

lncRNA	Expression in HCC	Target	Drug	Model	Type of cell line	Ref.
lncRNA PVT1	down	IL-6/STAT3 signaling	cisplatin	*in vitro*, *in vivo*	HepG2, SMMC-7721, QGY-7703, Huh-7, MHCC97h, SNU-449, Sk-hep1, L02	449
NR2F1-AS	up	ABCC1	oxaliplatin	*in vitro*, *in vivo*	Huh7, HepG2, Lo-2	450
p34710_v4	up	JAK-STAT signaling pathway	teriflunomide	*in vivo*	SMMC-7721	451
LINC000607	down	NF-κB p65/p53 signaling	5-FU, doxorubicin	*in vitro*, *in vivo*	MHCC97H, HCCLM3, PLC, Hep3B, HepG2, 7721	452
KCNQ1OT1	up	miR-7-5p/ABCC1 axis	oxaliplatin	*in vivo*	SMMC-7721, Huh7, SK-Hep-1, HepG2, Lo-2	453
TUC338	up	RASAL1	sorafenib	*in vivo*	HepG2, SMMC-7721, BEK-7402, Hep3B, Huh-7, L02	454
Growth arrest-specific 5 (GAS5)	down	miR-21-PTEN signaling pathway	doxorubicin	*in vitro*, *in vivo*	HepG2 HepB3, LO2	435
FOXD2-AS1	up	TMEM9 expression	sorafenib	human, *in vivo*	HepG2, HUH7	455
CASC2	up	miR-222	cispatin	*in vivo*, human	Huh7, SMMC-7721, HL-7702	456

knockdown could re-sensitize the cells to the effects of 5-FU. Additionally, bioinformatics research demonstrated that miR-197-3p could directly bind to TUG1, indicating that TUG1 might act as a miR-197-3p sponging ceRNA. TYMS (thymidylate synthase) was shown to be a direct target of miR-197-3p in CRC cells. The authors concluded that TUG1 could increase 5-FU resistance in CRC via the miR-197-3p/TYMS axis.[470]

Table 9 lists some lncRNAs that could affect the response to chemotherapy agents in CRC.

circRNAs AND RESPONSE TO CHEMOTHERAPY IN GI CANCER

The circ-ARHGAP26, known as circ_0074362, is located on chromosome 5 between location 142894237 and 142932125, with a length of 37,888 bp, and it has been detected in normal gastric cells and tissues.[472,473] Microarray analysis demonstrated that circ-ARHGAP26 was overexpressed in GC tissues in comparison with paired normal tissues, while the expression of circ-ARHGAP26 in GC tissues was found to be downregulated in other studies.[473,474]

A study by Wangxia et al.[475] reported that circ-ARHGAP26 was overexpressed in several GC cell lines (HGC-27, NCI-N87, AGS, SGC-7901, and BGC-823) compared to normal GSE-1 cells. Knockdown of circ-ARHGAP26 in HGC-27 cells decreased proliferation as measured by the CCK-8 assay at 48 and 72h, while flow cytometry showed that apoptosis was increased at 72 h. Western blotting showed that pro-apoptotic caspase-3 was increased while anti-apoptotic Bcl-2 was reduced at 72 h in the circ-ARHGAP26(−) group. Similar results were also found in AGS cells.[475]

It was shown that circRNAs may function as competitive inhibitors through binding to miRNAs, also known as "miRNA sponges," or alternatively these ncRNAs may function as target mimics and suppress the activity of certain miRNAs.[476–479] The circRNAs have binding sites for the complementary miRNA, which is located in the 3′ UTR or non-coding transcript of a particular gene.[480]

circ-PVT1 has been found to act as a ceRNA in an oral squamous carcinoma cell (OSCC) line to affect the miR-125b/STAT3 axis and thereby increase proliferation.[481] Upregulation of circ-PVT1 promoted invasion and proliferation in non-small cell lung cancer by activating E2F2 signaling.[482] Recent results showed that upregulation of circ-PVT1 also increased proliferation in GC and could be a prognostic marker.[483] A recent publication suggested that circ-PVT1 could increase resistance to DOX and cisplatin by regulating ABCB1 in osteosarcoma cells.[484]

Liu et al.[115] found that circ-PVT1 was overexpressed in PTX-resistant GC cells and tissues, and it could reduce the expression of miR-124-3p. Reduction of circ-PVT1 expression promoted PTX sensitivity in PTX-resistant GC cells. ZEB was suggested to be a direct target of miR-124-3p, and therefore circ-PVT1 could increase ZEB1 expression by sponging miR-124-3p. circ-PVT1 knockdown led to an increase in PTX sensitivity of GC tumors *in vivo*. Taken together, circ-PVT1 increased resistance to PTX by upregulating ZEB by sponging miR-124-3p and could be a target for GC treatment.[115]

Table 10 lists some circRNAs that can affect the response to chemotherapy agents in GI cancer.

CONCLUSIONS

Surgery is considered to be the main therapeutic approach for most GI cancers, but many cancers are diagnosed at an advanced stage, where they are then considered to be inoperable. Although chemotherapy and radiotherapy are then available, these approaches seldom result

Table 9. Various lncRNAs that affect chemotherapy response in colorectal cancer

lncRNA	Expression in colorectal cancer	Target	Drug	Model	Type of cell line	Ref.
PCAT6	up	HMGA2/PI3K signaling	5-FU	*in vitro*, *in vivo*	HCT116, HT-29, SW620, SW480, DLD-1, RKO, LoVo, HEK293, CCD-112CoN	471
TUG1	up	sponging miR-197-3p	5-FU	*in vivo*	HCT8Fu, HCT8	470
TUG1	up	miR186/CPEB2	methotrexate	*in vivo*	HT-29-P, HT-29-R, HCT-8	469
LINC00473	up	miR-15a	Taxol	*in vitro*, *in vivo*	FHC, HCT116, HCT116/Taxol, SW620, LoVo	443

in a complete cure. Thus, there is an urgent for major improvements in chemotherapy regimens in GI treatment. The poor response of most GI cancers to chemotherapy can be attributed to multiple mechanisms. Chemoresistance can have many causes such as reduced drug uptake, increased drug efflux, less activation of pro-drugs, changes in the molecular targets, better DNA repair mechanisms, disruption of the pro-apoptotic machinery, or overexpression of anti-apoptotic genes. Many new techniques derived from biotechnology and molecular biology, such as bioinformatics analysis, genome modification, high-throughput sequencing, pharmaceutical chemistry, and mouse modeling, have been used to reveal the wide involvement of a range of ncRNAs in the initiation, biology, progression, and response to treatment of various cancers. Put differently, the expression patterns of ncRNAs are very different in tumor tissue compared to the corresponding normal tissue. This enables ncRNAs to be used as biomarkers for disease progression and tumor stage. In addition, many lncRNAs, miRNAs, and circRNAs are specifically related to prognosis and therapeutic response, because they control resistance to radiotherapy and chemotherapy. Researchers have identified several genes in animal models with the use of single-stranded antisense oligonucleotides (ASOs) and double-stranded RNAi. As an example, inhibiting MALAT1 with ASO may promote differentiation and inhibit metastasis in mouse models of cancer,[494,495] including lung cancer.[496]

Researchers have attempted to employ ncRNA systems or carriers as therapeutic strategies, including oncolytic adenoviruses, nanoparticles (NPs), and direct delivery of modified ncRNAs. Some clinical trials have been based on ncRNA-mediated precision medicine (https://clinicaltrials.gov). Some clinical trials have reached phase 3, such as miR-31-5p and miR-31-3p for CRC,[497] as well as miR-200 and miR-21 for oral cancer.[498,499] Moreover, some circRNAs and lncRNAs have begun to be evaluated in trials, such as MALAT1 for breast cancer[494,495] or lung cancer,[500] and HOTAIR for thyroid cancer.[501] Furthermore, siRNAs are usually incorporated into lipid nanoparticles for delivery, and these have been tested in clinical trials. Phase 2 clinical trials of siRNAs include the use of Atu027 to knock down the *PKN3* gene to inhibit migration in metastatic pancreatic adenocarcinoma, and DCR-MYC to knock down the *MYC* gene to inhibit the cell cycle in HCC.[3] In the future, ncRNAs and modifiers may be used to improve the response of various cancers to therapies. However, there are many challenges to overcome before these techniques can be widely applied in clinics. First, ncRNAs vary widely in their length and number of nucleotides, as well as their modes of action. Second, ncRNAs are very different in different tumors, and therefore the selection of the appropriate target from multiple candidates would be difficult. Additional information on the functional parameters and genomic strategies is needed from fundamental and

Table 10. Various circular RNAs that affect chemotherapy response in GI cancer

Cancer	Circular RNA	Expression in GI cancers	Target	Drug	Model	Type of cell line	Ref.
Esophageal	circ-LARP4	down	miR-1323		*in vitro*	HEEPIC, ESCC (ECA109, TE-1, KYSE30, KYSE410)	485
Gastric	rc-ARHGAP26	up		not mentioned	*in vitro*	HGC-27, AGS, SGC-7901, BGC-823, NCI-N87, GSE-1	475
Gastric	circ-PVT1	up	ZEB1, miR-124-3p	paclitaxel	*in vitro*	MKN-45, HGC-27, MGC-803, AGS	115
Gastric	circ-MCTP2	down	MTMR3, miR-99a-5p	cisplatin	*in vitro*	BGC823, SGC7901, SGC7901CDDP	486
Gastric	ciRS-7	up	miR-7, PTEN, PI3K		*In vitro*	MGC-803, HGC-27, GES-1	487
Gastric	circ-FN1	up	miR-182-5p	cisplatin	*in vitro*	SGC7901CDDP, BGC823C, DDP, SGC7901, BGC823	488
Hepatocellular	circ-FBXO11	up	miR-605, FOXO3	oxaliplatin	human	HepG2, Hep3B, SMMC-7721, Huh7, Lo-2	489
Pancreatic	circ-HIPK3	up	miR-330-5p, RASSF1	gemcitabine	*in vitro*	PANC-1, SW 1990	490
Colorectal	circ_0032833	down	miR-125-5p, MSI1	5-FU, oxaliplatin	*in vitro*	HCT116	491
Colorectal	hsa_circ_001680	up	miR-340, BMI1	irinotecan	*in vitro*	FHC, HCT116, SW480, HCT15, SW620, CACO2, DLD1, LOVO, HT29, HCT8, RKO	492
Colorectal	ciRS-122	up	miR-122, PKM2	oxaliplatin	*in vitro*	SW480, HCT116, HEK293T	493

translational research. Third, besides the need for a suitable target, an effective delivery strategy that allows specific binding affinity is not easy. The tumor microenvironment has a highly heterogeneous composition, which makes application and delivery of ncRNAs very difficult. These challenges include off-target effects, low transfection efficacy, and a short half-life due to RNA degradation and instability. The present delivery systems will need to be significantly improved in future studies to overcome these challenges.

The use of targeted carriers or smart carriers may be an alternative option. For instance, the conjugation of nanoparticles to tissue-specific receptors could improve the target specificity. Another challenge is the bioavailability of nucleic acid-based therapeutics inside the tumor tissue, and reduction of cytotoxicity to normal tissues. Moreover, assay techniques must be agreed upon to ensure high quality and calculate the relative efficiency. Finally, most of the studies on the use of ncRNAs and modifiers are still in the preclinical phase, and most of them have been limited to a single type or a few types of cancer. After deciding on a suitable gene candidate and an efficient delivery carrier, further efforts will be needed to evaluate the patient responses to the clinical therapies. This is essential to understand the long-term outcomes of new cancer treatments that have never been assessed before. If these challenges can be overcome the use of ncRNAs/modifiers, either as tumor suppressors or inhibitors of oncogenes, could be an addition to standard chemotherapy or radiotherapy regimens to deal with resistance and improve patient survival in the coming years.

AUTHOR CONTRIBUTIONS

H.M. and M.R.H. contributed to conception, design, statistical analysis, and drafting of the manuscript. F.D., S.M.A.M., Nikta Rabiei, R.F., Negin Rabiei, H.P., and M.V. contributed to data collection and manuscript drafting. All authors approved the final version of the manuscript for submission.

DECLARATION OF INTERESTS

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