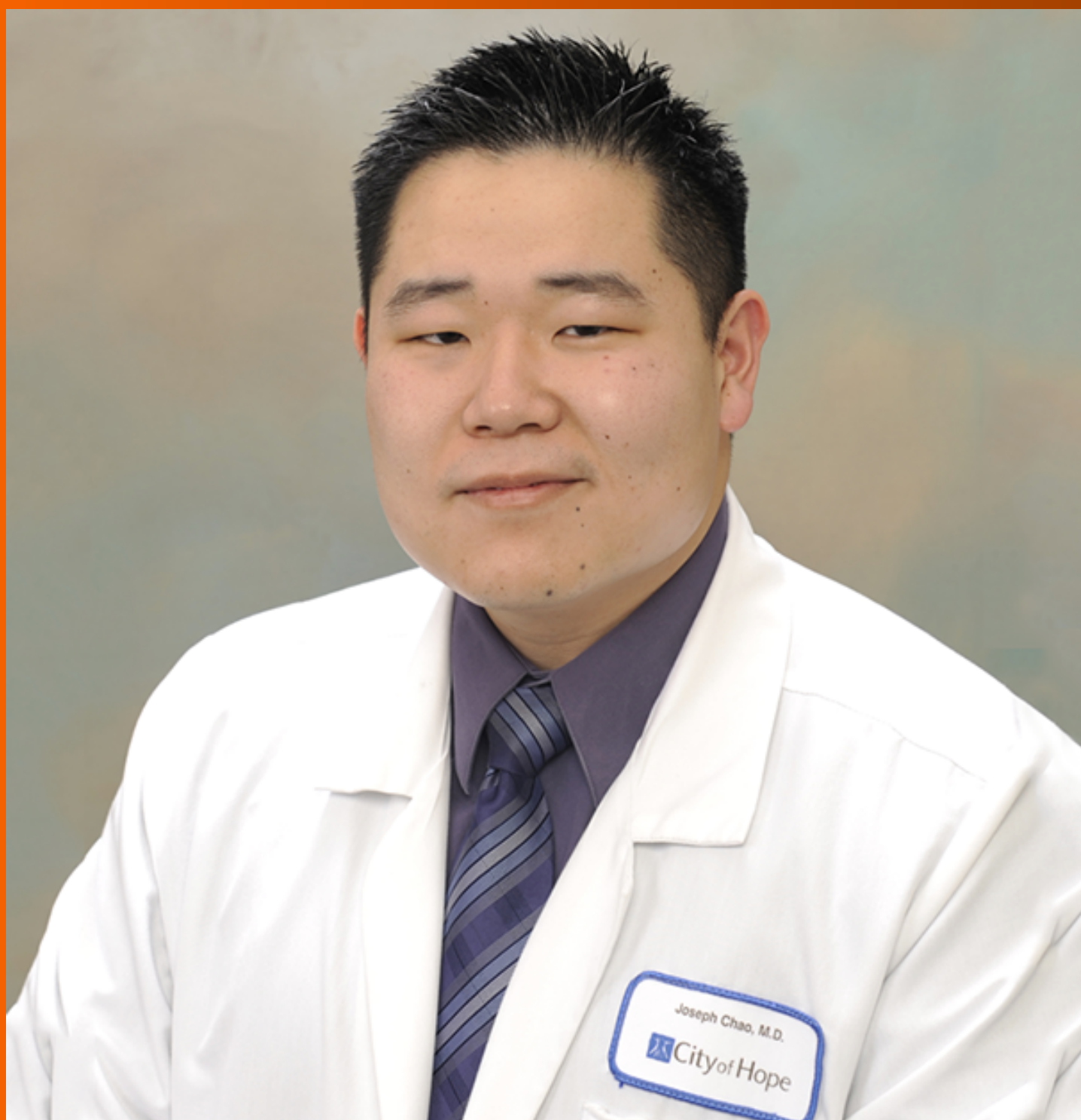


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Non-coding RNA in drug resistance of gastric cancer

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Abstract

Gastric cancer (GC) is the third leading cause of cancer-related mortality worldwide. The poorly prognosis and survival of GC are due to diagnose in an advanced, non-curable stage and with a limited response to chemotherapy. The acquisition of drug resistance accounts for the majority of therapy failure of chemotherapy in GC patients. Although the mechanisms of anticancer drug resistance have been broadly studied, the regulation of these mechanisms has not been completely understood. Accumulating evidence has recently highlighted the role of non-coding RNAs (ncRNAs), including long non-coding RNAs and microRNAs, in the development and maintenance of drug resistance due to their regulatory features in specific genes involved in the chemoresistant phenotype of GC. We review the literature on ncRNAs in drug resistance of GC. This review summarizes the current knowledge about the ncRNAs' characteristics, their regulation of the genes involved in chemoresistance and their potential as targeted therapies for personalized treatment in resistant GC.

Key words: Non-coding RNAs; Long non-coding RNAs; MicroRNAs; Drug resistance; Multidrug resistance; Gastric cancer

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Core tip: Many non-coding RNAs (ncRNAs, including long non-coding RNAs and microRNAs) are dysregulated in gastric cancer (GC) and involved in many cellular and genomic process and involved in drug resistance. The acquisition of drug resistance accounts for the majority of therapy failure of chemotherapy in GC patients. This review summarizes the current knowledge about the ncRNAs' characteristics, their regulation of

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the genes involved in chemoresistance of GC. These potential of ncRNAs as candidates to develop novel strategies to molecular targeted therapy or reverse the GC cell drug resistance for personalized treatment in GC.

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INTRODUCTION

Gastric cancer (GC) is one of the most prevalent malignant tumors with a high mortality rate^[1]. The standard curative treatment for GC is D2 surgical resection combined with chemotherapy, but in most patients, this is not possible because they are diagnosed in a non-curable stage for surgery. In spite of the advance in anti-cancer treatment for GC, the overall survival of GC patients remains dismal in recent years^[2]. The main reason for the low survival is drug resistance, which results in most of GC patients for limiting efficacy of chemotherapy. Although many novel anti-cancer agents are used in clinical practice, drug resistance is one of the causes of chemotherapy failure. Therefore, resistance to chemotherapeutic agents remains a major clinical challenge. Drug resistance is classified into two categories: intrinsic and acquired^[3]. The mechanism of drug resistance is complicated because of interaction various factors including apoptosis, the epithelial-mesenchymal transition (EMT), DNA damage repair, targets mutation or alteration and drug inactivation and efflux, resulting in multidrug resistance (MDR)^[4,5].

Non-coding RNAs (ncRNAs) are important regulators of gene expression and transcription, mainly in two distinct subtype forms: The most studied microRNAs (miRNAs) and the newly discovered long non-coding RNAs (lncRNAs). miRNAs are a class of single stranded ncRNAs of 19-25 nucleotides that negatively regulate gene expression by binding to the 3' or 5' untranslated region (UTR) of their target mRNAs which results in the mRNA silencing or degradation^[6]. Generally, lncRNAs are a class of no or limited protein-coding potential RNA transcripts with length longer than 200 nucleotides^[7]. ncRNAs have vital regulatory roles in many respects of genome function including gene epigenetics, splicing and transcription as well as biological processes related to cell differentiation, migration, cell cycle, apoptosis, angiogenesis, pluripotency and immune response^[8,9]. They plays a role in cancer development with disruption of their function through genomic imprinting, somatic mutations and post-transcriptional regulation^[10,11].

Interestingly, recent evidence suggests that ncRNAs, especially miRNAs and lncRNAs, play pivotal roles in regulating chemotherapy sensitivity in GC^[12,13]. ncRNAs are responsible for the resistance to chemotherapy as they moderate affect drug concentrations in intracellular, drug resistance-related genes, induce alternative signaling pathways, alter drug efficiency *via* blocking DNA damage response, cell cycle, prevent therapeutic-induced cell death and promote EMT^[3,14-16]. In this review, we summarize recent discoveries of the ncRNAs that in the regulation of drug resistance in the context of GC.

LONG NON-CODING RNAs

In recent studies, lncRNAs are widely recognized as crucial regulators in suppressing tumor and oncogenesis, and emerge as potentially vital mediators in regulating drug resistance through modulation of apoptosis, drug efflux system, drug metabolism, DNA repair, and EMT^[12,16,17]. The plenty of lncRNAs have been found to participate the development and progression of GC. However, only a little part has been confirmed their role in drug resistance regulation. We summarize the lncRNAs that have been related to MDR or single drug chemoresistance in GC in [Table 1](#) and [Table 2](#). As described below, the list of lncRNAs scientific paper involvement of in GC drug resistance, requires investigators to further for enhanced insight.

Dysregulated lncRNAs related with MDR in the treatment of GC

MDR occurs frequently during the long-term of traditional chemotherapy for GC,

Table 1 Summary of lncRNAs involved in multiple drug resistance in gastric cancer

| Dysregulation | LncRNA | Pathway/target | Corresponding drugs | Ref. |
|---------------|----------|---|---------------------|---------|
| Up-regulated | PVT1 | MDR1, MRP1, mTOR, HIF-1a | DDP | [22] |
| Up-regulated | AK022798 | MRP1, Caspase 3/8, P-gp, Notch1 | DDP | [23] |
| Up-regulated | HOTAIR | PI3K/AKT/MRP1, Wnt/ β -catenin, miR-34a | DDP | [24,25] |
| Up-regulated | MRUL | ABCB1, P-gp, PRL23, RPS13, JNK1, CPP32 | DOX, ADR | [26] |
| Up-regulated | ANRIL | MDR1, MRP1 | DDP, 5-Fu | [27] |
| Up-regulated | UCA1 | miR-27b, Bcl-2, Cleaved caspase-3 | DDP, 5-Fu, ADR | [28] |
| Up-regulated | MALAT1 | miR-23b-3p, ATG3/12, Autophagy | 5-Fu, VCR, DDP | [29] |
| Up-regulated | GHET1 | MDR1, MRP1, Bax, Bcl-2 | DDP | [30] |
| Up-regulated | CASC9 | MDR1 | PTX, ADR | [31] |
| Up-regulated | ZFAS1 | Wnt/ β -catenin, NKD2 | PTX, DDP | [32] |
| Up-regulated | HULC | Induced EMT, Suppressed apoptosis | DDP, ADR, 5-Fu | [33,34] |
| Up-regulated | BLACAT1 | ABCB1, MDR1, MRP1, LRP1, miR-361 | OXA | [35] |

DDP: Cisplatin; 5-Fu: 5-fluorouracil; VCR: Vincristine; ADR: Adriamycin; PTX: Paclitaxel; DOX: Doxorubicin; OXA: Oxaliplatin.

leading to the relapse of cancer and intractable tumor. Major mechanisms MDR are mediated by drug efflux transporter proteins^[18]. Notably, the ATP-binding cassette (ABC) transporter family regulate the drug flux across the multiple structurally plasma membrane and its unrelated drugs^[19]. The ABC transporter family at least have 48 members in humans, but only three have been studied extensively in relation to MDR, including breast cancer resistance protein, MDR protein 1 (MDR1) also known as P-glycoprotein (P-gp) and MDR-associated protein 1 (MRP1; also known as ABCB1)^[19]. GC patients who resistant to chemotherapy usually have a upregulation of various ABC transporter pumps, resulting in an increased drug efflux^[20]. The discovery of these various ABC transporters and its regulatory mechanism made potential targets for treatment chemotherapy resistance^[21].

LncRNA *PVT1* as an oncogene, which promotes the development of MDR in GC *via* increasing the expression of MDR related genes, such as *MDR1*, *MRP*, *mTOR* and *HIF-1a*^[22]. In another studies, lncRNA AK022798 was up-regulating by Notch 1 and could promote Cisplatin (DDP)-resistant GC formation *via* mediating MRP1, Caspase 3/8 and P-gp^[23]. LncRNA *HOTAIR* is an another oncogene related to MDR in GC, which not only inhibits DDP resistance of GC cells *via* suppressing the Wnt/ β -catenin and PI3K/Akt signaling by increasing miR-34a^[24], but also promotes DDP resistance by targeting miR-126 to activate the PI3K/AKT and MRP1 in GC^[25]. LncRNA *MRUL* promotes *ABCB1* expression and increases chemoresistance in MDR GC cell lines to P-gp related drugs. Moreover, down regulation of *MRUL* increases adriamycin (ADR) accumulation and ADR-induced apoptosis in MDR GC cell lines *via* mediating PRL23, RPS13, JNK1 and CPP32^[26]. Lan *et al*^[27] have found that lncRNA *ANRIL* was highly expressed in DDP-resistant and 5-fluorouracil (5-Fu)-resistant tissues and in GC cell lines of drug-resistant cells BGC823/DDP and BGC823/5-Fu. Furthermore, *ANRIL* positively correlated with the expression level of MRP1 and MDR1, and knockdown of *ANRIL* decreased the expression of MDR1 and MRP1. LncRNA *UCA1* was up-regulated in drug resistant GC cell lines SGC-7901/ADR, SGC-7901/DDP and SGC-7901/Fu, and *UCA1* could regulate miR-27b to increase ADR-induced cell apoptosis by decreasing expression of anti-apoptotic protein Bcl-2 and increasing expression of apoptotic protein cleaved caspase-3^[28]. *MALAT1* is a lncRNA that was identified to be related with cells carcinogenesis and was upregulated in 5-Fu/Vincristine (VCR)/DDP-resistant cells. Yiren *et al*^[29] provided a new insight into the function of *MALAT1* promotes autophagy related to drug resistance in GC cells through miR-23b-3p and demonstrated the capacity of lncRNA *MALAT1* to decrease chemosensitivity of GC cells. Additionally, *GHET1*, *CASC9* and *ZFAS1* were lncRNAs up-regulated in GC tissue. After transfected si-*GHET1* in BGC823/DDP and SGC7901/DDP cells, lncRNA *GHET1* reverse the MDR GC resistance by Bax, Bcl-2, MDR1 and MRP1^[30]. LncRNA *CASC9* could promote GC cell proliferation and inhibit GC cell apoptosis, and caused chemoresistance in BGC823/ADR and SGC7901/ADR GC cells associated with downregulation of MDR1^[31]. When knockdown *ZFAS1*, the migration, invasion, proliferation, cell cycle progress and EMT of SGC7901 cells were inhibited and chemotherapeutic resistance was decreased by blocking the Wnt/ β -catenin signaling^[32]. LncRNA *HULC* is a functional player in chemoresistance during the treatment of chemotherapy^[33]. To be specific, *HULC* could enhance

Table 2 Summary of other lncRNAs involved in single drug resistance in gastric cancer

| Drugs | lncRNA | Pathway/target | Dysregulation | Ref. |
|-------|--------|---|----------------|------|
| DDP | BCAR4 | β -catenin, Nanog, Klf4 Oct3/4, Sox2, c-Myc | Up-regulated | [36] |
| ADR | NEAT1 | Promoted cell apoptosis | Up-regulated | [37] |
| DOX | D63785 | miR-442a, MEF2D | Up-regulated | [38] |
| 5-Fu | LEIGG | Induced EMT, Vimentin, Snail, Slug, Zeb, Twist | Down-regulated | [39] |

DDP: Cisplatin; ADR: Adriamycin; DOX: Doxorubicin; 5-Fu: 5-fluorouracil.

chemoresistance through inducing EMT and suppressing apoptosis of GC cells^[34]. Accumulating evidence indicates that lncRNAs, which can be regulated cellular functions *via* sponging miRNA. lncRNA BLACAT1 was highly expression in the oxaliplatin (OXA) resistant GC, and BLACAT1 promotes OXA resistance through up-regulating ABCB1 expression by targeting miR-361 in GC^[35].

lncRNAs mediate single drug resistance of GC

Up-regulated lncRNAs in GC: lncRNAs play an irreplaceable role in the drug resistance of GC as an oncogene transcript. For instance, lncRNA BCAR4 was highly expressed in GC tissues and its expression level was related to tumor size, classification and the survival. Wang *et al*^[36] found BCAR4 was highly expression in DDP-resistant GC cell SGC7901/DDP. Furthermore, BCAR4 promotes drug resistance of ability of GC by regulating the level of Oct3/4, Sox2, c-Myc, β -catenin, Nanog and Klf4^[36]. Apoptosis is a critical underlying mechanism contributing to ADR resistance. lncRNA NEAT1 is up-regulated and functions as an oncogene in GC to regulate apoptosis and proliferation. And silence of NEAT1 could reverse ADR-resistant GC cell *via* targeting apoptosis-associated signaling pathways^[37]. lncRNA D63785 is also up regulated in GC and could accelerate cell invasion, proliferation and migration. Notably, D63785 promotes drug resistance by blocking MEF2D through targeting miR-422 in GC, which acts as a competitive endogenous RNA of miR-422a^[38].

Down-regulated lncRNAs in GC: lncRNAs also play an irreplaceable role in the drug resistance of GC as a tumour suppressor transcripts. For instance, lncRNA LEIGG is highly down-regulated as a tumour suppressor to enhances chemosensitivity to 5-Fu. Moreover, LEIGG also could suppress tumor growth, cell proliferation and EMT^[39].

MICRORNAS

Similar to lncRNAs, miRNAs isolated from GC tissues and body fluids also play a vital role in the diagnosis and prognosis of GC. Accumulating evidence indicates that the dysregulate pattern of miRNAs likely have a pivotal role in chemoresistance. More and more studies are confirming miRNAs play a critical role in the development and maintenance of drug resistance through the regulation of drug metabolizing enzymes or drug transporters, nuclear receptors and transcription factor, which may not only provide insight into miRNA biological functions, but advance the understanding of the integrated response of cells to xenobiotics^[13,40]. Therefore, we summarize the miRNAs that have been associated with MDR or single drug chemoresistance in GC in Table 3 and Table 4. The list of scientific literature depicting miRNAs in regulating drug resistance in GC, develops personalized treatment and targeted therapies for managing drug resistant GC.

Dysregulated miRNAs related with MDR in the treatment of GC

Upregulated miRNAs in GC: MiRNAs play a critical role in of GC as an oncogene transcript. For instance, miR-19a/b highly expressed in MDR GC cells and demethylation of miR-19a/b suppressed methyl CpG binding protein 2 expression through directly binding at the 3'-UTR, which leading to MDR^[41]. MiR-20a was elevated in GC and promoted the growth, migration and invasion of GC cells. It could not only adverse to DDP chemotherapy in DDP-treated GC patients and cells, but also make GC cells resistance to ADR and VCR. Du *et al*^[42] have found miR-20a could promote the development of DDP resistance by targeting NFKBIB in GC cells, leading to the activation of NFB and increase of its targets livin and survivin. Zhu *et al*^[43] revealed that miR-20a directly suppressed the level of CYLD, causing activation of the NFB signaling pathway which potentially induced GC drug resistance. In another

Table 3 Summary of miRNAs involved in multiple drug resistance in gastric cancer

| Dysregulation | miRNA | Pathway/target | Corresponding drugs | Ref. |
|----------------|------------|--|----------------------------|---------|
| Up-regulated | miR-19a/b | MeCP2 | 5-Fu, DDP | [41] |
| | miR-20a/b | LRIG1, EGFR, Livin, PI3K/ AKT, p65, CYLD, MAPK/ERK, Survivin, HIPK2, NFKB1B, NFB | 5-Fu, ADR, DDP, VCR | [42-46] |
| | miR-363 | FBW7, c-Myc, c-Jun, cyclin E | Docetaxel, DDP, 5-Fu | [47] |
| | miR-21 | PTEN, TIMP3, PI3K/ AKT | DOX, DDP, PTX, Trastuzumab | [48-52] |
| | miR-27a | HIF-1 α , GST- π , LRP, TS, MDR1/P-gp, Bcl-2 | OXA | [46,53] |
| | miR-135a | E2F1, P-gp, c-Myc, DAPK2, AP-2 α , Bcl-2 | OXA, ADR | [54,55] |
| Down-regulated | miR-23b-3p | MALAT1, ATG12, LC3-I, ATG3, HMGB2, LC3-II | VCR, DDP | [29,56] |
| | miR-34a | PI3K/ AKT/MRP1, HOTAIR, Wnt/ β -catenin, MET | DDP | [24,57] |
| | miR-495 | MDR1, ABCB1 | DDP, DOX, TAX | [58] |
| | miR1955p | ZNF139, P-gp, BCL-2, MRP1 | 5-Fu, OXA | [59] |
| | miR-30a | MDR1, P-gp, Snail, E-cadherin, N-cadherin, Vimentin | 5-Fu, DDP | [60-62] |
| | miR-101 | ANXA2, P-gp, VEGF-C | DDP, VCR | [64] |
| | miR-145 | CD44, Sox2, Oct4, Nanog | 5-Fu, DDP | [65] |
| | miR-129 | P-gp, Caspase-3/9, | DDP | [66] |
| | miR-27b | UCA1, Bcl-2, Cleaved caspase-3, HIF1A, MDR1, CCNG1 | ADR, DDP, 5-Fu | [28,67] |
| | miR-126 | EZH2 | VCR, ADR | [68] |
| | miR-16 | Cyclin J, FUBP1, hNIS, Bcl-2 | Lapatinib, ADR Trastuzumab | [69,70] |
| | miR-1284 | EIF4A1, Jun, MMP12, Myc | VCR | [71] |
| | miR-107 | Lin28, P-gp, c-Myc, cyclin D1, Bcl-2, CDK6, NF-kB, TOPOII, Cleaved caspase3/9 | OXA, PTX, 5-Fu, DOX | [72,73] |
| | miR-508-5p | P53, ABCB1, ZNRD1 | ADR, DDP, 5-Fu, VCR | [67] |
| | miR-218 | SMO, mTOR | OXA, 5-Fu, ADR, DDP | [74,75] |
| | let-7b | Lin28/Lin28B, c-Myc | DDP, VCR, 5-Fu | [76] |
| | miR-103 | Cav-1, P-gp | DOX, ADR | [73] |
| | miR-129-5p | ABCB1, ABCC5, ABCG1 | VCR, DDP, ADR, 5-Fu | [77] |
| | miR-185 | ARC, RUNX3 | DOX, DDP | [78] |
| | miR874 | ATG16L1, Autophagy | DDP | [79] |

5-Fu: 5-fluorouracil; DDP: Cisplatin; VCR: Vincristine; ADR: Adriamycin; PTX: Paclitaxel; TAX: Taxol; DOX: Doxorubicin; OXA: Oxaliplatin; P-gp: P-glycoprotein.

study, Li *et al* [44] found that miR-20a was involved in the chemoresistance of GC by regulation of the EGR2 signaling pathway. Furthermore, Zhou *et al* [45] also found miR-20a was highly expressed in MDR GC, which was identified to modulate LRIG1 expression by directly targeting its 3'-UTR, leading to chemoresistance *via* EGFR-mediated phosphatidylinositol 3 kinase/protein kinase B and MAPK/ERK signaling. Besides, miR-20b could directly regulate HIF1A expression, which increasing HIF-1 α levels, leading to MDR in GC hypoxia-induced chemoresistance [46].

Apart from those miRNAs mentioned above, miR-363, miR-21, miR-27a and miR-135a also show underlying ability to regulate MDR during the treatment of GC as an oncogene transcript. Up regulation of miR-363 not only as an independent predictor for postoperative relapse and lower survival, but also promotes GC cell proliferation and drug resistance by directly targeting F-box and WD repeat domain-containing 7 [47]. The miR-21 plays a vital role in modulating anti-tumor effect of MDR and contributes to the discrimination of chemoresistance in metastatic GC [48]. Notably, a recent clinical study found that trastuzumab provided a significant survival advantage in patients with HER2-positive GC. At present, acquisition of trastuzumab resistance is a primary limitation of trastuzumab-based chemotherapy. The miR-21 was proved to resistance to trastuzumab in GC by down-regulating PTEN and its downstream target p-AKT, which was significant for apoptosis signaling pathway [49]. Moreover, another studies demonstrated that miR-21 may modulate the sensitivity to paclitaxel (PTX) by regulating the expression of Pg [50], and exosomal transfer of tumor-related macrophages derived miR-21 contribute to DDP resistance in GC [51], even miR-21 contributes to doxorubicin (DOX) resistance in GC cells by targeting TIMP3 and PTEN [52]. The miR-27a was an another oncogene that could regulate HIF-1 α which is

Table 4 Summary of other miRNAs involved in single drug resistance in gastric cancer

| Drugs | miRNA | Pathway/target | Dysregulation | Ref. |
|-------------|---|--|----------------|----------|
| DDP | miR-193a-3p | CD44, SRSF2, Bcl-X, Bcl-2, caspase 9 | Up-regulated | [80] |
| DDP | miR-214 | PARP9, CD81, XRCC1, LIN28B | Up-regulated | [81] |
| DDP | miR-25 | FOXO3a, p27Kip1 | Up-regulated | [82] |
| DDP | miR-132 | SIRT1, CREB, ABCG2 | Up-regulated | [83] |
| DDP | miR-99a | CAPNS1, calpain1, calpain2, Caspase3, PARP1 | Up-regulated | [84] |
| DDP | miR-491 | | | |
| DDP | miR-421 | HIF-1 α , Snail, cleaved caspase-3, cleaved PARP, E-cadherin, N-cadherin, Fibronectin, Vimentin | Up-regulated | [85] |
| DDP | miR-493 | DKK1 | Up-regulated | [86] |
| DDP | miR-141 | KEAP1 | Up-regulated | [87] |
| DDP | miR-223 | FBXW7, CCND1/2/3, CCNE1/2, CCNE2, CDK2/4/6, p14, p16, p21, p27, c-Myc | Up-regulated | [88,89] |
| Trastuzumab | | | | |
| DDP | miR-604 | POLR2L, POLR2C, APRT, LMAN2 | Down-regulated | [90] |
| DDP | miR-17-5p | E2F1, p21, MCL1 | Down-regulated | [91] |
| DDP | miR-125b | HER2 | Down-regulated | [92] |
| DDP | miR-320a | ADAM10 | Down-regulated | [93] |
| DDP | miR-148a-3p | AKAP1, RAB12, DRP1 | Down-regulated | [94] |
| DDP | miR-200c | ZEB2 | Down-regulated | [95] |
| DDP | miR-524-5p | SOX9 | Down-regulated | [96] |
| DDP | miR-149 | FoxM1 | Down-regulated | [97] |
| DDP | miR-203 | Cleaved caspase-3/9, Bcl-w | Down-regulated | [98] |
| DDP | miR-29b | AKT2, PI3K/ Akt | Down-regulated | [99] |
| DDP | miR-26a | NRAS, E2F2 | Down-regulated | [100] |
| DDP | miR-143 | IGF1R, Bcl2 | Down-regulated | [101] |
| DDP | miR-503 | IGF1R, Bcl2 | Down-regulated | [102] |
| DDP | miR-1271 | IGF1R/IRS1, mTOR, Bcl2 | Down-regulated | [103] |
| DDP | miR-22 | ENO1 | Down-regulated | [105] |
| DDP/PTX | miR-181a | Autophagy, AKT/ERK | Down-regulated | [46,104] |
| 5-Fu | miR-193-3p | PTEN | Up-regulated | [106] |
| 5-Fu | miR-204 | TGFBR2, Induced EMT, TGF- β | Down-regulated | [107] |
| 5-Fu | miR-31 | RhoA | Down-regulated | [108] |
| 5-Fu | miR-939 | SLC34A2, Raf/MEK/ERK | Down-regulated | [109] |
| 5-Fu | miR-BART15-3p | TAX1BP1, NF-B | Down-regulated | [110] |
| 5-Fu | miR-197 | MAPK1 | Down-regulated | [111] |
| 5-Fu | miR-BART20-5p | BAD | Down-regulated | [112] |
| PTX | miR-3127-5p/ miR-1287/ miR-4713-5p | AKT/ERK | Up-regulated | [113] |
| PTX | miR-224/ miR-452/ miR-424/ miR-130a/ miR-193b | AKT/ERK | Down-regulated | [113] |
| Docetaxel | let-7a | HMGA2 | Up-regulated | [114] |
| DOX | miR-140 | SOX4, ABCC1, ABCG2 | Down-regulated | [115] |
| VCR | miR-647 | ANK2, FAK, MMP2, MMP12, CD44, SNAIL2 | Down-regulated | [116] |
| OXA | miR-361 | ABCB1, BLACAT1 | Down-regulated | [35] |
| TRAIL | miR-942 | ISG12a, AKT, ISG12a, Cleaved PARP | Up-regulated | [117] |
| Lapatinib | miR494 | FGFR2 | Down-regulated | [118] |

DDP: Cisplatin; 5-Fu: 5-fluorouracil; PTX: Paclitaxel; DOX: Doxorubicin; VCR: Vincristine; OXA: Oxaliplatin; TRAIL: Tumor necrosis factor-related

apoptosis-inducing ligand.

closely related to MDR in GC and may inhibits LRP, Bcl-2 and MDR1/P-gp^[46,53]. The miR-135a not only promotes OXA resistance by suppressing E2F1 and the Sp1/DAPK2 signaling^[54], but also increases Bcl-2 by AP-2 α and consequently increased cell to anti-apoptosis, leading to ADR resistance^[55].

Downregulated miRNAs in GC: As previously mentioned, miRNAs can regulate MDR of GC as a tumour suppressor transcripts. For instance, the miR-23b-3p not only acts as a competing endogenous RNA for lncRNA MALAT1 to inhibitory effect of ATG12, leading to chemo-induced autophagy and chemoresistance^[29], but also inhibited autophagy mediated by ATG12 and HMGB2 autophagy regulatory loop in MDR in GC^[56]. Similarly, the miR-34a also acts as competing endogenous RNA for lncRNA HOTAIR to regulate the activity of PI3K/AKT/MRP1 and Wnt/ β -catenin signaling pathways, leading to DDP resistance^[24]. Furthermore, the miR-34a could regulate GC cells the sensitivity to DDP by regulation of cell apoptosis and proliferation by targeting MET^[57]. In another study, Zou *et al*^[58] have found miR-495 could reduce expression of MDR1, leading to decrease drug efflux and improve the chemotherapeutic effect and reverse MDR in GC. The miR1955p was related to MDR of GC cells. Nie *et al*^[59] demonstrated that high expression of miR-195-5p negatively modulated the expression of ZNF139 and increased the chemosensitivity of GC cells through affecting the level of MRP1, P-gp and Bcl-2. EMT results in the acquisition of chemoresistance, miR-30a is an important miRNA modulating EMT of the cancer cells. Li *et al*^[60] found that miR-30a can decrease MDR of GC cells *via* modulating EMT. Wang *et al*^[61] also found that EMT is associated with DDP resistance and miR-30a modulating EMT and DDP sensitivity in GC. Moreover, miR-30 decreases MDR in human GC cells by LC3-II, modulating chemoresistance-associated autophagy^[62]. The miR-101 not only suppressed the proliferation and increased apoptosis of DDP-resistant GC cells *via* targeting VEGF-C^[63], but miR-101 negatively regulated ANXA2 expression, which reversed the effect of miR-101 on P-gp expression, alleviating chemoresistance of GC^[64]. The miR-145 targeting of CD44 plays vital roles in the modulation of caner growth and MDR in GC^[65], and the miR-129 targeting of P-gp regulates DDP-resistance in GC cells^[66]. Notably, the miR-27b could regulate lncRNA UCA1 to induce MDR of GC^[28] and miR27b was directly target of CCNG1 and was associated with miR-508-5p to regulate the level of P53, leading to MDR of GC^[67]. The miR-126 is another tumor suppressors that related to chemoresistance for GC, it is acts as a vital regulator in chemoresistance in GC cells through suppression EZH2 expression and by sensitizing GC cells to chemotherapy^[68]. The miR-16 role as tumor suppressor in GC, Venturutti *et al*^[69] miR-16 modulates lapatinib and trastuzumab response in ErbB-2-positive GC *via* its novel targets CCNJ and FUBP1. Besides, miR-16 plays a critical role in regulating the chemoresistance of GC cells to ADR, and miR-16 embed in magnetic nanoparticles, which hold great potential for increasing the sensitivity of GC cells to ADR in therapeutic application for treating drug-resistant GC^[70]. The miR-1284 modulates MDR of GC cells by directly increasing the level of Myc and reducing the level of MMP12, EIF4A1 and Jun^[71]. Teng *et al*^[72] found that miR-107 was down regulated by Lin28, thereby up-regulating C-myc, P-gp and down-regulating Cyclin D1, subsequently result in increasing GC cells resistance to the chemo-drugs OXA, PTX, DOX and 5-Fu. Zhang *et al*^[73] demonstrate that miR-107 was down-regulated in MDR GC cell lines and increased the sensitivity of GC cells to DOX *via* inhibiting drug efflux and suppressing P-gp expression. Importantly, miR-107 may reverse MDR by downregulating Cav-1 expression. The miR-218 promoted chemosensitivity of GC cells to DDP through its target mTOR^[74], and miR-218 inhibits MDR of GC cells by targeting Hedgehog/smoothened^[75]. Let-7 family consists of 11 closely related genes. Most of them acted as tumor suppressor like Let-7b. Let-7b promotes drug sensitivity in SGC7901/DDP and SGC7901/VCR GC cells *via* targeting c-Myc and that, overexpression let-7b could reverse MDR by promoting cell differentiation through a double-positive autoregulatory loop (Lin28/Lin28B/Myc) and double-negative autoregulatory loops (Lin28/let-7 and Myc/let-7) existing in GC cells^[76]. Besides, miR-103^[73], miR-129-5p^[77], miR-185^[78] and miR874^[79] also have shown a low expression and close correlation with MDR in GC.

MiRNAs mediate single drug resistance of GC

MiRNAs and cisplatin: Apoptosis is a critical underlying mechanism contributing to DDP resistance. Recently, numerous studies have shown that miRNAs work in regulating DDP resistance *via* targeting apoptosis-associated signaling. For instance, the miR-193a-3p was up-regulate in DDP resistance GC cells. Lee *et al*^[80] found that miR-193a-3p target SRSF2 and various isoforms of its downstream targets, including:

Bcl-X, Bcl-2 and caspase 9, leading to DDP resistance for GC cells. Wang *et al*^[81] reported that exosome-delivered anti-miR-214 could increase the sensitivity of GC cells to DDP. The miR-25 is upregulated in DDP-resistant GC cells, and contributes to DDP resistance in GC cells by inhibiting FOXO3a expression to promote cell cycle progression^[82]. Overexpression of miR-132 in GC stem cell-like cells promotes DDP-resistance through SIRT1/CREB/ABCG2 signaling^[83]. The miR-99a and miR-491 were up-regulated in DDP resistant GC cell lines and regulated DDP resistance in GC cells by targeting CAPNS1^[84]. The miRNA-421 regulated by HIF-1 α induces DDP resistance by targeting E-cadherin and caspase-3 in GC^[85]. The miR-493 played an oncogenic role in GC by directly targeting DKK1 and promoted invasion and DDP-resistance of GC cells^[86]. The miR-141 could mediate the level of KEAP1, leading to DDP resistance in *H. pylori* infection GC^[87]. The miR-223 increases the DDP resistance of GC cells through modulating cell cycle by targeting FBXW7^[88]. Another study revealed that the miR-223-FBXW7 axis could regulate the sensitivity to trastuzumab in HER2-positive GC cell lines due to change in HER2 downstream signaling^[89].

Apart from those oncogenic miRNAs mentioned above associated with DDP resistance, there are numerous miRNAs work as tumor suppressor gene also have shown DDP resistance. For instance, the miR-604 was significantly down-regulated in DDP-resistant GC. From bioinformation analysis, miR-604 has a very active sponge effect and can bind mRNAs from POLR2L, POLR2C, APRT, and LMAN2, which is associated with DDP resistance in GC^[90]. The miR-17-5p is down-regulated and inhibits drug resistance of GC cells partially through targeting p21^[91]. The miR-125b is significantly down-regulated in GC tissues and various cell lines. Meantime, miR-125b direct target HER2, and over expression of miR-125b could promote the chemosensitivity of DDP in GC cells and prolong the survival of GC patients^[92]. The miR-320a is down expression in GC cells and enhance the sensitivity of GC cells to DDP *via* directly regulate ADAM10^[93]. The miR-148a-3p downregulation as a key step involved in DDP resistance, and miR-148a-3p reconstitution in DDP-resistant GC cells inhibits the autophagy by suppressing RAB12 expression and mTOR1 activation^[94]. The miR-200c was significantly down-regulated in both GC tissues and SGC7901/DDP cells, and miR-200c regulates DDP resistance by targeting ZEB2 in GC cells^[95]. Overexpression of miR-524-5p increases the DDP sensitivity of GC cells *via* regulating metastasis and proliferation by targeting SOX9^[96]. The expression level of miR-149 was down-regulated in SGC7901/DDP cells, and miR-149 reverses DDP resistance of SGC7901/DDP cells by targeting FoxM1^[97]. In berberine treatment, miR-203 was modulated the Bcl-w apoptotic signaling to reduces DDP resistance of GC cells^[98]. The miR-29b could reduce DDP resistance of GC cell by targeting PI3K/Akt Pathway^[99]. The miR-26a was downregulated in DDP-resistant GC cells and miR-26a could promote the sensitivity of GC cells to DDP by targeting NRAS and E2F2^[100]. Both miR-143^[101], miR-503^[102] and miR-1271^[103] are involvement in DDP resistance of GC cells *via* targeting IGF1R and Bcl2. In addition, miR-181a^[104] and miR-22^[105] also have shown a low expression and associated with DDP resistance in GC.

MiRNAs and 5-fluorouracil: The miR-193-3p is aberrantly upregulated in GC, and downregulation of miR-193-3p inhibits 5-Fu resistance in human GC by regulating PTEN^[106]. Li *et al*^[107] found that miR-204 was significantly low expression in GC and decreased miR-204 associate with 5-Fu resistance through targeting the TGFBR2-mediated EMT in GC cells. The miR-31 suppresses RhoA-mediated cell invasion and 5-Fu resistance in MKN-45 GC cells^[108]. Furthermore, miR-939 acts as a tumor suppressor miRNA in GC, and decreased expression of miR-939 contributes to 5-Fu chemoresistance GC *via* dysregulation of SLC34A2 and Raf/MEK/ERK pathway^[109]. The miR-BART15-3p targets TAX1BP1 gene in GC cells, leading to promote apoptosis and chemosensitivity to 5-Fu^[110]. The miR-197 reverses the drug resistance of Fu-induced GC cells by targeting MAPK1^[111] and miR-BART20-5p increased chemoresistance to 5-Fu by directly targeting BAD^[112].

MiRNAs and Paclitaxel: PTX has shown encouraging activity in chemotherapy of advanced GC, but GC patients respond poorly to PTX-based chemotherapies. Wu *et al*^[113] reported that dysfunctions of miRNAs, including miR-130a, miR-181a-2-star, miR-224, miR-224-star, miR-424-3p, miR-452 and miR-193b-5p were downregulated in the PTX-resistant GC cell lines, whereas the other 3 miRs, including miR-1287, miR-3127-5p and miR-4713-5p were upregulated in the PTX-resistant GC cell lines. These miRs are associated with PTX-induced drug resistance in GC.

miRNAs and Docetaxel, DOX, VCR, OXA: Let-7a and HMGA2, its target, serve as biomarkers for chemoresistance against docetaxel in GC^[114]. The miR-140 was down-regulated in GC tissues and cell lines, which directly inhibits SOX4 to improve the viability effects of DOX^[115]. The miR-647 is decreased in GC and VCR-resistant GC

cells, and miR-647 regulates drug resistance through suppressing the levels of MMP2, MMP12, ANK2, FAK, CD44 and SNAIL2^[116]. The miR-361 acts as competing endogenous RNA for lncRNA BLACAT1 to modulates ABCB1 to promote OXA resistance of GC^[35].

miRNAs and TRAIL, Lapatinib: The miR-942 down-regulated of ISG12a through AKT leading to TRAIL resistance of GC cells^[117]. The miR494 could reverse lapatinib resistance in lapatinibresistant GC cells through down-regulated the expression level of FGFR2 and inhibited the formation of cancerinitiating cells^[118].

DISCUSSION

Chemoresistance is one of the main causes during the therapy of GC in clinic settings and need urgent solution. Thus, overcoming chemoresistance is critical for the treatment of GC. As part of the search for putative novel therapeutic targets in GC, ncRNAs have been studied popularity in recent years. Current studies have reported that lncRNAs and miRNAs are involved in all kinds of mechanisms of drug resistance in GC. Therefore, specific lncRNAs and miRNAs as therapies targeting might contribute to overcoming chemoresistance.

To achieve this goal, several strategies have been employed to develop ncRNA-based therapeutics have been devised that up-regulate the expression of ncRNAs that have a tumour-suppressive function or to down-regulate the function of oncogenic ncRNAs. Advanced experimental techniques including RNA-sequencing, high-throughput studies, genome wide association studies and CRISPR screens allow characterizing novel ncRNA roles in GC drug resistance. Molecular mechanisms of ncRNAs in GC constitute a complicated regulatory network. While, a large biological signal pathway of ncRNAs involved in drug resistance are still unknown. More mechanisms and functions of chemoresistance-related ncRNAs need to be further mined for advance of GC therapy, which may offer new approaches to reverse drug resistance. Interestingly, this paper finds that some miRNAs not only regulate mRNAs but have effects in regulating the lncRNA and circRNAs, a newly found large content of ncRNAs, which brings a bright research prospect. Characterising the underlying roles of those ncRNAs may be propitious to GC treatment. In addition, the knowledge of the emerging functions of lncRNAs, circRNAs and piRNAs in drug resistance or other biological behavior aspects in cancer are only the tip of the iceberg. Some reports have suggested that there are enormous regulation networks in the gene transcriptional level through miRNAs connected each other, thus playing roles in drug resistance. Further studies on the modulation of ncRNAs in drug resistance may help the identification of vital ncRNAs as promising candidates for treatment approaches and make a better understanding of GC biology. The evidence of ncRNAs in clinical application is still insufficient. More clinical trials need to be further launched in the future. We believe that targeting ncRNAs could be a novel strategy for achieving improved treatment outcomes for GC patients.

CONCLUSION

Many lncRNAs and miRNAs are dysregulated in GC and involved in many cellular and genomic process and also involved in carcinogenesis and drug resistance. Based on their characteristics of function and molecular mechanisms, ncRNAs places center stage in the biology of drug resistance of GC cells. Therefore, the potential of ncRNAs as candidates to develop novel strategies to molecular targeted therapy or reverse the GC cell drug resistance to chemotherapy.

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