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REVIEW

Research Progress in microRNA-Based Therapy for Gastric Cancer

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Abstract: Gastric cancer (GC) is one of the leading causes of tumor-related mortality. In addition to surgery and endoscopic resection, systemic therapy remains the main treatment option for GC, especially for advanced-stage disease and for cases not suitable for surgical therapy. Hence, improving the efficacy of systemic therapy is still an urgent problem to overcome. In the past decade, the essential roles of microRNAs (miRNAs) in tumor treatment have been increasingly recognized. In particular, miRNAs were recently shown to reverse the resistance to chemotherapy drugs such as 5-fluorouracil, cisplatin, and doxorubicin. Synthesized nanoparticles loaded with mimics or inhibitors of miRNAs can directly target tumor cells to suppress their growth. Moreover, exosomes may serve as promising safe carriers for mimics or inhibitors of miRNAs to treat GC. Some miRNAs have also been shown to play roles in the mechanism of action of other anti-tumor drugs. Therefore, in this review, we highlight the research progress on microRNA-based therapy in GC and discuss the challenges and prospects associated with this strategy. We believe that microRNA-based therapy has the potential to offer a clinical benefit to GC patients, and this review would contribute to and motivate further research to promote this field toward this ultimate goal.

Keywords: therapeutics, drug resistance, nanoparticles, treatment mechanism

Introduction

Gastric cancer (GC) has an extremely high rate of mortality and is ranked as one of the leading causes of cancer-related death worldwide.[1,2] Besides adequate surgical resection and endoscopic resection, adjuvant and neoadjuvant therapies are generally used to improve the disease-free survival and overall survival of patients with GC.[3,4] However, it remains an important challenge to develop more effective systematic treatments for GC, especially for patients with inoperable disease at diagnosis or recurrent disease after resection. The development of resistance to standard chemotherapy drugs such as 5-fluorouracil (5-FU), cisplatin, and doxorubicin has been the main cause of chemotherapy failure. Moreover, first-line targeted therapies such as trastuzumab and ramucirumab are not suitable for the majority of patients with GC.[5,6] Hence, extensive research effort has focused on solving this current treatment challenge by gaining a better understanding of the underlying pathogenic mechanisms and conducting preclinical studies for ultimate clinical application.

In the last decade, exploration of the roles of miRNAs in carcinogenesis, treatment response, and as potential therapeutic targets has attracted widespread attention, with substantial progress made in better understanding mechanisms.[7] On the basis of mechanism-related studies, there has been increasing effort made to

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further explore the practical applications of these fundamental findings, which have revealed the essential roles of microRNAs in tumor therapy.[8] For example, with respect to drug resistance, over-expression of miR-939 was shown to enhance 5-FU-induced chemosensitivity by suppressing cellular growth and inducing apoptosis both in vitro and in vivo.[9] Moreover, caudally injected exosomes loaded with the inhibitor of miR-214 (exo-anti-214) could reverse the chemoresistance to cisplatin in a nude mouse model of GC.[10] In addition, synthetic carriers have been used to deliver the confirmed anti-tumor miRNAs to the precise tumor site so as to directly inhibit GC, such as "PPP", which was constructed by modifying phenylboronic acid onto the surface of a polyamidoamine dendrimer and poly (ethylene glycol)-poly(ε-caprolactone) copolymers (PEG-PCL) nanoparticles coated with trastuzumab.[11,12] Indeed, these studies have led to a major advance in the clinical application of miRNAs. Moreover, these findings suggested that in addition to their function as biomarkers, miRNAs can also play roles in the treatment of tumors. Nevertheless, despite these many important findings, there has been no study that summarizes these recent advances in microRNA-based therapy for GC.

Therefore, in this review, we mainly focus on the advances in microRNA-based therapies for GC, including chemotherapy, targeted therapy, tumor immunotherapy, and others. In particular, we highlight the key miRNAs reported to affect the actions of commonly used chemotherapy drugs, which will facilitate further research on drug resistance. Moreover, the listed carriers that loaded mimics or inhibitors of miRNAs can emphasize the promising applications of anti-tumor miRNAs in targeted therapy and immunotherapy, which should promote their valuable consideration for clinical practice.

microRNA-Based Chemotherapy

Fluorouracil Resistance

According to the National Comprehensive Cancer Network clinical practice guidelines in GC, 5-FU is recommended as the first-line anti-tumor drug. Several miRNAs have been identified to participate in the anti-tumor mechanism of 5-FU by decreasing the expression levels of various target genes. For example, overexpression of miR-939, miR-623, miR-429, miR-204, miR-124 or miR-31 was shown to enhance 5-FU-induced chemosensitivity by compromising tumor cell growth or inducing apoptosis.[9,13–19] Among the above-mentioned miRNAs, miR-939 and miR-204 were the only two miRNAs with confirmed ability of reversing drug resistance both in vitro and in vivo, providing more convening evidence than others.[9,15] A role of miR-31 in chemosensitivity was reported by two separate research groups and may have more obvious effects.[17–19] Moreover, reduced miR-6785-5p, miR-193-3p, or miR-147 expression could also increase the chemosensitivity of GC to 5-FU.[20–22] Interestingly, miR-193-3p and miR-147 both target phosphatase and tensin homolog (*PTEN*) to exert their functions in GC.[21,22] In addition to miR-193-3p and miR-147, *PTEN* was identified as the target gene of numerous other miRNAs and to play a role in other drug resistance and treatment mechanisms of GC, which will be discussed in further detail below. The full list of miRNAs reported to be involved in the 5-FU resistance in GC to date is provided in Table 1.

Cisplatin Resistance

Cisplatin (DDP) is another first-line chemotherapy drug, and the mechanism of cisplatin resistance has been the most frequently studied according to our review of the literature. As shown in Table 2, the majority of reported miRNAs (34 at the time of writing this review) can reverse DDP resistance, whereas some miRNAs (13 included in this review) could induce DDP resistance. Overexpression of miR-421, miR-320a, miR-192-5p, miR-181a, miR-148a-3p, miR-145 and miR-let-7b, and reduced expression of miR-135b-5p and miR-21-5p could enhance the chemosensitivity to DDP, which was observed in both GC cell lines and in animal tumor models.[23–30] These miRNAs could become more promising targets for further clinical research after resolving some key technical problems, such as selecting suitable carrier for mimics and inhibitors of miRNAs. Moreover, although miR-218, miR-200c, miR-198, miR34a, and miR-30a were only investigated in cell lines, each of these microRNAs was reported to be involved in DDP resistance in more than one separate study,[32–40] suggesting that they warrant further attention.

The miRNAs reported to be involved in the mechanism of DDP resistance mainly influence the phosphatidylinositol 3-kinase (PI3K)/AKT, mitogen-activated protein kinase (MAPK), and nuclear factor kappa B (NF-κB) signaling pathway.[29,30,38,39,41–49] However, different miRNAs may have opposite effects on the same pathway. For example, miR-206 targets MAPK to enhance the chemosensitivity to DDP, and miR-135b-5p targets mammalian ste20-like kinase 1 (MST1) through the MAPK signaling pathway to induce drug resistance.[29,43] Thus, it may be necessary to consider the antagonistic effects of different miRNAs in reversing drug

Table 1 miRNAs Involved in the 5-Fluorouracil (5-FU) Resistance in Gastric Cancer

miRNA	Target(s)*	Expression Level**	Mechanism	Object***	Reference
miR-6785-5p	FOX4	↓	Apoptosis	Cell lines (SGC-7901/5-Fu)	[20]
miR-939	SLC34A2	↑	Enhance cell growth and apoptosis via Raf/EMK/EPK pathway	Cell lines (SGC7901, MNK45 and AGS) and in vivo (SGC7901)	[9]
miR-623	CCND1	↑	Apoptosis	Cell lines (SGC7901 and BGC823)	[13]
miR-429	Bcl-2	↑	Apoptosis	Cell lines (AGS)	[14]
miR-204	TGFBR2	↑	Suppressed TGFBR2-mediated EMT via TGFβ pathway	Cell lines (AGS and SGC7901) and in vivo (AGS)	[15]
miR-193-3p	PTEN	↓	Not investigated	Cell lines (AGS and MKN45)	[21]
miR-147	PTEN	↓	PI3K/AKT signaling pathway/ apoptosis	Cell lines (AGS and BGC823)	[22]
miR-124	EZH2	↑	Apoptosis	Cell line (AGS)	[16]
miR-31	ZH2	↑	G_2/M cell cycle arrest	Cell lines (AGS)	[17]
	RhoA	↑	Not investigated	Cell line (MKN45)	[18]
	E2F6/SMUG1	↑	Not investigated	Cell line (MKN45)	[19]

Notes: *Targets genes were confirmed by Western blotting, RT-qPCR or dual-luciferase. **Upregulation (↑) or downregulation (↓) of miRNAs enhance chemosensitivity. ***The drug resistance properties of microRNAs were investigated in cell lines or in vivo.

resistance in future studies. In addition, some genes were identified to be targets of more than one miRNA, such as survivin (miR-218, miR-34a), *PTEN* (miR-106a, miR-21-5p), P-glycoprotein (P-gp) (miR-129, miR-30a), and insulin-like growth factor 1 receptor (*IGF1R*) (miR-1271, miR-143).[30,32,38,46,48,50–53] Thus, it will be worth considering whether there is a synergistic effect between different miRNAs in future research on DDP resistance. Furthermore, some long non-coding RNAs (HOTAIR, MALAtl, CASC2) and circular RNAs (hsa_circ0081143, circAKT3) were found to function as competing endogenous RNAs in the regulation of cisplatin resistance.[36,39,45,54–56] These findings also provide more possibilities for microRNA-based therapies in GC treatment.

Other Single-Drug Resistance

Some studies have also indicated roles of miRNAs in the resistance of other clinically used chemotherapy drugs, including doxorubicin (DOX; also named adriamycin, ADR), paclitaxel (PTX), oxaliplatin (OXA), vincristine (VCR), taxol, and docetaxel (Table 3). DOX, as an anthracycline-based anti-tumor agent, is widely used for the treatment of various solid tumors such as GC. Increased expression levels of miR-494, miR-422a, miR-140, miR-103/107, and miR-16-1, and reduced levels of miR-501-5p and miR-21-5p promoted the chemosensitivity to DOX (for more details, refer to Table 3).[57–64] Among these, miR-103 and miR-107 were the only miRNAs demonstrated to have effects on resistance both in vitro and in vivo.[60] Another important miRNA that is taking the spotlight in chemotherapy resistance research is miR-21. miR-21-5p targets *PTEN* to induce both DOX and DDP resistance.[30,48,64] Other studies showed that miR-21 targets P-gp to induce PTX resistance.[65] Notably, *PTEN* is not only a target gene of miR-21-5p but is also a target of miR-193-3p, miR-147, and miR-106a.[21,22,46] Through targeting *PTEN*, miRNAs regulate 5-FU, DDP, and DOX resistance in GC.[21,22,30,46,48,64] Hence, we speculated that miR-21-5p and its target gene *PTEN* may play essential and broad roles in regulating drug resistance in GC.

As shown in Table 3, limited studies have been conducted to investigate the roles of miRNAs in the resistance mechanisms to other chemotherapy drugs. MiR-155-5p, miR-34c-5p, and miR-21 were found to be related to PTX resistance;[65–67] miR-361-3p, miR-135a, and miR-27a affect OXA resistance;[68–70] miR-1284 and miR-647 regulated VCR resistance;[71,72] and miR-200a inhibited taxol resistance, while miR-361-5p suppressed docetaxel

Table 2 miRNAs Involved in the Cisplatin (DDP) Resistance in Gastric Cancer

miRNA	Target(s)*	Expression Level**	Mechanism	Object***	Reference
miR-4295	LRIG1	↓	LRIG1-mediated EGFR/PI3K/Akt signaling pathway	Cell lines (MKN28 and MKN45)	[41]
miR-1271	IGF1R, IRS1, mROR, BCL2	↑	Apoptosis	Cell lines (SGC7901/DDP)	[52]
miR-646	CDK6	↑	hsa_circ_0081143/miR-646/CDK6	Cell lines (SGC7901 and MGC803)	[54]
miR-524-5p	SOX9	↑	Modulate proliferation and metastasis	Cell lines (SC-M1 and AZ521)	[116]
miR-421	E-cadherin, caspase-3	↑	HIF-1α/miR-421/E-cadherin and caspase	Cell lines (SGC7901 and AGS) and in vivo (SGC7901)	[23]
miR-375	ERBB2	↑	ERBB2/PI3K/Akt pathway	Cell lines (SGC7901 and SGC7901/DDP)	[42]
miR-320a	ADAM10	↑	Not investigated	Cell lines (SGC7901 and BGC823) and in vivo (SGC7901)	[24]
miR-218	survivin	↑	Not investigated	Cell lines (SGC7901 and SGC7901/DDP)	[32]
	Not investigated	↑	Not investigated	Cell lines (SGC7901)	[33]
miR-214	PARP9, XRCC, LIN28B, CD81	↓	Not investigated	Cell lines (SGC7901 and SGC7901/DDP)	[10]
miR-206	MAPK	↑	MAPK signaling pathway	Cell lines (SGC7901, SGC7901/DDP, BGC823 and BGC823/DDP)	[43]
miR-200c	ZEB2	↑	Not investigated	Cell lines (SGC7901/DDP)	[34]
	VEGFR, MMP9, RhoE	↑	Apoptosis	Cell line (KATOIII)	[35]
miR-198	PIK3R1	↑	circAKT3/miR-198/PIK3R1	Cell lines (BGC823/CDDP, SGC7901/CDDP)	[36]
	FGFR1	↑	Apoptosis	Cell line (SGC7901)	[37]
miR-193a-3p	SRSF2	↓	Mitochondrial apoptosis pathway	Cell lines (CD44+ MKN45 and CD44- MKN45)	[117]
miR-192-5p	ERCC3, ERCC4	↑	NER pathway	Cell lines (SGC7901 and SGC7901/DDP) and in vivo (SGC7901/DDP)	[25]
miR-181a	ATG5	↑	Autophagy	Cell lines (SGC7901/DDP) and in vivo (SGC7901/DDP)	[26]
miR-149	FoxM1	↑	Not investigated	Cell lines (SGC7901/DDP)	[118]
miR-148a-3p	AKAP1, RAB12	↑	Autophagy	Cell lines (BGC823/DDP and SGC7901/DDP) and in vivo (BGC823 and BGC823/CDDP)	[27]
miR-145	APRIL	↑	NF-κB signaling pathway	Cell lines (SGC7901 and AGS) and in vivo (AGS)	[31]
miR-143	IGF1R, BCL2	↑	Apoptosis	Cell lines (SGC7901/DDP)	[53]

(*Continued*)

Table 2 (Continued).

miRNA	Target(s)*	Expression Level**	Mechanism	Object***	Reference
miR-138-5p	ERCC1, ERCC4	↑	Not investigated	Cell lines (SGC7901/DDP)	[119]
miR-136	AEG-1, BCL2	↑	Apoptosis	Cell line (AGS)	[120]
miR-135b-5p	KLF4	↓	NF-κB signaling pathway	Cell lines (SNU1 and MKN45)	[44]
	MST1	↓	MAPK signaling pathway	Cell lines (MKN28 and MKN45) and in vivo (Not Mentioned)	[29]
miR-129	P-gp	↑	Apoptosis	Cell lines (BGC823/DDP and MKN45/DDP)	[50]
miR-126	EGFA, PIK3R2	↑	HOTAIR/miR-126/VEGFA and PIK3R2→PI3K/AKT/MRP1 pathway	Cell lines (SGC7901 and SGC7901/DDP)	[45]
miR-125b	HER2	↑	Not investigated	Cell lines (HGC27 and MGC803)	[121]
miR-106a	PTEN	↓	PTEN/Akt pathway	Cell line (SGC7901 and SGC7901/DDP)	[46]
miR-99a and miR-491	CAPNS1	↓	Not investigated	Cell lines (BGC823, BGC823/DDP, SGC7901 and SGC7901/DDP)	[122]
miR-34a	survivin	↑	PI3K/AKT/surviving signaling pathway	Cell lines (SGC7901 and SGC7901/DDP)	[38]
	ABCB1, ABCC, ABCG2	↑	HOTAIR/miR-34a→PI3K/Akt and Wnt/β-catenin signaling pathway	Cell lines (BGC823/DDP, and SGC7901/DDP)	[39]
	MET	↑	Proliferation and apoptosis	Cell lines (SGC7901 and SGC7901/DDP)	[40]
miR-30b	ATG5	↑	MALAt1/miR-30b/ATG5	Cell lines (AGS/DDP and HGC27/DDP)	[55]
miR-30a	Snail, Vimentin	↑	EMT	Cell lines (SGC7901 and SGC7901/DDP)	[123]
	P-gp	↑	Autophagy	Cell lines (SGC7901 and SGC7901/DDP)	[51]
miR-26a	NRAS, E2F2	↑	Not investigated	Cell lines (SGC7901 and SGC7901/DDP)	[124]
miR-25	FOXO3a	↓	Not investigated	Cell lines (SGC7901 and SGC7901/DDP)	[125]
miR-22	ENO1	↑	miR-22↑/ENO1↓/glycolysis↓→reverse cisplatin-resistance	Cell lines (BGC823/DDP and MGC803)	[126]
miR-21-5p	Caspase-8	↓	NF-λB/miR-21/caspase-8/P-gp	Cell lines(BGC823, BGC823/DDP, SGC7901 and SGC7901/DDP)	[47]
	PTEN	↓	PTEN/PI3K/Akt pathway	Cell lines (SGC7901 and SGC7901/DDP)	[48]
	PTEN	↓	PTEN/PI3K/Akt pathway	Cell lines (MFC and MGC803) and in vivo (MFC)	[30]
miR-20a	CYLD	↓	NF-κB signaling pathway	Cell lines (SGC7901 and SGC7901/DDP)	[49]
miR-19a	Not investigated	↓	CASC2(lncRNA)/miR-19a	Cell lines (BGC823, BGC823/DDP, SGC7901 and SGC7901/DDP)	[56]
miR-7	mTOR	↑	Not investigated	Cell line (SGC7901)	[127]

(*Continued*)

Table 2 (Continued).

miRNA	Target(s)*	Expression Level**	Mechanism	Object***	Reference
miR-let-7b	AURKB	↑	Not investigated	Cell lines (SGC7901/DDP) and in vivo (SGC7901/DDP)	[28]

Notes: *Targets genes were confirmed by Western blotting, RT-qPCR or dual-luciferase. **Upregulation (↑) or downregulation (↓) of miRNAs enhance chemosensitivity. ***The drug resistance properties of microRNAs were investigated in cell lines or in vivo.

resistance.[73,74] Among the above-mentioned miRNAs, only miR-135a, miR-1284, and miR-647 were studied both in vitro and in vivo.[69,71,72] Interestingly, miR-361-3p and miR-361-5p were reported to regulate the resistance of different drugs.[68,74] This indicates that to best exploit the potential of microRNA-based tumor therapies, we need to pay attention to both the 3p- and 5p-arms of the same miRNA in addition to considering the functions of different miRNAs.

Multidrug Resistance

Although chemotherapy resistance is a challenge for all cancer treatments, it is considered to be a particularly more complex problem in the clinical treatment of GC. In addition to single-drug resistance, multidrug resistance (MDR) may be even more common in clinical practice. Some studies have focused specifically on the roles of miRNAs in MDR (Table 4). Both in vitro and in vivo studies confirmed that miR-508-5p, miR-23b-3p, and miR-590-5p strongly regulate MDR.[75–79] Shang's group revealed that the restoration of miR-508-5p reversed the 5-FU, DDP, DOX, and VCR resistance of a xenograft in an animal model by targeting ATP binding cassette subfamily B member 1 (*ABCB1*) and zinc ribbon domain-containing 1 (*ZNRD1*).[75] The same group further identified that the miR-27b-*CCNG1-P53*-miR-508-5p axis regulated the MDR of GC.[76] They transplanted SGC7901/VCR cells into the right flanks of mice, which were then treated with an agomir for miR-27b or control oligonucleotides before 5-FU or DDP therapy, demonstrating that miR-27b overexpression reversed drug resistance. An et al[77] found that miR-23b-3p sensitized GC cells to 5-FU, DDP, and VCR by targeting autophagy-related gene 12 (*ATG12*) and high-mobility group box 2 (*HMGB2*). Subsequently, another study showed that the long non-coding RNA MALAT1 regulates autophagy-associated chemoresistance via the miR-23b-3p/ATG12 pathway.[78] Shen et al[79] found that miR-590-5p reduces the sensitivity of GC cells to DDP and PTX. To further verify the effect of miR-590-5p, stable miR-590-5p-expressing SGC7901 cells were inoculated into nude mice and the tumor-bearing mice were treated with DDP, demonstrating that miR-590-5p reduced chemosensitivity. Compared with other reported miRNAs related to MDR (see Table 4 for the full list), there is more sufficient and reliable preclinical evidence for these three above-mentioned miRNAs, demonstrating their suitability for further research toward their potential clinical application.

Figure 1 schematically illustrates the proposed relationship between chemotherapy drugs and relevant miRNAs based on the results of studies of single-drug resistance and MDR. Figure 2 shows the relationship between miRNAs that have an effect on drug resistance and their target genes. It is now clear that some miRNAs can regulate the resistance of different drugs simultaneously. Therefore, this review should be beneficial for the design of future drug resistance studies to select the most suitable miRNAs according to different clinical application purposes. Given the pace of this field along with continuous advances in sequencing technologies, we also believe that more miRNAs that participate in the drug resistance mechanisms will be discovered with further research.

microRNA-Based Targeted Therapy

Thus far, the majority of research focused on microRNA-based targeted therapy has focused on miRNAs that affect the resistance to targeted drugs (trastuzumab and lapatinib) and development of new types of transport carriers (synthetic nanoparticles/compounds and exosomes).

Trastuzumab and Lapatinib

Trastuzumab as a HER2-targeting antibody has been successfully used in combination with chemotherapy for the treatment of HER2-neu overexpressing GC. Trastuzumab resistance is considered to be a difficult problem in clinical application. Increased miR-223, miR-200c, and reduced miR-21 were reported to reverse trastuzumab resistance via different mechanisms.[80,81] MiR-223 could modulate apoptosis to enhance the sensitivity of a HER2-positive GC cell line to trastuzumab through targeting F-box and WD repeat domain-containing 7 (*FBXW7*),[80] whereas miR-200c inhibits TGF-β-induced epithelial–mesenchymal transition to restore

Table 3 miRNAs Involved in Other Drug Resistance in Gastric Cancer

miRNA	Drug	Target(s)*	Expression Level**	Mechanism	Object***	Ref.
miR-1284	VCR	EIF4A1	↑	Not investigated	Cell lines (SGC7901/VCR) and in vivo (SGC7901/VCR)	[71]
miR-647	VCR	ANK2	↑	Apoptosis	Cell lines (SGC7901/VCR) and in vivo (SGC7901/VCR)	[72]
miR-501-5p	DOX	BLID	↓	Akt signaling pathway	Cell lines (SGC7901 and SGC7901/ADR)	[62,63]
miR-494	DOX	PDE4D	↑	Not investigated	Cell line (AGS/DOX)	[57]
miR-422a	DOX	MEF2D	↑	lncR-D63785 /miR-422a/ MEF2D	Cell line (BGC823)	[58]
miR-361-3p	OXA	ABCB1	↑	lncR-BLACAT1 /miR-361/ ABCB1	Cell lines (BGC823/OXA and SGC7901/OXA)	[68]
miR-361-5p	Docetaxel	FOXM1	↑	PI3K/Akt/ mTOR pathway	Cell lines (SGC7901 and MKN28)	[74]
miR-200a	Taxol	β-catenin	↑	Wnt/β-catenin signaling pathway	Cell lines (SGC7901 and BGC823)	[73]
miR-155-5p	PTX	GATA3, TP53INP1	↓	Not investigated	Cell lines (MGC803 and MGC803/PTX)	[66]
miR-140	DOX	SOX4	↑	Not investigated	Cell line (HGC27)	[59]
miR-135a	OXA	E2F1	↓	Sp1/DAPK signaling pathway	Cell lines (SGC7901/OXA and MGC803/OXA) and in vivo(SGC7901/OXA and MGC803/OXA)	[69]
miR-103/107	DOX	Cav-1	↑	Not investigated	Cell lines (SGC7901/ADR) and in vivo (SGC7901/ADR)	[60]
miR-34c-5p	PTX	MAPT	↑	Not investigated	Cell lines (SGC7901 and SGC7901/VCR)	[67]
miR-27a	OXA	P-gp, LRP, Bcl-2	↑	HIF-α/miR-27a/ P-gp, LRP, Bcl-2	Cell line (OCUM-2MD3/OXA)	[70]
miR-21-5p	DOX	PTEN,TIMP3	↓	Not investigated	Cell line (SGC7901/DOX)	[64]
miR-21	PTX	P-gp	↓	Not investigated	Cell line (SGC7901 and SGC7901/PTX)	[65]
miR-16-1	DOX	FUBP1	↑	Not investigated	Cell line (SGC7901/DOX)	[61]

Notes: *Targets genes were confirmed by Western blotting, RT-qPCR or dual-luciferase. **Upregulation (↑) or downregulation (↓) of miRNAs enhance chemosensitivity. ***The drug resistance properties of microRNAs were investigated in cell lines or in vivo.
Abbreviations: VCR, vincristine; DOX (ADR), doxorubicin (adriamycin); OXA, oxaliplatin; PTX, paclitaxel.

trastuzumab sensitivity through inhibiting zinc finger E-box binding homeobox 1 (*ZEB1*) and *ZEB2*,[81] and miR-21 significantly suppressed trastuzumab-induced apoptosis and decreased the sensitivity of GC cells to trastuzumab through regulating *PTEN* expression.[82] In addition to the above three miRNAs, Sun et al[83] reported a correlation between miR-125b and trastuzumab resistance according to the clinicopathologic characteristics of patients with GC. Nishida et al[84] reported that the inhibitory effect of miR-125a-5p on GC proliferation was enhanced in combination with trastuzumab. As an alternative strategy, nanoparticles coated with trastuzumab were used as carriers to transfer miRNAs or

Table 4 miRNAs Involved in Multidrug Resistance (MDR) in Gastric Cancer

miRNA	Drug	Target(s)*	Expression Level**	Mechanism	Object***	Reference
miR-874	DDP, 5-FU, VCR	ATG16 L1	↑	Apoptosis	Cell lines (SGC7901 and SGC7901/DDP)	[128]
miR-633	DDP, DOX,	FADD	↑	Foxo3a/miR-633/FADD	Cell lines (SGC7901)	[129]
miR-590-5p	DDP, PTX	RECK	↓	AKT/ERK and STAT3 signaling pathway	Cell lines (SGC7901 and BGC823) and in vivo (SGC7901)	[79]
miR-567	5-FU, OXA	PIK3AP1	↑	miR-567-PIK3AP1-PI3K/AKT-c-Myc	Cell lines (MGC803 and BGC823)	[130]
miR-508-5p	5-FU, DDP, VCR, DOX	ABCB1, ZNRD1	↑	Not investigated	Cell lines (SGC7901/VCR and SGC7901/ADR) and in vivo (SGC7901/VCR)	[75]
miR-495	5-FU, DDP, DOX, MMC	ERBB2	↑	mTOR signaling pathway	Cell line (SGC7901)	[131]
miR-363	5-FU, DDP, Docetaxel	FBW7	↓	Not investigated	Cell lines (MGC803 and HGC27)	[132]
miR-217	DOX, PTX	Not investigated	↑	HOTAIR/miR-217	Cell line (SGC7901)	[133]
miR-200c	DDP, Cetuximab	RhoE	↑	Not investigated	Cell line (SGC7901/DDP)	[134]
miR-195-5p	5-FU, OXA	ZNF139	↑	Not investigated	Cell line (MKN28)	[135]
miR-185	5-FU, DOX, XOA	Not investigated	↓	ZNF139/miR-185	Cell line (SGC7901 and SGC7901/ADR)	[136]
miR-181b	5-FU, DDP, DOX, VCR, VP-16	BCL2	↑	Not investigated	Cell lines (A549/DDP and SGC7901/VCR)	[137]
miR-126	VCR, DOX	EZH2	↑	Not investigated	Cell lines (SGC7901/VCR and SGC7901/ADR)	[138]
miR-107	5-FU, DOX, PTX, OXA	Not investigated	↑	Lin-28/miR-107	Cell lines (MKN45 and MKN48)	[139]
miR-101	DDP, VCR	ANXA2	↑	Not investigated	Cell lines (SGC7901/DDP andSGC7901/VCR)	[140]
miR-96	DDP, DOX	FOXO1	↓	miR-96/FOXO1/p21	Cell lines (SGC7901)	[141]
miR-33b-5p	DDP, Docetaxel	HMGA2	↑	Not investigated	Cell lines (SGC7901 and MGC803)	[142]
miR-30a	DDP, 5-FU	P-gp	↑	Decrease the MDR-related protein P-gp	Cell lines (SGC7901 and SGC7901/DDP)	[143]
miR-29c	DDP, Docetaxel	CTNND1	↑	Not investigated	Cell lines (MGC803 and HGC27)	[144]

(*Continued*)

Table 4 (Continued).

miRNA	Drug	Target(s)*	Expression Level**	Mechanism	Object***	Reference
miR-27b	5-FU, DDP, DOX	Not investigated	↑	LncRNA-UCA1 /miR-27b/	Cell lines (SGC7901/ADR)	[145]
	5-FU, DDP, VCR, DOX	CCNG1	↑	miR-27b/CCNG1/ P53/miR-508-5p/ ABCB1, ZNRD1	Cell lines (SGC7901, SGC7901/ADR and SGC7901/VCR)	[75,76]
miR-23b-3p	5-FU, DDP, VCR	ATG12, HMGB2	↑	miR-23b-3p/ATG12/ HMGB2/autophagy	Cell lines (5-FU, DDP, VCR)(SGC7901 and SGC7901/VCR) and in vivo (5-FU, DDP) (SGC7901/VCR)	[77]
		ATG12	↑	Lnc RNA MALAT1/ miR-23b-3p/ autophagy	Cell lines (5-FU, DDP, VCR)(SGC7901 and SGC7901/VCR) and in vivo (DDP) (SGC7901/VCR)	[78]
miR-BART20 -5p	5-FU, Docetaxel	BAD	↓	Not investigated	Cell lines (AGS)	[146]
miR-19a/b	5-FU, DDP	MeCP2	↓	Not investigated	Cell lines (SGC7901)	[147]
miR-17	5-FU, DDP	DEDD	↓	Apoptosis	Cell lines (SGC7901 and AGS)	[148]
miR-15b, miR-16	DDP, DOX, VCR, VP-16	BCL2	↑	Apoptosis	Cell lines (SGC7901 and SGC7901/VCR)	[149]

Notes: *Targets genes were confirmed by Western blotting, RT-qPCR or dual-luciferase. **Upregulation (↑) or downregulation (↓) of miRNAs enhance chemosensitivity. ***The drug resistance properties of microRNAs were investigated in cell lines or in vivo.
Abbreviations: DDP, cisplatin; 5-FU, 5-fluorouracil; VCR, vincristine; DOX (ADR), doxorubicin (adriamycin); PTX, paclitaxel; OXA, oxaliplatin; L-OHP, oxaliplatin; VP-16, etoposide; MMC, mitomycin.

chemotherapy drugs to the target, which will be discussed further in the following section.

Lapatinib, a type of tyrosine kinase inhibitor, is also commonly used in GC targeted treatment. The resistance to lapatinib can be reversed by miR-494.[85] Like trastuzumab, lapatinib can induce miR-16 upregulation in GC sensitive cells via inhibition of c-Myc and the PI3K/AKT and Erk1/2 pathways.[86]

Synthetic Nanoparticles and Compounds

As mentioned above, some studies have explored the applications of nanoparticles loaded with mimics/inhibitors of miRNAs or some other tumor-targeting compounds. Song's team constructed a tumor-targeted gene carrier, PPP, through modification of phenylboronic acid onto the surface of a polyamidoamine dendrimer.[11] The carrier PPP showed favorable miRNAs binding and condensation ability, protected miRNAs against nuclease degradation, and mediated the cellular uptake of miRNAs.[11] Jang's team used nanovesicles containing poly (l-lysine-graft-imidazole) (PLI)/ miRNA complexes (NVs/miR) to systemically deliver miRNA to the target site.[87] Incorporation of hydrophilic PEG molecules on the nanoparticle surface could further prolong the blood circulation. Li's team loaded sorafenib (SRF) and all-trans retinoic acid (ATRA) in PEGylated solid lipid nanoparticles (SLNs) composed of Gelucire, and loaded miRNA onto the surface of the SLNs based on the electrostatic interaction.[88] Liu's team employed intelligent gelatinases-stimuli nanoparticles to co-deliver miRNA and docetaxel to inhibit cancer stem cells.[89] Hu's team and Wu's team each introduced PCL-PEG nanoparticles coated with trastuzumab (HER-PEG-PCL NPs) to control the delivery of the inhibitor of miRNA.[12,90] These studies, respectively, verified the inhibitory function of miR-34a, miR-21, miR-542-3p, and miR-200c on GC in vitro or in vivo. Importantly, these strategies involve the use of synthetic nanoparticles and compounds to attempt to solve the problem of improving microRNAs-targeted transport to tumors so as to promote the clinical application of microRNA-based targeted therapies.

Exosomes

Exosomes are nanosized extracellular membrane-derived vesicles that are secreted by various cells. In 2007, miRNAs were first identified to be transferred in exosomes.[91] In a study

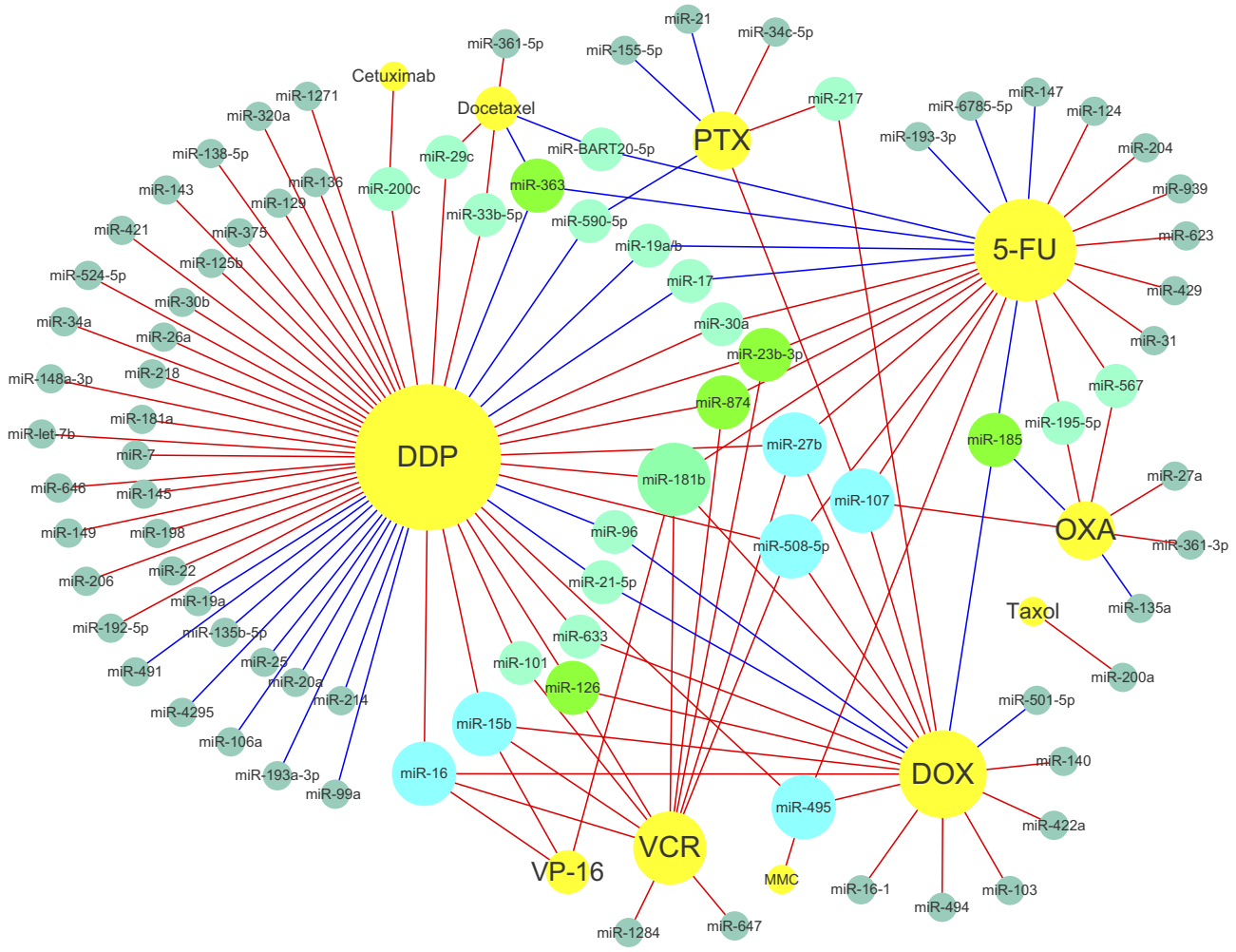

Figure 1 Schematic diagram showing the proposed relationship between chemotherapy drugs and relevant miRNAs based on the results of studies of single-drug resistance and MDR. Increased miRNAs (red lines connected) and reduced miRNAs (blue lines connected) could enhance chemosensitivity.
Abbreviations: DDP, cisplatin; 5-FU, 5-fluorouracil; VCR, vincristine; DOX (ADR), doxorubicin (adriamycin); PTX, paclitaxel; OXA, oxaliplatin; L-OHP, oxaliplatin; VP-16, etoposide; MMC, mitomycin.

on the DDP resistance mechanism, miR-21 was identified within the exosomes secreted by tumor-associated macrophages and could be directly transferred from macrophages to GC cells to promote DDP resistance.[30] Similarly, the exosomal transfer of miR-501-5p from DOX-resistant GC SGC7901/ADR cells to SGC7901 cells enhanced recipient cell growth, metastasis, and chemoresistance.[62] Moreover, the exosomal delivery of miR-155-5p was suggested to induce chemoresistant phenotypes from paclitaxel-resistant GC cells to sensitive cells.[66] Given the potential of genetic exchange between cells via exosomes, they have been considered as an alternative promising tool for therapeutic purposes, including in microRNA-based treatment. To support this possibility, one study transfected inhibitors of miR-214 and a negative control into HEK293T cells, and exosomes extracted from the cell medium after 48 h were verified to contain the inhibitor of miR-214, which reversed the resistance to DDP both in GC cells and in vivo.[10] In applications for reversing drug resistance or directly suppressing tumors, exosomes containing mimics or inhibitors of miRNAs are likely safer than synthetic nanoparticles and compounds. However, more research is needed to solve exosome-related technical problems, such as the lack of methods to interfere with the packaging of cargo or with vesicle release, before microRNA-based targeted therapies can become a reality.[92]

microRNA-Based Tumor Immunotherapy

In the past decade, tumor immunotherapy has made great progress in both scientific research and clinical application. Novel drugs target immune checkpoint molecules, such as programmed cell death protein 1 (PD-1), PD-1

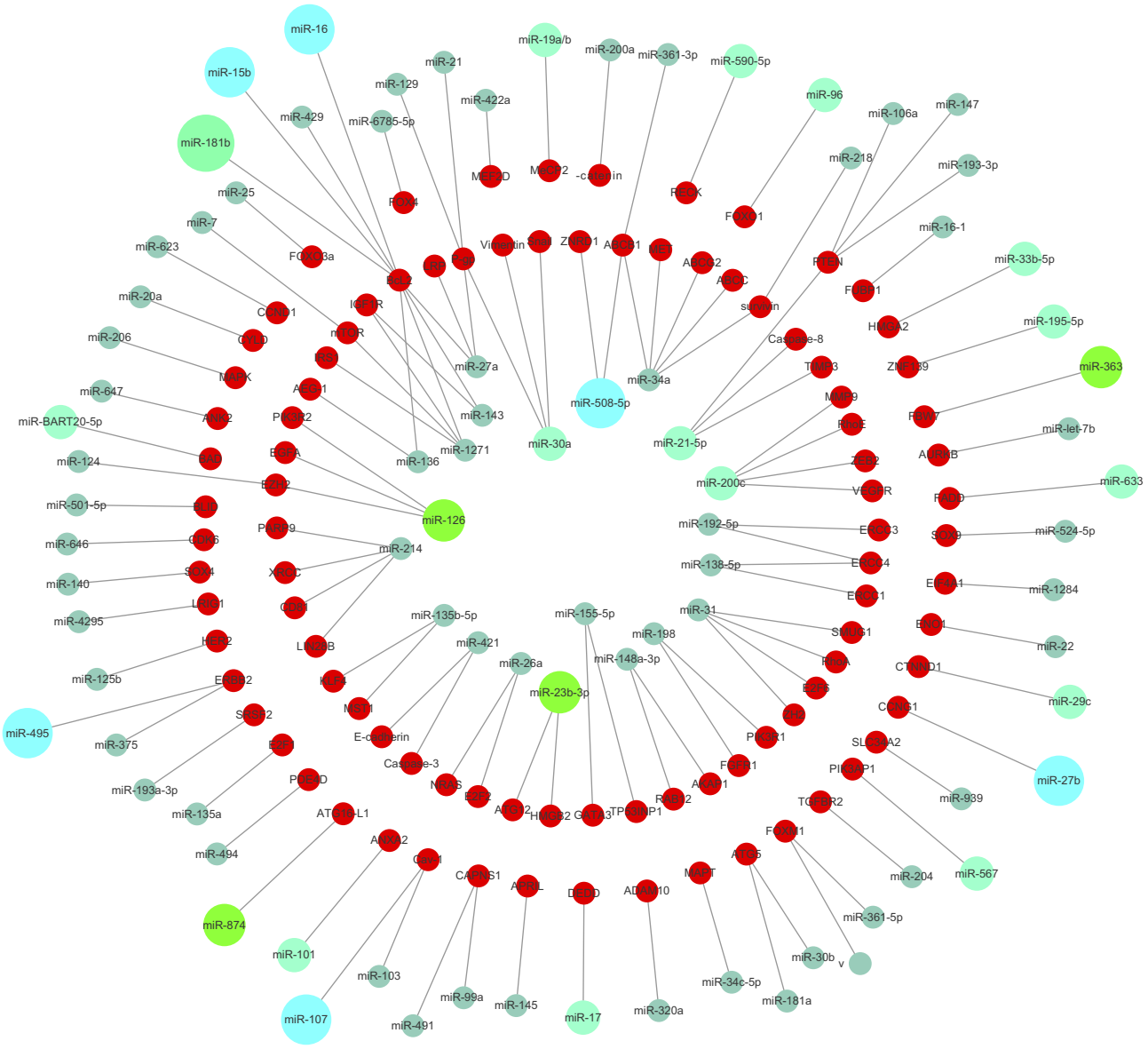

Figure 2 Schematic diagram showing the relationship between target genes and miRNAs related to drug resistance.

ligand cytotoxic, and T lymphocyte antigen-4 (CTLA-4), and augment T-cell activity. The use of immune checkpoint inhibitors has been approved in several tumors, and they are showing remarkable clinical effects. However, only a limited number of GC patients respond to tumor immunotherapy. Few studies have focused on the functions of miRNAs in immunotherapy for GC. Fan et al[93] reported that Cbl proto-oncogene B (Cbl-b) as a target gene of miR-940 interacted and ubiquitinated signal transducer and activator of transcription 5a (STAT5a) and down-regulated the expression of STAT5a and anti-programmed death ligand-1 (PD-L1). The miR-940/Cbl-b/STAT5a/PD-L1 axis promoted the proliferation and migration of gastric cancer cells. Accordingly, similar researches can perhaps provide some new ideas and conjectures for microRNA-based immunotherapies of GC.

microRNA-Based Other Therapies

The upstream regulatory mechanism of miRNAs, such as hypermethylation in the promoter region and transcription factor dysregulation, affects the expression of miRNAs. Some miRNAs play key roles in GC tumorigenesis, proliferation, metastasis, and recurrence. In theory, many genes and miRNAs in these processes could become potential therapeutic targets. However, there are too many possible miRNAs and related mechanisms involved in GC to give a detailed

Table 5 miRNAs Involved in Treatment Mechanisms of Anti-Tumor Drugs

miRNA	Drug	Mechanism	Object*	Reference
miR-4670-5p	Aspirin	Aspirin→miR-4670-5p↓→suppress proliferation	Cell lines (MKN45, NUGC3 and AGS) and in vivo (MKN45)	[99]
miR-940	PD-L1	miR-940↑→Cbl-b↓→ubiquitination regulation of STAT5a→ PD-L1↑→promote proliferation and migration of GC	Cell lines (MGC803, AGS, NCI-N87 and MKN74) and in vivo (MGC803)	[93]
miR-494	Cinobufacini	Cinobufacini→miR-494↑→BAG-1↓→inhibit cell proliferation and promote apoptosis	Cell lines (BGC823 and SGC7901)	[97,98]
	TNF-related apoptosis-inducing ligand (TRAIL)	miR-494↑→survivin↓→sensitize GC cells to TRAIL-induced cytotoxicity	Cell lines (BGC823 and MGC803)	[103]
miR-493	Dickkopf-1 (DKK1)	miR-493↑→DKK1↓→promote proliferation, invasion and chemo-resistance	Cell lines (SGC7901, MKN28, AGS and MGC803) and in vivo (MGC803 and SGC7901)	[100]
miR-388-5p	Anticancer bioactive peptide-3 (ACBP-3)	ACBP-3→miR-338-5p↑, BAK↑, BIM↑→inhibit gastric cancer stem cell (GCSC) proliferation and induce apoptosis and lower the required effective dose of DDP or 5-FU	Cell lines (MKN45, MKN74 and GES-1)	[150]
miR-298	Bufalin	Bufalin →miR-298↓→BAX↑→inhibit proliferation and promote apoptosis	Cell lines (MKN45, MGC803, SGC7901 and GES-1)	[151]
miR-203	Berberine (BER)	BER→miR-203↑→Bcl-w→reduce DDP resistance	Cell lines (SGC7901, BGC823, SGC7901/DDP and BGC823/DDP)	[152]
miR-195	Propofol	Propofol→miR-195↑→inactivate JAK/STAT and NF-λB pathway→suppress proliferation, migration, invasion and promote apoptosis	Cell lines (MKN45)	[153]
miR-181a	Kaempferol	Kaempferol→miR-181a↑→inactivate MAPK/ERK and PI3K pathway→suppress proliferation and promote autophagy, but not apoptosis	Cell lines (SNU216 and GES-1)	[154]
miR-133a	Ursolic acid (UA)	UA→miR-133a↑→Bax/caspase 3/Bcl2↓→inhibit GC growth and metastasis	Cell lines (BGC823)	[155]
miR-124	Sulforaphane (SFN)	SFN→miR-124↑→IL-6R↓, STAT3↓→enhance the anti-cancer function of DDP	Cell lines (MGC803 and BGC823)	[104]
	Paeoniflorin	Paeoniflorin→ miR-124↑→inhibit PI3K/Akt and STAT3 signaling→inhibit cell viability and induce apoptosis	Cell lines (MGC803 and GES-1)	[105]
miR-106b	Docosahexaenoic acid (DHA)	DHA+docetaxel→MMP2↓and DHA lower the docetaxel-mediated upregulation of miR-106b	Cell lines (MKN45)	[156]
miR-34a	Luteolin	Luteolin→miR-34a↑→HK1↓→p53/p21 and MAPK/ERK pathway→inhibit GC and induce G1 phase arrest→modulate the susceptibility of GC to luteolin	Cell lines (AGS, BGC823 and SGC7901)	[106]
		Luteolin→miR-34a↑→Bcl-2↓→inhibit proliferation and induce apoptosis	Cell lines (BGC823 and SGC7901)	[107]
	Diallyl disulfide (DADS)	DADS→miR-34a↑→inhibit PI3K/Akt signaling pathway→inhibit invasion and induce apoptosis	Cell lines (SGC7901)	[108]
	Chrysin	Chrysin loaded PLGA-PEG-PLGA rather than free chrysin→miR-34a↑	Cell lines (AGS)	[109]

(*Continued*)

Table 5 (Continued).

miRNA	Drug	Mechanism	Object*	Reference
miR-30e	3,3′-Diindolylmethane (DIM)	DIM→miR-30e↓→ATG5↑→block autophagy and inhibit the proliferation	Cell lines (BGC823 and SGC7901) and in vivo (BGC823)	[101]
miR-21	Cyclooxygenase-2 inhibitor NS398	NS398→miR-21↓→Bcl2↓, Bax↑, Bak↑, PTEN↑→induce apoptosis and decrease invasiveness	Cell lines (AGS)	[110]
	Celastrol	Celastrol→miR-21↓→inactivate PTEN/PI3K/AKT and nuclear factor κB signaling pathway→inhibit proliferation, migration, invasion and induce apoptosis, G2/M cell cycle arrest.	Cell lines (MKN45)	[111]
	Aspirin and lapatinib	Aspirin and lapatinib→ VEGF↓→miR-21↓→PPARα↑→attenuate PI3K/AKT signaling→inhibit proliferation and migration	Cell lines (MKN1, MKN45, MKN74 and IM95)	[112]
miR-18a, miR-21, miR-221	Chrysin	Chrysin loaded PLGA-PEG nanoparticles more effective than free chrysin→miR-18a↓, miR-21↓, miR-221↓	Cell lines (AGS)	[157,158]
miR-17-5p	Shenqifuzheng (SQFZ)	SQFZ→amplify the effects of si-HOTAIR, miR-17-5p inhibitor and overexpression of PTEN on boosting the chemosensitivity of GC	Cell lines (MGC803, SGC7901, BGC83, MKN28 and GES-1)	[159]
miR-16-5p	Melatonin	Melatonin→miR-16-5p↓→Smad3↑→inhibit the growth and induce apoptosis of GC	Cell lines (BSG823 and SGC7901)	[160]
miR-9 and miR-326	Sulforaphane extracted from broccoli sprout (SEBS)	SEBS→aberrant expression of miR-9, miR-326, CDX1, CDX2 →anti-proliferative effects	Cell lines (AGS)	[113]
miR-9 and Let-7	Chrysin	Chrysin-PLGA-PEG nanoparticles are more effective than pure chrysin→miR-9↑, Let-7a↑	Cell lines (AGS)	[114]
miR-7	Canolol	Canolol→miR-7↑→block up of COX-2/PGE signaling pathway→inhibit the gastritis-related tumor initiation and progression	Cell lines (AGS) and in vivo (K19-C2mE transgenic mice model which could develop hyperplastic tumors spontaneously in the glandular stomach)	[102]

Notes: *The drug resistance properties of microRNAs were investigated in cell lines or in vivo.

description of them in just one paper. Some miRNAs, regarded as potential therapeutic targets, have also had been reviewed elsewhere.[94–96] Our review focused more on discussing miRNAs that are more promising for clinical use. We believe that miRNAs that have an effect on GC treatment (including chemotherapy, targeted therapy, immunotherapy, and others) could also become core targets in microRNA-based therapies. It is reported that some drugs with anti-tumor effects may play roles by altering the expression of miRNAs and their related pathways. For example, cinobufacini, which is widely used in the treatment of advanced cancers, was reported to suppress cell proliferation and induce apoptosis in GC by regulating the miR-494-BAG-1 (BCL2 associated athanogene 1) axis.[97,98] Table 5 summarizes the 24 microRNAs reported to be involved in the mechanism of other anti-tumor drugs in GC treatment. Some miRNAs, such as miR-4670-5p, miR-940, miR-493, miR-30e, and miR-7, have been shown to have anti-tumor effects both in vitro and in vivo,[99–102] and other miRNAs, such as miR-494, miR-124, miR-34a, miR-21, and miR-9, have been investigated in more than one study.[97–114]

Future Prospects and Challenges

Since Ma et al[115] first reported that miRNAs affected the biological behavior of tumors in 2007, more and more functions of miRNAs have been described and more and more miRNAs have been identified in different tumors, including GC. With the continual development of research on miRNAs, scientists are no longer satisfied with

exploration of mechanisms but are now actively trying to realize the goal of clinical application and translation of achievements from the laboratory to clinical practice. Hence, microRNAs-based therapy is expected to become a promising research direction and ultimately benefit patients with GC.

The goal of the present review was not only to summarize the relevant literature and advances on the roles of miRNAs in GC treatment, but to further attempt at answering several existing questions. First, we wondered which aspects of GC treatment will microRNA-based therapies be best suited for. As reviewed herein, miRNAs can function in reversing drug resistance, directly inhibiting tumors, or enhancing the anti-tumor effects of drugs. Here, we have mainly focused on the potential for curbing drug resistance and the enhancing the anti-tumor effects of drugs. In terms of directly inhibiting tumors, we have highlighted only some key representative studies, as this field is extremely rich and therefore a comprehensive review is outside of the overall scope. Second, we have tried to assess which miRNAs are most suitable for therapeutic applications. We believe that the miRNAs verified in animal experiments and in more than one study are more reliable for further investigation. Of course, we also acknowledge that this perspective is limited by the extent and scope of current research. Therefore, further verification and screening are needed in future studies. Third, we want to determine the best method to realize the utilization of these miRNAs. Synthesized oligonucleotides of miRNA mimics or inhibitors have been used in an animal tumor model for several years with good results. However, before clinical application, more safety, targeting, and stability issues of this approach need to be considered. Recently, the application of synthetic nanoparticles/compounds and exosomes provides more promising possibilities; however, these techniques also require the combined efforts of doctors, pharmacists, and scientists of other disciplines.

Overall, we believe that this field is currently at an explosive stage of discovery, and hope that this review will promote further applications of this research to realize the ultimate goal of improving the quality of life and outcome of patients with GC.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare they have no conflicts of interest.

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