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Review Article

Prospects of circular RNAs: the regulators of drug resistance and metastasis in gastric cancer

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Abstract: Gastric cancer (GC) is one of the most common malignant tumors. Although there are multiple therapeutic methods, the 5-year survival rate for GC remains low primarily due to metastasis and resistance to chemotherapy. GC treatments, which include chemotherapy drugs, targeted drugs, and immunologic drugs, improve the prognosis of advanced GC patients. Nevertheless, resistance to these drugs may result in treatment failure. Tumor metastasis also plays a key role in tumor progression and limits the clinical efficacy of treatments. Recently, it has been reported that circular RNAs (circRNAs), non-coding RNAs, regulate GC drug resistance and metastasis to improve prognosis. In this review, we summarized systematically the underlying mechanisms of circRNA regulation of gastric neoplasm drug resistance and tumor metastasis. Thus we shed light on the potential of circRNAs to function as potential GC biomarkers and therapeutics.

Keywords: circular RNA, metastasis, drug resistance, gastric cancer, prognosis

Introduction

Gastric cancer (GC) is the fifth most common cancer and the third leading cause of cancer-related death worldwide [1, 2]. Although great progress has been made in GC treatment techniques, most patients are diagnosed at such an advanced stage that they miss the optimal time for surgery [3, 4]. Because of the low survival rate and prognosis, GC remains a serious threat to human health. It has been shown that the prognosis of GC is associated with tumor metastasis and drug resistance [5]. Therapeutic drugs for GC are classified as chemotherapy, targeted, or immunologic drugs. It has been shown that implementation of chemotherapy and targeted therapy increased the 5-year survival rate of patients with GC [6]. The chemotherapeutic drugs used include cisplatin (DDP), pemetrexed (MTA), oxaliplatin (OXA), doxorubicin, 5-fluorouracil (5-FU), and paclitaxel (PTX). The targeted therapy drugs used include Herceptin and apatinib. However, drug resistance has emerged gradually leading to poor prognosis [7, 8]. Thus, determining the mechanisms involved in GC drug resistance is critical. The complex mechanisms of drug resistance involve DNA damage repair, apoptosis, cell cycle checkpoints, cell proliferation, and autophagy [9-11]. In addition, metastatic spread of cancer cells to other organs is one of the most common causes of GC related death. Thus, determining the underlying mechanism of metastasis is crucial to the GC treatment.

Circular RNAs (circRNAs) are novel non-coding transcripts first identified in viruses by Sanger 40 years ago [12]. They were considered to result from splicing errors and did not gain significant attention [13]. However, with the development of high-throughput sequencing technologies and bioinformatics methods, circRNAs were identified as special, highly stable closed-loop structures lacking 5' end caps and 3' polyadenylated tails [14, 15]. Recent studies have suggested that circRNAs function as competitive endogenous RNAs (ceRNAs), which modulate various physiological and pathological processes [16-19], and circRNAs are associated with tumorigenesis and chemoresistance [20-22]. For example, circ_0043949 was upregulated in glioma and enhanced the resistance of

glioma cells to temozolomide by sponging miR-7161-3p [23]. circ-PVT1 contributed to cisplatin resistance by regulating ABCB1 in osteosarcoma cells [24]. Knockdown of circ_0006528 weakened the resistance of mammary gland cells to adriamycin through the miR-7-5p/RAF1 axis [25]. CircPTK2 inhibited tumor metastasis in non-small cell lung cancer by sponging miR-429, which regulates TIF1γ expression [26]. Hsa_circRNA_0067934 promoted metastasis of hepatocellular carcinoma via the miR-1324/FZD5/Wnt/β-catenin axis [27].

CircRNAs are also associated with GC drug resistance and metastasis. Because the field is comparatively new, we summarized the role of circRNAs in GC chemoresistance and metastasis to shed light on potential future GC therapy methods.

CircRNAs and drug resistance

CircRNAs, novel non-coding RNAs (ncRNAs), function in numerous biological processes. Increasingly, studies have demonstrated that circRNAs play roles in the development of various tumors. Because chemotherapy remains the primary cancer treatment method, drug resistance remains a significant challenge to effective treatment. It has been reported that circRNAs function in the molecular mechanisms of drug resistance. Multiple circRNAs were upregulated in drug-resistant cells compared to drug-sensitive cells. However, the roles of circRNAs in cancer drug resistance have not been investigated well. The roles of circRNAs in cancer cells resistant to DDP, pemetrexed, OXA, doxorubicin, 5-FU, as well as other drugs are summarized below.

CircRNAs and chemotherapy resistance

Cisplatin (DDP): As one of the most widely used chemotherapeutic drugs, DDP treats various malignant neoplasms, including GC. DDP exerts its anticancer function by binding with genomic DNA (gDNA) or mitochondrial DNA (mtDNA) to cause DNA lesions [28]. DDP also affects cell apoptosis by blocking mRNAs and proteins and arresting DNA replication [29]. CircRNAs have been associated with DDP resistance in GC.

Exosomes participate in the communication between cells and neighboring or distant cells and are key regulators in diverse biological processes, including tumor development and drug resistance [30-32]. Targeting exosomal circRNAs has become a research focus upon the discovery of exosomes carrying ncRNAs, including circRNAs [33, 34]. One study showed that exosomal circ-PVT1 is a significant player in DDP resistance in GC [35]. Exosomal circ-PVT1 represses miR-30a-5p expression, which leads to overexpression of Yes-associated protein 1 (YAP1). YAP1 promotes apoptosis and suppresses autophagy in GC. In addition, B lymphoma Mo-MLV insertion region 1 (BMI1) was shown to mediate chemoresistance in endometrial cancer and breast cancer [36, 37]; however, the role of BMI1 in GC has not been well-investigated. It has been recently revealed that circDONSON correlates with DDP resistance in GC via the miR-802/BMI1 pathway [38]. circDONSON downregulated miR-802 expression and upregulated BMI1 expression. CircAKT3 facilitated DDP resistance in GC by inhibiting expression of miR-198, which forms a ceRNA network that regulates PIK3R1 and activates PI3K/AKT signaling [39]. Moreover, previous studies demonstrated that PI3K/AKT signaling plays essential roles in tumor onset and progression, including drug resistance [40, 41]. Circ_0110805 was elevated in GC and induced DDP resistance through the miR-299-3P/endothelial protein disulfide isomerase (ENDOPDI) axis [42]. Mechanistically, circ_0110805 functions as a ceRNA by sponging miR-299-3P to hinder the inhibitory effect of miR-299-3P on its target gene ENDOPDI, and this ultimately leads to proliferation, invasion, and DDP resistance in GC cells.

B-cell lymphoma-2 (BCL2) interacts with the apoptotic pathway and can function as a repressor of apoptosis [43]. It has been shown that BCL2 is downstream of miR-618 and that circCCDC66 suppresses apoptosis by sponging miR-618 [44]. Furthermore, knockdown of circCCDC66 reverses resistance to DDP through miR-618/BCL2 signaling in GC. Hsa_circ_0081143 has been shown to induce DDP resistance in GC by binding to miR-646 and increasing expression of cell division protein kinase 6 (CDK6) [45]. CDK6, a member of the CDK family, is associated with cancer development and drug resistance [46, 47]. The transcription factor STAT3 regulates cell survival and promotes chemoresistance [48, 49]. circVAPA enhances resistance to DDP by binding to miR-125b-5p, which leads to an increase in STAT3 expression [50]. Depletion of circVAPA increases miR-125b-5p expression, which leads to a reduction in STAT3 expression.

Table 1. CircRNA and cisplatin resistance in GC

CircRNA	Sponging miRNAs	Targets	Functions	References
circ-PVT1	miR-30a-5p	YAP1	Promotes cisplatin resistance	[35]
circDONSON	miR-802	BMI1	Promotes cisplatin resistance	[38]
circAKT3	miR-198	PIK3R1	Promotes cisplatin resistance	[39]
circ_0110805	miR-299-3p	ENDOPDI	Promotes cisplatin resistance	[42]
circCCDC66	miR-618	BCL2	Promotes cisplatin resistance	[44]
hsa_circ_0081143	miR-646	CDK6	Promotes cisplatin resistance	[45]
circVAPA	miR-125b-5p	STAT3	Promotes cisplatin resistance	[49]
circCUL2	miR-142-3p	ROCK2	Suppresses cisplatin resistance	[50]
circ_0001017	miR-543	PHLPP2	Suppresses cisplatin resistance	[52]
circMCTP2	miR-99a-5p	MTMR3	Suppresses cisplatin resistance	[58]

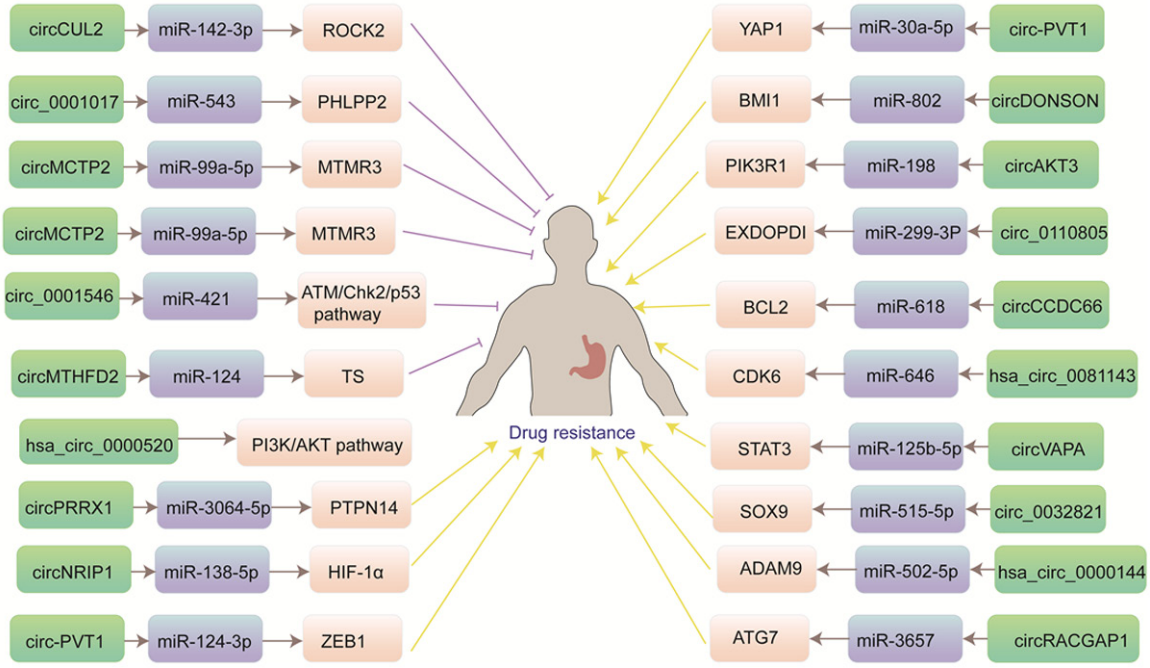

Figure 1. CircRNAs are involved in drug resistance in gastric cancer.

CircCUL2, which is located between nucleotides 35,349,801-35,360,267 on chromosome 10, functions as a tumor suppressor via the miR-142-3p/ROCK2 axis [51]. circCUL2 sponges miR-142-3p and inhibits ROCK2 expression, thereby promoting sensitivity to DDP in GC. Circ_0001017 upregulates expression of PH domain and leucine-rich repeat protein phosphatase 2 (PHLPP2), which is involved in GC cell tumor progression and drug resistance [52, 53], by sponging miR-543 [54]. It has been revealed that expression of circ_0001017 is lower in GC tissue than in other tissues and that it mitigates resistance to DDP. Autophagy refers to a complex system that delivers damaged and useless molecules to lysosomes for degradation and plays a critical role in modulating tumorigenesis [55]. Myotubularin-related protein 3 (MTMR3), an important member of the myotubularin family, mediates autophagy by hydrolyzing PtdIns3P (PI3P), which is essential for autophagy [56, 57]. It has been demonstrated that MTMR3 functions downstream of miR-99a-5p and is regulated by circMCTP2, which further represses DDP resistance in GC [58]. The roles of circRNAs in DDP resistance in GC cells are shown in **Table 1** and **Figure 1**.

Oxaliplatin (OXA): OXA is used broadly to treat GC and has better efficacy and fewer side effects than DDP [59]. Previous studies show-

Table 2. CircRNA and oxaliplatin resistance in GC

circRNA	Sponging miRNAs	Targets	Functions	References
circ_0032821	miR-515-5p	SOX9	Promotes oxaliplatin resistance	[63]
hsa_circ_0000144	miR-502-5p	ADAM9	Promotes oxaliplatin resistance	[65]
circ_0001546	miR-421	ATM/Chk2/p53 pathway	Suppresses oxaliplatin resistance	[70]

ed that OXA binds to DNA and forms crosslinks, which suppress DNA replication and transcription and ultimately causes cell death [60, 61]. CircRNAs modulate resistance to OXA in GC.

SOX9 is a transcription factor that increases resistance to endocrine therapy in breast cancer [62], however, the influence of SOX9 in GC remains unclear. It was shown that circ_0032821 derived from tumor cells contributed to OXA resistance by modulating SOX9 via miR-515-5p in GC [63]. Exosomal circ_0032821 sponges miR-515-5p, which binds to the SOX9 3'UTR to downregulate its expression. Emerging research has reported that hsa_circ_0000144 located between nucleotides 160472466-160472794 on chromosome 1 is derived from SLAM family member 6 (SLAMF6) and correlates with tumor growth in GC [64]. Furthermore, hsa_circ_0000144 induces OXA resistance in GC through miR-502-5p/ADAM9 signaling [65]. Mechanistically, hsa_circ_0000144 sponges miR-502-5p and upregulates expression of A disintegrin and metalloproteinase 9 (ADAM9), thereby promoting proliferation, metastasis, and OXA resistance of GC cells. Ataxia-telangiectasia mutated (ATM) belongs to the PI3K-associated kinase family [66] and plays a pivotal regulatory role in DNA repair [67]. Moreover, ATM participates in chemoresistance by mediating p53 expression via phosphorylation of checkpoint kinase 2 (Chk2) [68]. However, a previous study indicated that the ATM/Chk2/p53 pathway plays a critical role in cell cycle arrest and apoptosis [69]. Hsa_circ_001546 represses resistance to OXA by sponging miR-421 to modulate the ATM/Chk2/p53 pathway in GC [70]. **Table 2** and **Figure 1** summarize the effects of circRNAs on resistance to OXA in GC.

Pemetrexed (MTA): MTA, the novel multitargeted antifolate, inhibits various enzymes that participate in pyrimidine and purine synthesis, such as thymidylate synthase (TS), which is necessary for DNA synthesis [71, 72]. Circ-MTHFD2 facilitates MTA resistance in GC by sponging miR-124 and downregulating TS expression [73], however, the mechanism underlying the regulatory effect of miR-124 on TS remains to be ascertained.

Doxorubicin: Doxorubicin is used commonly as an anticancer treatment, and it functions by damaging DNA and inhibiting topoisomerase II and free radical generation [74-76]. Nonreceptor tyrosine phosphatase 14 (PTPN14) interacts with the Hippo signaling pathway via YAP, which further inhibits tumor development [77]. Recent research has shown that silencing circPRRX1 reverses resistance to doxorubicin in GC by modulating PTPN14 expression via miR-3064-5p [78]. Exosomal circPRRX1 targets miR-3064-5p to increase expression of PTPN14, which ultimately contributes to doxorubicin resistance.

5-Fluorouracil (5-FU): 5-FU plays an essential role in the treatment of various cancers. As an analogue of uracil, 5-FU enters the cell by the same mechanism as uracil [79], but inhibits TS and incorporation of TS metabolites into DNA and RNA [80]. CircNRIPI facilitates resistance to 5-FU under hypoxic conditions by binding to miR-138-5p in GC [81]. Previous studies have reported that hypoxia influences drug resistance through various mechanisms, including inhibition of chemotherapeutic agent delivery, regulation of oncogenic signaling pathways, and modulation of HIF-1α [82, 83], which is downstream of miR-138-5p [84]. Thus, circNRIPI modulates resistance to 5-FU induced by hypoxia in GC cells through the miR-138-5p/HIF-1α signaling pathway.

Paclitaxel (PTX): PTX is one of the most popular anticancer agents for the treatment of multiple tumors. PTX increases the percentage and decreases the critical concentration of assembled tubulin subunits at the same time [85]. PTX also enhances tubulin polymerization and suppresses mitosis [86, 87]. Circ-PVT1 plays a critical role in both DDP resistance [35] and PTX resistance in GC [88]. Knockdown of circ-

Table 3. CircRNA and other chemotherapy resistance in GC

circRNA	Sponging miRNAs	Targets	Functions	References
circMTHFD2	miR-124	TS	Promotes pemetrexed resistance	[73]
circPRRX1	miR-3064-5p	PTPN14	Promotes doxorubicin resistance	[78]
circNRIP1	miR-138-5p	HIF-1α	Promotes 5-fluorouracil resistance	[81]
circ-PVT1	miR-124-3p	ZEB1	Promotes paclitaxel resistance	[88]

Table 4. CircRNA and targeted drug resistance in GC

circRNA	Sponging miRNAs	Targets	Functions	References
circRACGAP1	miR-3657	ATG7	Promotes apatinib resistance	[97]
hsa_circ_0000520	unknown	PI3K/AKT pathway	Suppresses herceptin resistance	[103]

PVT1 enhances sensitivity to PTX via the miR-124-3p/ZEB1 axis. Mechanistically, circ-PVT1 targets and sponges miR-124-3p, thereby upregulating Zinc finger E-box binding homeobox 1 (ZEB1) expression, which leads to invasion and migration via E-cadherin and expedites the epithelial-mesenchymal transition (EMT) [89-91]. The EMT transdifferentiates epithelial cells into motile mesenchymal cells and is critical for cell acquisition of invasive and migratory characteristics [92, 93]. The roles of circRNAs on resistance to MTA, doxorubicin, 5-FU, and PTX in GC are outlined in **Table 3** and **Figure 1**.

CircRNAs and targeted therapy resistance

Apatinib: Apatinib, an anti-angiogenic and anti-tumor medication, is used in the treatment of various cancers [94, 95]. Apatinib targets the intracellular ATP-binding site of vascular endothelial growth factor receptor 2 (VEGFR2), which inhibits phosphorylation and pro-angiogenic signaling [96]. CircRACGAP1 contributes to apatinib resistance in GC cells by regulating expression of autophagy-related gene 7 (ATG7) through binding to miR-3657 [97]. CircRACGAP1 functions as an endogenous sponge of miR-3657 to increase expression of ATG7, which ultimately leads to apatinib resistance.

Herceptin: Herceptin is a highly selective drug that targets HER-2 and inhibits HER-2 signaling. It has been found that HER-2 expression is higher in certain cancer cells than in normal tissues, and high HER-2 expression correlates with a low survival rate and drug resistance [98-100]. Although Herceptin is used widely to treat GC, the emergence of Herceptin resistance affects treatment outcomes negatively [101, 102]. Hsa_circ_0000520 inhibits Herceptin resistance in GC cells by silencing the PI3K-AKT pathway [103]. The roles of this circRNA on targeted therapy in GC are shown in **Table 4** and **Figure 1**.

CircRNAs and tumor metastasis

Tumor metastasis is one of the main causes of poor prognosis and death of GC patients, and it has been shown that circRNAs play essential roles in tumor metastasis of GC cells.

Vascular endothelial growth factor A (VEGFA) is an important regulator of tumor growth, metastasis, and angiogenesis [104, 105]. In addition, VEGFA has been shown to be downstream of miR-877-3p, and circ-RanGAP1 targets miR-877-3p to induce invasion and metastasis of GC cells [106]. Circ_100876 correlates with poor prognosis in non-small cell lung cancer and esophageal squamous cell carcinoma [107, 108], but its impact on GC has not been well-investigated. A recent study showed that circ_100876 induces proliferation and metastasis of GC cells through the miR-136/MINE1 axis [109]. Moreover, circ_100876 sponges miR-136, which targets MINE1, thereby affecting GC cell proliferation and metastasis. Specificity protein 1 (Sp1), a member of the Sp/KLF family, mediates gene expression of tumor development-associated pathways [110, 111]. Recent research has shown that circ_0005529 functions as a ceRNA by sponging miR-527, thereby abolishing the negative effect of miR-527 on Sp1, which ultimately promotes cell migration, proliferation, and metastasis [112].

The EMT is a significant biological process in tumor invasion and migration. CircRNA_000-

Table 5. CircRNA and tumor metastasis in GC

CircRNA	Sponging miRNAs	Targets	Functions	References
circ-RanGAP1	miR-877-3p	VEGFA	Induces invasion and metastasis	[106]
circ_100876	miR-136	MINE1	Induces proliferation, invasion, and metastasis	[109]
circ_0005529	miR-527	Sp1	Induces proliferation, migration, and metastasis	[112]
circ_0005075	miR-431	EMT, p53 pathway	Induces proliferation, migration, and metastasis	[113]
hsa_circ_0017639	miR-224-5p	USP3	Induces proliferation, migration, and metastasis	[114]
circPAMC3	miR-296-5p	PTEN	Inhibits proliferation and metastasis	[115]
hsa_circ_100269	unknown	PI3K/AKT pathway	Inhibits proliferation, migration, invasion, and metastasis	[116]
circ-OXCT1	miR-136	TGF-β/SMAD4 pathway	Inhibits migration, invasion, and metastasis	[117]

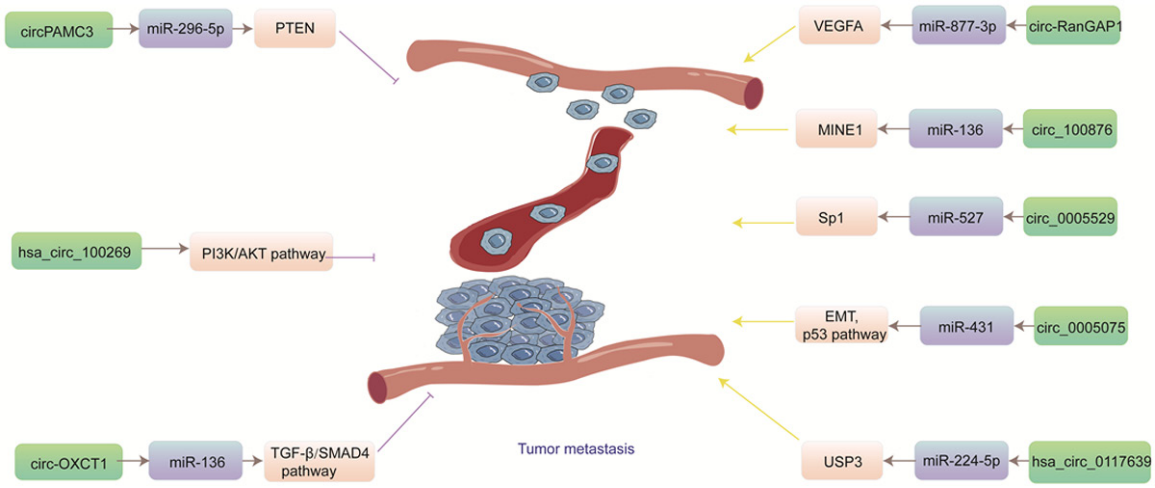

Figure 2. CircRNAs are involved in metastasis in gastric cancer.

5075 facilitates metastasis in GC through the EMT [113]. Mechanistically, circRNA_0005075 binds to and sponges miR-431, which interacts with the p53 pathway to regulate proliferation, invasion, and migration of GC cells. The downstream target of hsa_circ_0017639 is miR-224-5p, and hsa_circ_0017639 upregulates USP3 expression via miR-224-5p to promote metastasis and development of GC cells [114].

A recent study revealed that circPAMC3 represses metastasis and tumor progression through the miR-296-5p/Phosphatase and Tensin Homolog (PTEN) signaling pathway in GC [115]. CircPAMC3 sponges miR-296-5p and reduces its expression, and PTEN is downstream of miR-296-5p. Hsa_circ_100269 suppresses tumorigenesis and metastasis in GC by targeting PI3K/AKT signaling [116]. Hsa_circ_100269 also arrests the cell cycle in the G0/G1 phase and promotes cell apoptosis. One study showed that circ-OXCT1 inhibits metastasis through the TGF-β/SMAD4 pathway [117]. TGF-β/SMAD4 signaling stimulates the EMT and tumor metastasis [118]. Circ-OXCT1 sponges miR-136, thereby downregulating the TGF-β/SMAD4 signaling pathway ultimately leading to repression of migration, invasion, EMT, and lung metastasis in an *in vivo* study. **Table 5**, **Figures 2-4** summarize the roles of circRNAs on metastasis of GC cells.

Challenges and future perspectives

Although one of the most common tumors globally, GC is often diagnosed at the advanced stage, thus the prognosis and survival rate are relatively poor. Therefore, finding effective therapeutic methods for GC treatment is of great significance. Although circRNAs were first discovered 40 years ago, mechanistic research on their physiological and pathological functions has occurred recently [119, 120]. Accumulating data suggest that circRNAs are involved in cell proliferation, migration, and metastasis, as well as in regulating chemoresistance. For example, circ_0006282 enhances proliferation and invasion of GC cells via the miR-155/

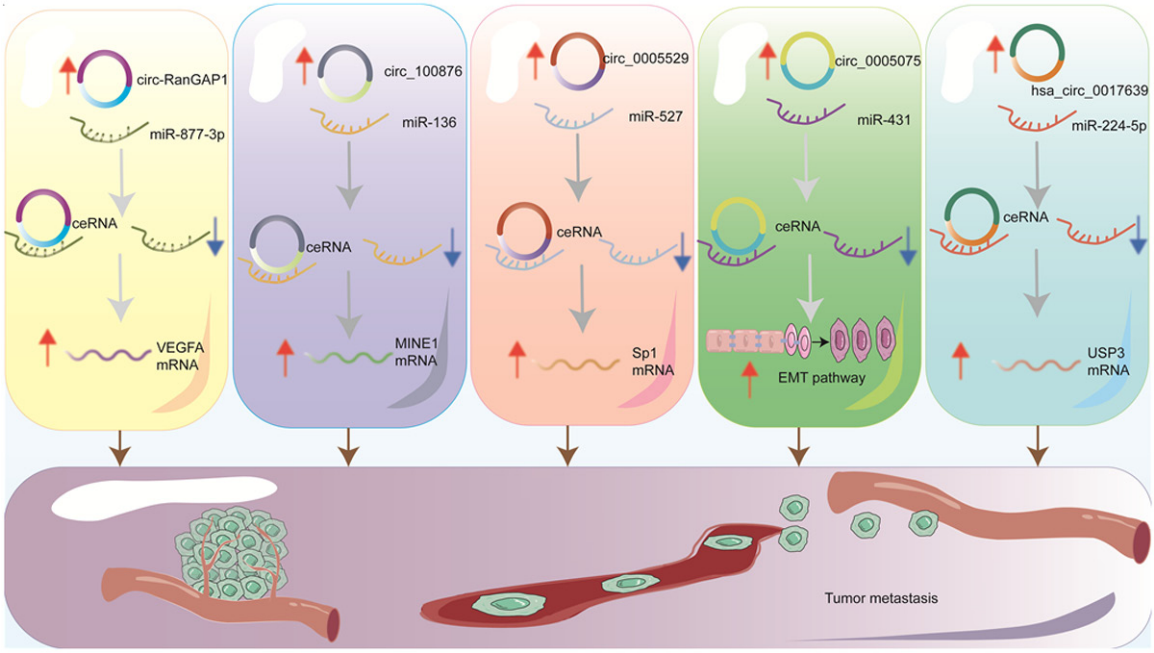

Figure 3. Mechanisms of circRNAs in modulating metastasis in gastric cancer.

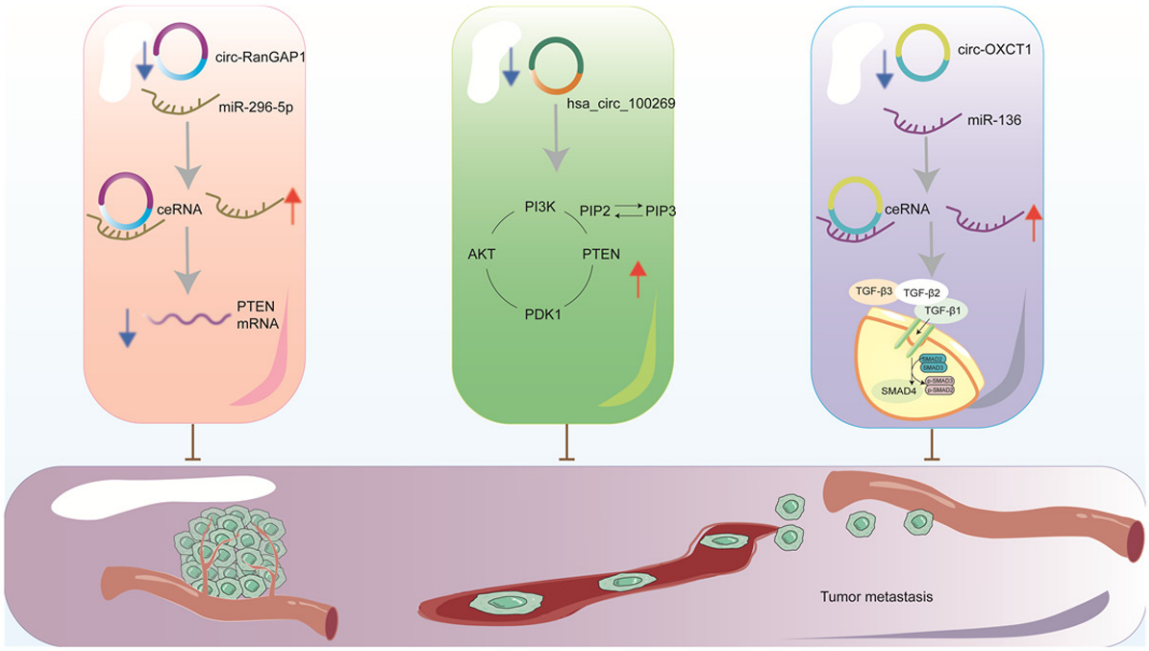

Figure 4. Mechanisms of circRNAs in modulating metastasis in GC.

FBXO22 axis [121] and circ-LDLRAD3 sponges miR-224-5P to regulate cell proliferation, migration, invasion, and apoptosis [122]. On the other hand, it has been demonstrated that circ_0005963 contributes to OXA resistance in colorectal cancer [123] and that circ_0025202 suppresses tamoxifen resistance through the miR-182-5p/FOXO3 pathway [124]. This study aimed to explore the roles of circRNAs in metastasis and drug resistance in GC.

Although there has been much research on the mechanisms of circRNAs in GC, the studies

have been preliminary. Most of the research has been basic studies with few clinical studies. Translation from basic studies to clinical research requires substantial manpower and material resources and as such, is slow. In addition, the mechanisms of circRNA regulation remain relatively unclear and require further research. Mounting research indicates that circRNAs contribute to metastasis and drug resistance in GC. As more insights into circRNAs arise, they may have promise as therapeutic targets. In addition, circRNAs may be used as biomarkers to predict chemoresistance and metastasis in GC, and regulation of circRNAs may reverse the metastasis and drug resistance.

Disclosure of conflict of interest

None.

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