Emerging roles of circular RNAs in gastric cancer metastasis and drug resistance

Xiaolin Wang¹, Jiahui Zhang²,³, Guozhen Cao²,³, Jinghan Hua²,³, Ge Shan¹,⁴* and Wenchu Lin²,³,⁵*

Abstract

Gastric cancer (GC) is an aggressive malignancy with a high mortality rate and poor prognosis, primarily caused by metastatic lesions. Improved understanding of GC metastasis at the molecular level yields meaningful insights into potential biomarkers and therapeutic targets. Covalently closed circular RNAs (circRNAs) have emerged as crucial regulators in diverse human cancers including GC. Furthermore, accumulating evidence has demonstrated that circRNAs exhibit the dysregulated patterns in GC and have emerged as crucial regulators in GC invasion and metastasis. However, systematic knowledge regarding the involvement of circRNAs in metastatic GC remains obscure. In this review, we outline the functional circRNAs related to GC metastasis and drug resistance and discuss their underlying mechanisms, providing a comprehensive delineation of circRNA functions on metastatic GC and shedding new light on future therapeutic interventions for GC metastases.

Keywords: circRNA, Gastric cancer, Metastasis, miRNA sponge, RNA binding protein, Drug resistance

Background

Gastric cancer (GC) is an aggressive and heterogeneous malignancy [1, 2]. With a median overall survival (OS) of 16 months among all patients, GC remains the fourth leading cause of cancer-related mortality worldwide [1–3]. Metastasis is a crucial process characterized by increased invasion and the ability of cancer to spread from its site of origin to other regions of the body, accounting for 90% of cancer-related deaths [4, 5]. Most GC patients are diagnosed at advanced stages and are frequently accompanied by invasion and metastasis, such as lymph node and peritoneum metastases [6, 7]. In metastatic (late) GC patients, the clinical outcomes are extremely poor, while the 5-year overall survival rate of early GC patients can reach over 90% [4, 7]. In addition, metastatic GC has long been considered less effective for surgical treatment and more resistant to drug therapy [8, 9]. Up to date, no effective methods or approaches are applied to treat metastatic GC [8, 9]. Recently, significant advances have been made in clarifying GC metastasis [5, 10]; however, the overall delineation of the molecular mechanisms is limited and ambiguous. Therefore, an in-depth understanding of GC metastasis at the molecular and cellular levels is imperative to identify potential biomarkers for diagnosis and therapeutic targets for intervention.

Covalently closed circular RNAs (circRNAs) are single-stranded endogenous RNA molecules with loop structures and are resistant to exonuclease activity [11–13]. The biogenesis of circRNAs is widely acknowledged via a back-splicing event from precursor RNA (pre-RNA), which is facilitated by the flanking reverse complementary sequences, such as Alu elements, and is regulated by some RNA binding proteins (RBPs), including QKI, DHX9, FUS, Sam68, hnRNP L, hnRNPM and ADARs (Fig. 1A) [14–23].

Thousands of circRNAs across species have been identified and characterized through high-throughput sequencing combined with bioinformatic analyses in the...
past decade [24, 25]. Most circRNAs are chiefly derived from known protein-coding genes, consist of a single or multiple exon(s) (exonic circRNAs, ecircRNAs), and generally localize to the cytoplasm [13]. The most prominent function of cytoplasmic ecircRNAs is to serve as competing endogenous RNAs (ceRNAs) or miRNA sponges to lift the inhibitory effects of miRNAs on their downstream targets (Fig. 1B) [24, 26–28]. Interestingly, the intronic sequences between the circularized exons may be retained, forming exon-intron circRNAs (ElciRNAs) [29]. ElciRNAs are proved to enhance their parental gene expressions in cis via binding to the U1 small nuclear ribonucleoprotein (snRNP) complex in the nucleus (Fig. 1C) [29]. Intronic lariat precursors escaping from debranching produce intronic circRNAs (ciRNAs), which could regulate RNA polymerase II (Pol II)-mediated transcription in the nucleus [30, 31]. Besides, circRNAs directly interact with RBPs to regulate key targets as protein scaffolds or antagonists in various biological processes as well (Fig. 1D) [32–34]. In addition, a small fraction of ecircRNAs undergoes cap-independent translation to encode small peptides through the internal ribosome entry site (IRES)-driven mechanisms, although the vast majority of circRNAs are thought to be non-coding RNAs (Fig. 1E) [35–37]. Recently, a novel class of circRNAs encoded by mitochondria (mecciRNAs) has been reported to facilitate the mitochondrial entry of nuclear-encoded proteins by serving as molecular chaperones [38].

Accumulating evidence has pointed out the aberrant expression patterns of circRNAs and their regulatory roles in cancer progression and metastasis [39–44]. Systematic and comprehensive knowledge regarding circRNAs related to GC metastasis expands our understanding of the underlying mechanisms of metastatic GC. In the present review, we overview the current research status of circRNAs related to GC metastasis, including modulating epithelial-mesenchymal transition (EMT), regulating angiogenesis, exosomal circRNAs, and drug resistance, and discuss the potential clinical application value of circRNAs in GC. We hope to provide insights into circRNAs-mediated GC metastasis and their potential as putative biomarkers or therapeutic targets of GC in the future.

**CircRNAs participate in EMT**

EMT, a highly complex and dynamic process, is recognized as a vital step driving the early phase of cancer metastasis [45, 46]. Recently, several circRNAs have been reported to participate in EMT by modulating various signaling pathways, such as TGF-β/SMAD, Wnt/β-catenin, and PI3K/AKT pathways [47]; thereby, we summarized up-to-date information on circRNAs engaged in these signaling pathways in GC metastasis (Table 1).

**TGF-β/SMAD signaling pathway**

The TGF-β/SMAD signaling is a classic pathway in cancer metastasis [47]. The circRNA circTHBS1, which is highly expressed in GC and associated with poor prognosis, is reported to promote the malignant behaviors and EMT of GC cells by triggering the INHBA/TGF-β pathway [48]. Mechanistically, circTHBS1 behaves as
Table 1  A list of circRNAs related to GC metastasis

| CircRNA      | CircBase ID   | Expression | Property in metastasis | Molecular mechanism                              | Refs               |
|--------------|---------------|------------|-------------------------|--------------------------------------------------|-------------------|
| circTHBS1    | hsa_circ_0034536 | Up         | Enhancer                | Modulate the miR-204-5p/INHBA axis and interact with the RBP, HuR | [48]              |
| circCCDC66   | hsa_circ_0001313 | Up         | Enhancer                | Activate c-Myc/TGF-β signaling pathway           | [49]              |
| circ_0001829 | hsa_circ_0001829 | Up         | Enhancer                | Sponge miR-155-5p to upregulate SMAD             | [50]              |
| circOXCT1    | hsa_circ_0004873 | Down       | Repressor               | Sponge miR-136 to upregulate SMAD4               | [51]              |
| circAXIN1    | hsa_circ_0005838 | Up         | Enhancer                | Encode a novel protein, AXIN1-129aa              | [52]              |
| circFGD4     | hsa_circ_000390 | Down       | Repressor               | Sponge miR-532-3p to upregulate APC              | [53]              |
| circREPS2    | hsa_circ_0139996 | Down       | Repressor               | Sponge miR-558 to upregulate RUNX3               | [54]              |
| circAKT3     | hsa_circ_0000199 | Up         | Enhancer                | Sponge miR-198 to upregulate PIK3R1              | [55]              |
| circ_0023409 | hsa_circ_0023409 | Up         | Enhancer                | Sponge miR-542-3p to upregulate IRS4             | [56]              |
| cirs-7       | hsa_circ_0001946 | Up         | Enhancer                | Sponge mir-7 to upregulate PTEN                 | [57]              |
| circTNPO3    | hsa_circ_0001741 | Down       | Repressor               | Interact with the RBP, IGF2BP3                   | [58]              |
| circFNDC3B   | hsa_circ_0006156 | Up         | Enhancer                | Interact with the RBP, IGF2BP3                   | [59]              |
| circ_100876  | hsa_circ_0023404 | Up         | Enhancer                | Sponge miR-665 to upregulate YAP1               | [60]              |
| circPRRX1    | hsa_circ_0004370 | Down       | Repressor               | Sponge miR-665 to upregulate YWHAZ               | [61]              |
| circRanGAP1  | hsa_circ_0063526 | Up         | Enhancer                | Regulate the miR-877-3p/VEGFA axis              | [62]              |
| circ_0044366 | hsa_circ_0044366 | Up         | Enhancer                | Sponge mir-29a to upregulate VEGF               | [63]              |
| cicURB1      | hsa_circ_000921 | Up         | Enhancer                | Interact with the splicing factor hnRNPM         | [64]              |
| ebv-circLMP2A |              | Up         | Enhancer                | Form a positive feedback loop with HIF1a         | [65]              |
| circNRP1     | hsa_circ_0004771 | Up         | Enhancer                | Sponge mir-149-5p to upregulate AKT1            | [66]              |
| circNEK9     | hsa_circ_0032683 | Up         | Enhancer                | Sponge miR-409-3p to upregulate MAP7            | [67]              |
| circRELL1    | hsa_circ_0001400 | Up         | Repressor               | Sponge miR-637 to upregulate EPHB3              | [68]              |
| circSHKBP1   | hsa_circ_0000936 | Up         | Enhancer                | Modulate the miR-582-3p/HuR/VEGFA axis and interact with HSP90 | [69]              |
| circMRPS35   | hsa_circ_000384 | Down       | Repressor               | Recruit the histone modifier, KAT7              | [70]              |
| cicMAPK1     | hsa_circ_0004872 | Down       | Repressor               | Encode a MAPK1-109aa protein                    | [71]              |
| circRPL15    | hsa_circ_0064574 | Up         | Enhancer                | Sponge mir-502-3p to upregulate OLFM4           | [72]              |
| circUBE2Q2   | hsa_circ_0005151 | Up         | Enhancer                | Modulate the mir-370-3p/STAT3 axis              | [73]              |
| circAGO2     | hsa_circ_0135889 | Up         | Enhancer                | Interact with the RBP, HuR                      | [74]              |
| cicHuR       | hsa_circ_0049027 | Down       | Repressor               | Transcriptionally repression in cis             | [75]              |

A miR-204-5p sponge to enhance the INHBA expression, and it also stabilizes the INHBA mRNA mediated by HuR, consequently activating the TGF-β pathway (Fig. 2A1) [48]. The circCCDC66 expression is elevated in GC and related to tumor stage and lymphatic metastasis [49]. Gain- and loss-of-function studies have revealed that circCCDC66 promotes GC metastasis by activating c-Myc and the TGF-β signaling pathways [49]. In another case, hsa_circ_0001829 promotes GC cell migration and invasion in vitro and GC metastasis in vivo via modulating the miR-155-5p/SMAD axis [50]. A similar ceRNA mechanism also applies to circOXCT1, which interacts with miR-136 to relieve the repressive effect on its target SMAD4, inhibiting GC EMT and metastasis [51].

Wnt/β-catenin signaling pathway

The Wnt/β-catenin signaling pathway is indispensable among the pathways regulated by circRNAs in EMT [47, 52–54]. The circAXIN1 expression is significantly up-regulated in GC compared to the corresponding non-tumor gastric tissues [52]. Silencing of circAXIN1 suppresses GC cell proliferation, migration, and invasion, whereas the ectopic expression of circAXIN1 promotes GC malignancy in vitro and in vivo [52]. Mechanistically, a novel protein AXIN1-295aa encoded by circAXIN1 competes with parental AXIN1 protein to bind APC and release β-catenin, consequently activating the canonical Wnt/β-catenin signaling pathway to facilitate GC progression (Fig. 2AII) [52]. Additionally, Dai et al. have proposed that the circFGD4 expression is markedly attenuated in GC tissues and negatively correlated with lymphatic metastasis and the short prognosis of GC patients [53]. Furthermore, circFGD4 shows its anti-tumor effect on GC tumorigenesis and metastasis by modulating the miR-532-3p/APC/β-catenin axis [53]. Similarly, circREPS2 exhibits a decreased level in GC and inhibits GC migration and invasion via repression of the RUNX3/β-catenin pathway by sequestering miR-558 [54].
PI3K/AKT signaling pathway

The PI3K/AKT signaling pathway is frequently activated in EMT during metastasis and a series of dysregulated circRNAs have been found to interfere with this pathway [47, 55–57]. For example, GC-specific circAKT3 activates the PI3K/AKT signaling by repressing miR-198-mediated inhibition of PIK3R1, a regulatory subunit of PI3K (Fig. 2AII) [55]. The circRNA hsa_circ_0023409 is highly expressed in GC tissues and markedly correlated with tumor size, histological grade, and TNM staging, nominating it as a potential prognostic marker for GC [56]. Functionally, hsa_circ_0023409 exerts the oncogenic effects on GC progression and metastasis by competitively sponging miR-542-3p to enhance the expression of IRS4, which contributes to activating the PI3K/AKT pathway [56]. A well-characterized circRNA, CDR1as (cirs-7), is markedly up-regulated in GC and linked to poor survival in an independent validation cohort, and promotes GC cell migration and metastasis via antagonizing the miR-7-mediated expression of PTEN, which is broadly regarded as a negative regulator of the PI3K/AKT signaling pathway [57, 76].

Other pathways

Several additional circRNAs have been gradually characterized to engage in other EMT signaling pathways [58–61]. For example, circTNPO3 is significantly down-regulated in GC compared with matched noncancerous tissues and plasma circTNPO3 owns the ability to serve as a potential diagnostic biomarker [58]. In vitro and in vivo observations reveal that circTNPO3 suppresses GC proliferation and metastasis [58]. Mechanistically, circTNPO3 competitively interacts with IGF2BP3 and subsequently destabilizes the MYC mRNA, ultimately inhibiting MYC and its target SNAIL, a primary and key inducer of EMT (Fig. 2AIV) [58]. The circRNA circFNDC3B appears to be increased in GC significantly and facilitates cell migration, invasion and EMT of GC cells by forming a ternary complex of circFNDC3B-IGF2BP3-CD44 mRNA (Fig. 2AV) [59]. In addition, circ_100876, a significantly up-regulated circRNA in GC, contributes to GC migration and invasion by serving as a molecular sponge for miR-665 to regulate the expression of YAP1, which activates a transcriptional program involved in EMT (Fig. 2AVI) [60]. Collectively, these findings strongly indicate that circRNAs can modify several critical biological pathways relevant to GC metastasis.

CircRNAs regulate angiogenesis

Angiogenesis, defined as the formation of new blood vessels sprouting from preexisting vessels, is well-regarded as an important initial step in cancer metastasis [77–79]. Several signaling pathways, including VEGFA and HIF1α signaling, can continuously induce angiogenesis, aggravating cancer progression [80, 81]. Recently, several circRNAs have been reported to participate in GC metastasis by regulating VEGFA- or HIF1α-mediated angiogenesis [62–65].

The circRNA circRanGAP1 is validated to sponge miR-877-3p to increase the VEGFA expression, stimulate angiogenesis and promote GC metastasis (Fig. 2BII) [62]. A similar ceRNA mechanism also applies to circ_0044366, which binds to miR-29a to derepress the VEGF expression and thus facilitates angiogenesis and migration in GC [63]. The circRNA circURI1 back-spliced from exons 3–4 of URI1 has been identified from circRNA profiling of 5 paired GC and adjacent non-cancerous tissues and plasma, sequencers the splicing factor, hnRNPM protein in a sequence-dependent manner to modulate alternative splicing of a subset of migration-related genes, such as VEGFA, consequently inhibiting GC metastasis. 3. Evi-circLMP2A promotes angiogenesis through forming a positive feedback loop with HIF1α to improve the VEGFA expression. Under hypoxia, HIF1α up-regulates ebi-circLMP2A, and ebi-circLMP2A interacts with KHSRP to destabilize the VHL mRNA, resulting in VHL down-regulation and HIF1α accumulation. 4. Exosomal circRNA in GC. The circRNA circSHKBP1 promotes GC progression via the miR-582-3p/HuR/VEGFA axis, and sequestering HSP90 to suppress STUB1-mediated HSP90 ubiquitination. Additionally, increased exosomal circSHKBP1 could facilitate co-cultured cell growth. D. Other pivotal pathways or targets involved in GC metastasis. I. The circRNA circMRPS35 inhibits GC tumorigenesis through the recruitment of histone acetyltransferase KAT7 to the promoters of FOXO1/3a genes, activating the FOXO1/3a transcription, consequently triggering the FOXO1/3a pathway. II. The circRNA circAG02 exerts an anti-tumor effect on GC invasion via generating a 109aa protein forming as a molecular sponge for MEKI, thus inhibiting the phosphorylation of MAPK1 and eventually leading to the inactivation of the MAPK pathway. III. The circRNA circAG02 interacts with HuR protein to promote its activation and enrichment on the 3′UTR of HuR targets, resulting in repressing the AGO2/miRNA-mediated gene silencing involved in cancer progression. IV. The circRNA circHuR sequencers CNBP from the HuR’s promoter, leading to the repressions of HuR and GC progression.
(paraGC) specimens [64]. *CircURI1* exhibits a remarkably higher expression in GC than paraGC tissues and is negatively associated with metastasis in GC patients [64]. Functional studies perform that *circURI1* inhibits GC metastasis in vitro and in vivo. Mechanistically, *circURI1* behaved as a decoy of hnRNPM in a sequence-dependent manner to modulate alternative splicing of a subset of genes related to cell migration, thus suppressing GC metastasis (Fig. 2BII) [64]. VEGFA is a direct and functional target of *circURI1*, and *circURI1* can promote exon 7 inclusion of VEGFA (VEGFA7IN) [64]. *CircURI1*-induced VEGFA7IN possesses a greater ability to prevent the *circURI1*-silencing-mediated promoting effect on GC cell invasion than exon 7 exclusion of VEGFA [64, 82].
This study firstly reported the engagement of circRNA-modulated alternative splicing in cancer metastasis [64]. Additionally, virus-encoded circRNA has also been found to engage in angiogenesis in GC [65, 83]. Epstein-Barr virus (EBV)-derived circRNA LMP2A (ebv-circLMP2A) is correlated with distant metastasis and poor prognosis in EBV-associated GC (EBVaGC) [65]. Furthermore, the ebv-circLMP2A expression is positively correlated with the expressions of HIF1α and VEGF in clinical samples of EBVaGC and a mouse model [65]. Ectopic expression of ebv-circLMP2A promotes angiogenesis and GC cell migration under hypoxia, while ebv-circLMP2A knockdown reverses these effects [65]. Mechanistic studies reveal that HIF1α and ebv-circLMP2A form a positive feedback loop, which promotes angiogenesis in EBVaGC [65]. Briefly, under hypoxia, HIF1α induces the ebv-circLMP2A expression, and ebv-circLMP2A interacts with KHSRP to enhance the VHL mRNA decay mediated by KHSRP, resulting in HIF1α accumulation (Fig. 2BIII) [65].

**Exosomal circRNAs and GC metastasis**

Exosomes are small extracellular vesicles with an average diameter of ~100 nanometers, containing an abundant cargo of proteins and different RNA species, including circRNAs, which can enhance substance exchange between cells and improve signal transduction [84, 85]. Accumulating evidence has demonstrated that exosomes play emerging roles in regulating cancer metastasis and treatment through the transfer and exchange of molecules during cell-cell communications [86, 87]. Recently, circRNAs have been shown to be abundant in exosomes and exosomal circRNAs might be regarded as circulating biomarkers for metastatic disease in GC patients [88, 89].

Multiple exosomal circRNAs from the plasmas of GC patients are involved in GC invasion and metastasis [66–69]. CircNRIP1 possesses a significantly higher expression level in exosomes from GC plasma than in normal tissues and engages in exosomal crosstalk between GC cells [66]. GC cells co-cultured with exosomes derived from circNRIP1-overexpressed cells exhibit higher metastatic potential than control cells via the tail vein metastasis model [66]. Simultaneously, exosomal circNRIP1 promotes GC metastasis in vivo and regulates EMT by activating the AKT1/mTOR signaling pathway via sponging miR-149-5p [66]. Similarly, circNEK9, an up-regulated circRNA in GC tissues, accelerates GC proliferation by serving as a ceRNA against miR-409-3p to target MAP7 [67]. Additionally, the exosome-mediated transfer of circNEK9 performs promotive effects on GC cell migration and invasion [67]. Sang et al. have uncovered that exosomal circREL1L1 is down-regulated in GC, and its delivery mediated by GC cells-derived exosomes stimulates autophagy by modulating the miR-637/EPHB3 axis in GC progression [68]. In another case, circSHKBP1 is remarkably upregulated in both GC tissues and serum and is significantly associated with advanced TNM stage and poor survival [69]. Mechanistically, exosomal circSHKBP1 promotes GC cell migration and invasion via modulating the miR-582-3p/HuR/VEGF axis, and inhibiting HSP90 ubiquitination through sequestering HSP90 to obstruct its interaction with STUB1 (Fig. 2C) [69]. These promising results provide novel insights into therapy and the predictions of GC prognosis.

**Other metastasis-related pivotal pathways or targets**

**FOXO1/3a pathway**

The FOXO1/3a pathway stimulates the expressions of the downstream targets, including p21, p27, Twist1, and E-cadherin [70, 90]. The circRNA circMRPS35 is identified from circRNA profiles of three paired GC and the corresponding non-tumor tissues, whose level is associated with clinicopathological characteristics and prognosis in GC patients [70]. Biologically, in vivo observations and in vitro experiments reveal that circMRPS35 inhibits GC cell proliferation and invasion [70]. Furthermore, mechanistic studies reveal that circMRPS35 combats GC tumorigenesis by recruiting histone acetyltransferase KAT7 to transcriptionally activate the FOXO1/3a genes, consequently triggering the FOXO1/3a pathway (Fig. 2DII) [70].

**MEK-MAPK pathway**

The MEK-MAPK signaling pathway is mainly involved in GC proliferation and metastasis [71, 91]. The circRNA circMAPK1 exhibits a decreased level in GC compared to the corresponding adjacent non-tumor tissues and is inversely correlated with GC tumor size, lymphatic invasion, TNM stage, and poor OS [71]. Functional investigations implicate that circMAPK1 suppresses GC proliferation and invasion in vitro and in vivo [71]. Mechanistically, circMAPK1 exerts the anti-tumor effect through encoding a MAPK1-109aa protein as a molecular sponge for MEK1, thus suppressing the phosphorylation of MAPK1 and eventually resulting in the inactivation of the MAPK pathway (Fig. 2DII) [71].

**STAT3 pathway**

Signal transducer and activator of transcription 3 (STAT3) is a widely-characterized oncogene in diverse human cancers [92, 93]. The circRNA circRPL15, up-regulated in GC tissues and correlated with short survival, enhances GC cell migration and invasion, and inhibits apoptosis by sequestering miR-502-3p from the OLFM4 mRNA to activate the STAT3 pathway [72]. A similar ceRNA mechanism also applies to circUBE2Q2, which
interacts with miR-370-3p to relieve the inhibitory effect on its target STAT3 in GC, promoting proliferation, glycolysis, and metastasis [73].

**Human antigen R**

Human antigen R (HuR), a classic RBP, is frequently upregulated in multiple human cancers including GC and plays a vital role in cancer progression and metastasis [94]. An intronic circRNA circAGO2 generated from the first intron of AGO2 is increased in GC and boosts GC metastasis in vitro and in vivo [74]. Mechanistic studies reveal that circAGO2 physically interacts with HuR protein to facilitate its activation and enrichment on the 3' UTR of HuR targets, inhibiting AGO2/miRNA-mediated gene silencing associated with cancer progression (Fig. 2DIII) [74]. In another case, circHuR, predominantly localized in the nucleus, is downregulated in GC tissues and suppresses GC cell growth, invasion, and metastasis [75]. Mechanistically, circHuR interacts with CNBP and subsequently represses its binding to the promoter of HuR, leading to the repression of HuR and GC progression (Fig. 2DIV) [75].

**Interplay between circRNAs and drug resistance in GC**

Although chemo- and radio-therapy are recognized as the most effective and extensive treatment methods for GC patients after surgery during the past few decades, the clinical applications are still limited owing to the intrinsic and acquired resistance, resulting in the occurrence of distant metastasis in GC patients [1, 3, 95]. Additionally, targeted therapy and immunotherapy with immune checkpoint inhibitors for GC have emerged [96]. Convincing evidence has confirmed that diverse circRNAs influence drug resistance in GC therapeutic responses (Table 2) [55, 112].

Cisplatin (CDDP) is one of the most effective chemotherapeutic agents for patients with GC, especially those in advanced stages [113, 114]. The circVAPA expression is elevated in CDDP-resistant GC cells, and circVAPA facilitates GC cell migration, invasion, and CDDP resistance [97]. Further mechanistic investigations indicate that circVAPA exerts its oncogenic activity through sponging with miR-125b-5p to increase the STAT3 expression [97]. Similarly, several other circRNAs such as circAKT3, circPVT1, circFN1, and circ_0000260, also enhance CDDP resistance and malignant progression in GC [55, 98–102]. Oxaliplatin (OXA) is a widely used anti-cancer medicine [115]. The circRNA circ_0032821 is significantly increased in OXA-resistant GC cells and their derived exosomes, and contributes to OXA resistance, GC cell migration and invasion through derepressing SOX9 via sequestering miR-515-5p [103]. Paclitaxel (PTX) is an effective first-line chemotherapy drug in GC treatment, and circPVT1 contributes to PTX resistance and GC cell invasion via serving as a ceRNA against miR-124-3p to target ZEB1, a crucial transcriptional inhibitor of E-cadherin [104]. 5-fluorouracil (5-FU) is currently a first-line agent for the clinical treatment of GC, and circNRP1 promotes hypoxia-induced 5-FU resistance via modulating the miR-138-5p/HIF-1α axis in GC [105]. Anti-programmed cell death protein 1 (PD-1) monoclonal antibody is a commonly used immune-checkpoint blockade agent for GC immunotherapy [116].

### Table 2: CircRNAs involved in drug resistance in GC

| CircRNA    | CircBase ID | Drug          | Expression | Drug resistance | Targets                                                                 | Refs |
|------------|-------------|---------------|------------|----------------|-------------------------------------------------------------------------|------|
| circVAPA   | hsa_circ_000690 | Cisplatin     | Up         | Enhance        | miR-125b-3p, STAT3                                                      | [97] |
| circAKT3   | hsa_circ_0000199 | Cisplatin     | Up         | Enhance        | miR-198, PIK3R1                                                         | [55] |
| circARCF   | hsa_circ_0092330 | Cisplatin     | Up         | Enhance        | miR-1205, FGFR1                                                         | [98] |
| circCCDC6  | hsa_circ_0001313 | Cisplatin     | Up         | Enhance        | miR-618, BCL-2                                                          | [99] |
| circFN1    | hsa_circ_0058147 | Cisplatin     | Up         | Enhance        | miR-182-5p                                                              | [100]|
| circPVT1   | hsa_circ_0000260 | Cisplatin     | Up         | Enhance        | miR-30a-5p, YAP1                                                        | [101]|
| circ_0032821 | hsa_circ_00032821 | Oxaliplatin   | Up         | Enhance        | miR-515-5p, SOX9                                                        | [102]|
| circPVT1   | -            | Paclitaxel    | Up         | Enhance        | miR-124-3p, ZEB1                                                        | [103]|
| circNRP1   | hsa_circ_0004771 | 5-fluorouracil| Up         | Enhance        | miR-138-5p, HIF-1α                                                      | [104]|
| circDEG1   | hsa_circ_0008583 | anti-PD-1     | Up         | Enhance        | miR-141-3p, CXCL12                                                      | [105]|
| circCUL2   | hsa_circ_0000234 | Cisplatin     | Down       | Suppress       | miR-142-3p, ROCK2                                                       | [106]|
| circMCTP2  | hsa_circ_0000657 | Cisplatin     | Down       | Suppress       | miR-99a-5p, MTMR3                                                       | [107]|
| circ_0000144 | hsa_circ_0000144 | Oxaliplatin   | Down       | Suppress       | miR-502-5p, ADAM9                                                       | [108]|
| circ_0000376 | hsa_circ_0000376 | Bupivacaine   | Down       | Suppress       | miR-145-5p                                                             | [109]|
| circ_0000520 | hsa_circ_0000520 | Herceptin     | Down       | Suppress       | PI3K-AKT pathway                                                       | [110]|
circRNA circDLG1 facilitates GC progression and anti-PD-1 resistance via miR-141-3p-mediated the regulation of CXCCL12 [106].

On the other hand, various circRNAs reverse drug resistance in GC treatment [107–109]. Peng et al. have unveiled that circCUL2 displays a decreased level in GC tissues and possesses a repressively regulatory function in CDDP resistance, GC cell migration, and invasion via miR-142-3p/ROCK2-mediated autophagy activation [107]. Another circRNA circMCTP2 is reported to inhibit CDDP resistance of GC cells via the mir-99a-5p/MTMR3 axis [108]. The circRNA hsa_circ_0000144 exerts inhibitory effects on OXA resistance, GC cell proliferation, and metastasis through up-regulating ADAM9 mediated by miR-502-5p [109]. Bupivacaine, a local anesthetic commonly used in the resection operation of GC patients, reduces the circ_0000376 level in GC cells, and circ_0000376 partially reverses bupivacaine-mediated repressive effects on GC cell viability and metastasis via sponging mir-145-5p [110]. Herceptin, a targeted therapy drug, is a humanized monoclonal antibody specifically binding to HER2 and acts as an antitumor role in GC [117]. The circRNA hsa_circ_0000520 is significantly reduced in GC and reverses the Herceptin resistance of GC cells by inhibiting the PI3K/AKT signaling pathway [111].

Taken together, these studies provide the possibility that a combination of circRNAs-based therapy with chemotherapy, targeted therapy or immunotherapy may be a valuable approach to overcome drug resistance and prevent metastasis in GC in the future.

**Clinical significance of circRNAs in GC**

CircRNAs have multiple remarkable characteristics which provide tremendous potential for serving as biomarkers and therapeutic targets owing to the covalently closed-loop structure, disease-specific and dynamic expression pattern and high conservation across species [118–122]. For example, according to a study by Liang and colleagues, hsa_circ_0110389 has been identified as a diagnostic/prognostic biomarker and therapeutic target for GC [123]. Similarly, circOSBPL10 might serve as a novel proliferation factor and prognostic marker of GC [123]. In another case, Chen et al. have displayed that the circPVT1 level is an independent prognostic biomarker for OS and DFS in GC patients [125].

Since exosomes can be detected in various body fluids, including plasma, saliva, urine, and cerebrospinal fluid, exosomal circRNAs might be ideal noninvasive biomarkers for the diagnosis and/or prognosis of gastric cancer [88, 126]. For instance, the circSHKBP1 expression is significantly increased in GC serum and positively correlated with advanced TNM stage and poor survival [69]. Furthermore, GC cell exosomes enhance co-cultured cell growth by delivering circSHKBP1 [69]. These findings indicate that circSHKBP1 is a promising circulating biomarker for GC diagnosis and prognosis [69]. Additionally, the circRNA circRanGAP1 exhibits a significantly higher expression in plasma exosomes derived from GC patients than the healthy controls. It promotes GC cell migration and invasion, indicating that plasma exosomal circRanGAP1 might serve as a promising biomarker for GC patients [62]. The circRNAs that show potential as biomarkers in GC are summarized in Table 3.

**Conclusions and future perspectives**

Current active research in circRNAs has brought us a range of exciting findings implying that circRNAs are of great importance in various diseases [11, 118, 127–129]. A tremendous amount of evidence has demonstrated the abnormal expression pattern of circRNAs in GC and the involvement of circRNAs in GC metastasis and drug resistance [11, 64, 126]. We have systematically described a series of dysregulated circRNAs in GC and elucidated their underlying molecular mechanisms in GC metastasis and drug resistance (Tables 1 and 2).

To date, various circRNA candidates have been validated and engaged in GC metastasis based on a series of molecular and cellular experiments [64, 66–69, 124, 125]. However, a global and comprehensive understanding of circRNAs related to GC metastasis is still scarce. To gain better and deeper insight into the aberrant expression pattern of circRNAs involved in GC metastasis, genome-wide circRNA profiling with high throughput sequencing from metastatic and non-metastatic GC tissues is a powerful approach to address this issue.

Four subclasses of circRNAs have been identified, including ecircRNAs, EicircRNAs, ciRNAs and mitochondria-encoded circRNAs (mecciRNAs) [11, 38, 130]. Current literature about circRNAs in GC metastasis generally includes ecircRNAs and ciRNAs, their functions and the molecular mechanisms [72–75, 94, 126]. Nevertheless, two other kinds of circRNAs and their functions have not been evaluated, which presents an exciting field to explore further.

The well-characterized mechanism of circRNAs is to sequester miRNAs to regulate the expressions of targeted genes [11–13]. A single circRNA could function as a scaffold for several different miRNAs [123]. Conversely, a miRNA can target multiple circRNAs as well [60, 61]. Identification and construction of the circRNA-miRNA regulatory network will help to systematically decipher the roles of circRNAs in GC metastasis in the future. In addition to the ceRNA mechanism, circRNAs have various molecular modes of action, including participating in...
epigenetic regulations, modulating alternative splicing, and generating protein [64, 71, 75]. We expect a burst of circRNA studies to elucidate some novel mechanisms of action in GC metastasis in the upcoming years.

Considering that circRNAs possess unique features such as tissue- and developmental stage-specific patterns, structural resistance to exonucleases and longer half-lives, and specific circRNAs play essential roles in GC metastasis and drug resistance, manipulating circRNA abundance appears to be a promising therapeutic strategy for the advanced GC treatment [126–128, 131, 132]. Furthermore, combining circRNAs-based therapeutic interventions with traditional chemotherapy or targeted therapy offers a unique opportunity to conquer drug resistance in advanced GC patients [97–111, 113–117]. However, choosing crucial target circRNAs of interest is still a problem. Furthermore, precisely and effectively delivering circRNAs into targeted cells for tumor treatment is also a significant issue that needs to be solved.

### Conclusions

In summary, the advances in circRNAs research will be essential to unravel their potential significance in GC. Furthermore, a better understanding of the association between circRNAs and GC would make circRNAs promising candidates as valuable biomarkers or potential targets in GC treatment.

### Abbreviations

- S-FU: 5-fluorouracil
- BVI: Blood vessel infiltration
- CDDP: Cisplatin
- ceRNA: Competing endogenous RNA
- circRNA: Circular RNA
- ciRNA: Intronic circRNA
- DFS: Disease-free survival
- ecircRNA: exonic circRNA
- EicRNA: exon-intron circRNA
- EMT: Epithelial-mesenchymal transition
- EBV: Epstein-Barr virus
- EBVaGC: EBV-associated GC
- EBV: Epstein-Barr virus
- FOC: Blood vessel infiltration
- IRES: Internal ribosome entry site
- LNM: Lymph node metastasis
- LVI: Lymphatic vessel infiltration
- mecciRNA: mitochondria-encoded circRNA
- OS: Overall survival
- OXA: Oxaliplatin
- paraGC: adjacent non-cancerous GC
- PD-1: Programmed cell death protein 1
- Pol II: Polymerase II
- pre-RNA: precursor RNA
- PTX: Paclitaxel
- RBP: RNA binding protein
- snRNP: small nuclear ribonucleoprotein
- STAT3: Signal transducer and activator of transcription 3
- VEGFAe7IN: Exon 7 inclusion of VEGFA

### Table 3  Clinical significance of circRNAs in GC (Cases more than 50)

| CircRNA        | CircBase ID     | Sample       | Expression | Clinicopathologic Features                          | Prognosis | Refs |
|----------------|-----------------|--------------|------------|----------------------------------------------------|-----------|------|
| circTHBS1      | hsa_circ_0034536 | Tissue       | Up         | Size, stage, grade, LNM                            | OS        | [48] |
| circCCDC66     | hsa_circ_0001313 | Tissue       | Up         | Stage, LNM                                          | -         | [49] |
| circOXCCT1     | hsa_circ_0004873 | Tissue       | Down       | Stage, LNM                                          | OS        | [51] |
| circAXIN1      | hsa_circ_0005838 | Tissue       | Up         | Stage, grade, LNM                                  | -         | [52] |
| circFGD4       | hsa_circ_0000390 | Tissue       | Down       | Grade, LNM                                          | OS        | [53] |
| circREPS2      | hsa_circ_0139996 | Tissue       | Down       | Size, stage, grade                                  | -         | [54] |
| circAKT3       | hsa_circ_0000199 | Tissue       | Up         | Size, stage, grade, chemoresistance                 | OS        | [55] |
| circ_0023409    | hsa_circ_0023409 | Tissue       | Up         | Size, stage, grade                                  | OS        | [56] |
| ciRS-7         | hsa_circ_0001946 | Tissue       | Up         | Stage, LNM                                          | OS        | [57] |
| circTNPO3      | hsa_circ_0001741 | Tissue, plasma| Down       | Differentiation                                     | -         | [58] |
| circ_100576    | hsa_circ_0023404 | Tissue       | Up         | Stage, LNM, BVI, LVI                               | DFS       | [60] |
| circRanGAP1    | hsa_circ_0063526 | Tissue, plasma| Up         | Size, stage, LNM                                   | OS        | [62] |
| circUR1        | hsa_circ_0009291 | Tissue       | Up         | Stage, tumor metastasis                             | -         | [64] |
| ebv-circLMP2A  | -               | Tissue       | Up         | Stage, LNM, tumor metastasis                        | OS, DFS   | [65] |
| circNRP1       | hsa_circ_0004771 | Tissue       | Up         | Size, LNM                                          | OS, DFS   | [66] |
| circRELL1      | hsa_circ_0001400 | Tissue, plasma| Down       | Stage, LNM, differentiation                         | OS, DFS   | [68] |
| circSHKBP1     | hsa_circ_0000936 | Tissue       | Up         | Size, stage, vascular invasion                      | OS        | [69] |
| circMRPS35     | hsa_circ_0003842 | Tissue       | Down       | Size, stage, LNM                                   | OS        | [70] |
| circMAPK1      | hsa_circ_0004872 | Tissue       | Down       | Size, stage, LNM                                   | OS        | [71] |
| circUBE2Q2     | hsa_circ_0005151 | Tissue, plasma| Up         | Size, lymphatic invasion                            | -         | [73] |
| circAGO2       | hsa_circ_0135889 | Tissue       | Up         | -                                                  | OS        | [74] |
| circHuR        | hsa_circ_0049027 | Tissue       | Down       | Stage, tumor metastasis                             | OS        | [75] |
| circVAPA       | hsa_circ_0006990 | Tissue       | Up         | -                                                  | -         | [97] |
| circFN1        | hsa_circ_0058147 | Tissue       | Up         | Stage, grade, chemoresistance                      | -         | [100]|
| circCUL2       | hsa_circ_000234  | Tissue       | Down       | Stage, LNM, differentiation                         | OS        | [107]|
| circMCTP2      | hsa_circ_000657  | Tissue       | Down       | Size, stage, grade, chemoresistance                 | OS, DFS   | [108]|
| circ_0113089   | hsa_circ_0113089 | Tissue       | Up         | Stage, differentiation                              | OS, DFS   | [123]|
| circOSBPL10    | hsa_circ_0008549 | Tissue       | Up         | Stage, grade                                       | OS, DFS   | [124]|
| circPVT1       | -               | Tissue       | Up         | Stage, nervous invasion                             | OS, DFS   | [125]|
Acknowledgments
A portion of this work was supported by the High Magnetic Field Laboratory of Anhui Province.

Authors' contributions
X.W. was responsible for the table and figure generation. X.W., G.S. and W.L. wrote this manuscript. X.W., J.Z., G.C., J.H. and W.L. discussed and approved the final manuscript.

Funding
This study was supported by the National Key Research and Development Program of China (2019YFA0802600 and 2018YFC1004500), National Natural Science Foundation of China (81972191 and 81672647), and Science and Technology Major Project of Anhui Province (18030801140).

Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Declarations

Consent for publication
All authors agree to the content of the paper and are listed as co-authors of the paper.

Competing interests
The authors declare that they have no competing interests.

Author details
1Department of Clinical Laboratory, The First Affiliated Hospital of USTC, Chinese Academy of Sciences (CAS) Key Laboratory of Innate Immunity and Chronic Disease, School of Basic Medical Sciences, Division of Life Science and Medicine, University of Science and Technology of China (UTSC), Hefei 230027, Anhui, China. 2High Magnetic Field Laboratory, Hefei Institutes of Physical Science (HIPS), Chinese Academy of Sciences, Hefei 230031, Anhui, China. 3University of Science and Technology of China, Hefei 230027, Anhui, China. 4Sir Run-Shan Shaw Hospital, Zhejiang University School of Medicine, Zhejiang 310016, Hangzhou, China. 5Key Laboratory of High Magnetic Field and Ion Beam Physical Biology, HIPS, Chinese Academy of Sciences, Hefei 230031, Anhui, China.

Received: 27 January 2022   Accepted: 4 July 2022
Published online: 11 July 2022

References
1. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. Lancet. 2020;396:635–48.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209–49.
3. Van Cutsem E, Ducreux M. Colorectal and gastric cancer in 2015: The expanding regulatory mechanisms and cellular functions of circular RNAs. Nat Rev Mol Cell Biol. 2020;21:475–91.
4. Biagioni A, Skalamera I, Peri S, Schiavone N, Cianchi F, Giommoni E, et al. Update on gastric cancer treatments and gene therapies. Cancer Metastasis Rev. 2019;38:537–48.
5. Li GZ, Doherty GM, Wang J. Surgical Management of Gastric Cancer: A Review. JAMA Surg. 2022;157:446–54.
6. Yeoh KG, Tan P. Mapping the genomic diaspora of gastric cancer. Nat Rev Cancer. 2022;22:71–84.
7. Chen L, Huang C, Shan G. Circular RNAs in physiology and non-immunological diseases. Trends Biochem Sci. 2022;47:250–64.
8. Chen LL. The expanding regulatory mechanisms and cellular functions of circular RNAs. Nat Rev Genet. 2019;20:675–91.
9. Chen L, Huang C, Wang X, Shan G. Circular RNAs in eukaryotic cells. Curr Genomics. 2015;16:312–8.
10. Jeck WR, Sorrentino JA, Wang K, Stevin MK, Burd CE, Liu J, et al. Circular RNAs are abundant, conserved, and associated with ALU repeats. RNA. 2013;19:141–57.
11. Zhang KO, Wang HB, Zhang Y, Lu X, Chen LL, Yang L. Complementary sequence-mediated exon circulatory cell. Circulation. 2014;159:134–47.
12. Conn SJ, Pillman KA, Toubia J, Conn VM, Salamindis M, Phillips CA, et al. The RNA binding protein quaking regulates formation of circRNAs. Cell. 2015;160:1125–34.
13. Aktas T, Aygap Ilik, I Maticzka D, Bhardwaj V, Posačević R, Mittler G, et al. DHX9 suppresses RNA processing defects originating from the Alu invasion of the human genome. Nature. 2017;544:115–9.
14. Errichelli D, Dini Modigliani S, Lanape P, Colanton C, Legnini I, Capauto D, et al. FUS affects circular RNA expression in murine embryonic stem cell-derived motor neurons. Nat Commun. 2017;8:14741.
15. Fei T, Chen Y, Xiao T, Li W, Cato L, Zhang P, et al. Genome-wide CRISPR screen identifies HNRNPL as a prostate cancer dependency regulating RNA splicing. Proc Natl Acad Sci U S A. 2017;114:E5207–15.
16. Pagliarini V, Joly A, Biellie P, Di Rosa V, De la Grange P, Sette C. Sam68 binds Alu-rich introns in SMN and promotes pre-mRNA circularization. Nucleic Acids Res. 2020;48:633–45.
17. Ho JS, Di Tullio F, Schwarz M, Low D, Incarnato D, Gay F, et al. HNRNP A controls circRNA biogenesis and splicing fidelity to sustain cancer cell fitness. Elife. 2021;10:e59654.
18. Shen H, An Q, Ren X, Song Y, Tang SJ, Ke YY, et al. ADARs act as potent regulators of circular transcriptome in cancer. Nat Commun. 2022;13:1508.
19. Memczak S, Jens M, Elefsioti A, Fort T, Krueger J, Rybak A, et al. Circular RNAs are a large class of animal RNAs with regulatory potency. Nature. 2013;493:333–8.
20. Vo JN, Cieslik M, Zhang Y, Shukla S, Xiao L, Zhang Y, et al. The landscape of circular RNA in cancer. Cell. 2019;176:869–81.
21. Liu C, Ge HM, Liu BH, Dong R, Shan K, Chen X, et al. Targeting pericyte-endothelial cell crosstalk by circular RNA-cPWWP2A inhibition aggravates diabetes-induced microvascular dysfunction. Proc Natl Acad Sci U S A. 2019;116:7455–64.
22. Hansen TB, Jensen TI, Clausen BH, Branson JF, Bingens B, Damgaard CK, et al. Natural RNA circles function as efficient microRNA sponges. Nature. 2013;495:384–8.
23. Zheng Q, Bao C, Guo W, Li S, Chen J, Chen B, et al. Circular RNA profiling reveals an abundant circHIPK3 that regulates cell growth by sponging multiple miRNAs. Nat Commun. 2016;7:11215.
24. Li Z, Huang C, Bao C, Chen L, Lin M, Wang X, et al. Exon-intron circular RNAs regulate transcription in the nucleus. Nat Struct Mol Biol. 2015;22:256–64.
25. Zhang Z, Zhang XQ, Chen T, Xiang JF, Yin QF, Xing YH, et al. Circular intronic long noncoding RNAs. Mol Biol Cell. 2015;26:802–806.
26. Zhang J, Hou L, Zuo Z, Ji P, Zhang X, Xue Y, et al. Comprehensive profiling of circular RNAs with nanopore sequencing and CIRI-long. Nat Biotechnol. 2021;39:836–45.
27. Ashwal-Fluss R, Meyer M, Pamudurti NR, Ivanov A, Bartok O, Hanan M, et al. Mutations in circular RNAs cause disease in immunodeficiency and neurological diseases. Trends Biochem Sci. 2022;47:250–64.
28. Chen L, Huang C, Shan G. Circular RNAs in physiology and non-immunological diseases. Trends Biochem Sci. 2022;47:250–64.
29. Chen LL. The expanding regulatory mechanisms and cellular functions of circular RNAs. Nat Rev Genet. 2019;20:675–91.
in the cytoplasm and interacting with YB1 in the nucleus. Cancer Lett. 2019;442:222–32.

34. Dudekula DB, Panda AC, Grammatikakis I, De S, Abdelmohsen K, Gorospe M. Circinteractome: A web tool for exploring circular RNAs and their interacting proteins and microRNAs. RNA Biol. 2016;13:34–42.

35. Yang Y, Fan X, Mao M, Song X, Wu P, Zhang Y, et al. Extensive translocation of circular RNAs driven by N6-methyladenosine. Cell Res. 2017;27:626–41.

36. Legnini I, Di Timoteo G, Rossi F, Morlando M, Briganti F, Sthandier O, et al. Circ-2NF669 is a circular RNA that can be translated and functions in myogenin-mediated cell survival. Cell. 2017;66:23–37.

37. Wang J, Zhu S, Meng N, He Y, Lu R, Yan GR. ncRNA-Encoded Peptides and Proteins. Mol Ther. 2019;27:1718–25.

38. Liu X, Wang X, Li J, Hu S, Deng Y, Yin H, et al. Identification of meciRNAs and their roles in the mitochondrial entry of proteins. Sci China Life Sci. 2020;63:1429–49.

39. Li J, Sun D, Pu W, Wang J, Peng Y. Circular RNAs in Cancer: Biogenesis, Function, and Clinical Significance. Trends Cancer. 2020;6:319–36.

40. Chen S, Huang V, Xu X, Livingstone J, Soares F, Jeon J, et al. Widespread and functional RNA circularization in localized prostate cancer. Cell. 2019;176:831–43.

41. Hua J, Wang X, Ma L, Li J, Cao G, Zhang S, et al. CircVAPA promotes small cell lung cancer progression by modulating the miR-377-3p and miR-198-5p/EGFR axis. Mol Cancer. 2022;21:123.

42. Du WW, Yang W, Liu E, Yang Z, Dhalwai P, Yang B. Fbox3 circular RNA retards cell cycle progression via forming ternary complexes with p21 and CDK2. Nucleic Acids Res. 2016;44:2846–58.

43. Yang L, Han B, Zhang Y, Bai Y, Chao J, Hu G, et al. Engagement of circular RNA HECW2 in the nonautophagic role of ATG5 implicated in the endothelial-mesenchymal transition. Autophagy. 2018;14:404–18.

44. Goodall GJ, Wickramasinghe VQ. RNA in cancer. Nat Rev Cancer. 2019;20:646–56.

45. Niu Q, Dong Z, Liang M, Luo Y, Lin H, Lin M, et al. Circular RNA circMRPS35 promotes gastric cancer progression by regulating the circ-OXCT1/miR-136/SMAD4 axis. Cancer Lett. 2022;526:259–72.

46. Zhang X, Wang S, Wang H, Cao J, Huang X, Chen Z, et al. Circular RNA circRIP31 acts as a microRNA-149-3p sponge to promote gastric cancer progression via the AKT1/mTOR pathway. Mol Cancer. 2019;18:20.

47. Li J, Xie L, Liu X, Yu Y, Wang S. Plasma exosomal circC1909 accelerates the progression of gastric cancer via miR-409-3p/MAP7 axis. Dig Dis Sci. 2021;66:4274–89.

48. Sang H, Zhang W, Peng L, Wei S, Zhu X, Huang K, et al. Exosomal circC1907L1 serves as a miR-637 sponge to modulate gastric cancer progression via regulating autophagy activation. Cell Death Dis. 2022;13:56.

49. Xie M, Yu T, Jia X, Ma L, Fan Y, Yang F, et al. Exosomal circSHARKP1 promotes gastric cancer progression via regulating the miR-582-3p/HUR/VEGF axis and suppressing HSP90 degradation. Mol Cancer. 2020;19:112.

50. Jie M, Wu Y, Gao M, Li X, Liu C, Ouyang Q, et al. CircHPR553 suppresses gastric cancer progression via recruiting KAT7 to govern histone modification. Mol Cancer. 2020;19:56.

51. Jiang T, Xie Y, Lv J, Li B, Li Y, Wang S, et al. A novel protein encoded by circMAPK1 inhibits progression of gastric cancer by suppressing activation of MAPK signaling. Mol Cancer. 2020;20:66.

52. Li Y, Gong Y, Ma J, Gong X. Overexpressed circ-RPL15 predicts poor survival and promotes the progression of gastric cancer via regulating miR-502-3p/OLFM4/STAT3 pathway. Biomed Pharmacother. 2020;127:102119.

53. Yang J, Zhang X, Cao J, Xu P, Chen Z, Wang S, et al. Circular RNA UBE2Q2 promotes malignant progression of gastric cancer by regulating signal transducer and activator of transcription 3-mediated autophagy and glycolysis. Cell Death Dis. 2021;12:910.

54. Chen Y, Yang F, Fang E, Xiao W, Mei H, Li H, et al. Circular RNA circAGO2 drives cancer progression through facilitating HU-R repressed function of AGO2-miRNA complexes. Cell Death Dis. 2019;26:1346–64.

55. Yang F, Hu A, Li D, Wang J, Guo Y, Liu Y, et al. Circ-HU-R suppresses HU-R expression and gastric cancer progression by inhibiting CNBP transcription. Mol Cancer. 2019;18:158.

56. Lee MS, Jeong IH, Lee HW, Han HI, Ko A, Hewitt SM, et al. PI3K/AKT activation induces PTEN ubiquitination and destabilization accelerating tumourigenesis. Nat Commun. 2015;6:7769.

57. Ferrana N, Kerbel RS. Angiogenesis as a therapeutic target. Nature. 2005;438:967–74.
78. Roviello G, Petrioli R, Marano L, Polom K, Marrelli D, Perrella A, et al. Angiogenesis inhibitors in gastric and gastroesophageal junction cancer. Gastric Cancer. 2016;19:31–41.

79. Steeg PS. Targeting metastasis. Nat Rev Cancer. 2016;16:201–18.

80. Apte RS, Chen DS, Ferrara N. VEGF in signaling and disease: beyond discovery and development. Cell. 2019;176:1248–64.

81. Gonzalez FJ, Xie C, Jiang C. The role of hypoxia-inducible factors in metabolic diseases. Nat Rev Endocrinol. 2018;15:21–32.

82. Wang X, Hua J, Li J, Zhang J, Dzakah EE, Cao G, et al. Mechanisms of non-coding RNA-modulated alternative splicing in cancer. RNA Biol. 2022;19:541–7.

83. Gong LP, Chen JN, Dong M, Xiao ZD, Feng ZY, Yan HY, et al. Epstein-Barr virus-derived circular RNA LMP2A induces stemness in EBV-associated gastric cancer. EMBO Rep. 2020;21:e49689.

84. Kalluri R, LeBelVeus LS. The biology, function, and biomedical applications of exosomes. Science. 2020;367:eaa6977.

85. Meldolesi J. Exosomes and ectosomes in intercellular communication. Curr Biol. 2018;28:R435–44.

86. Wortzel I, Dör R, Kenific CM, Lyden D. Exosome-mediated metastasis: communication from a distance. Dev Cell. 2019;49:347–60.

87. Kalluri R. The biology and function of exosomes in cancer. J Clin Invest. 2016;126:1208–15.

88. Li S, Li Y, Chen B, Zhao J, Yu S, Tang Y, et al. exoRBase: a database of circRNA, lncRNA and mRNA in human blood exosomes. Nucleic Acids Res. 2018;46:D106–12.

89. Li Y, Zheng Q, Bao C, Li S, Guo W, Zhao J, et al. Circular RNA is enriched and stable in exosomes: a promising biomarker for cancer diagnosis. Cell Res. 2015;25:981–4.

90. Shin S, Buel GR, Nagiec MJ, Han MJ, Roux PP, Blenis J, et al. ERK2 regulates epithelial-to-mesenchymal plasticity through DOK1-dependent Rac1/FoxO1 activation. Proc Natl Acad Sci U S A. 2019;116:2967–76.

91. Roskoski Jr. ERK1/2 MAP kinases: structure, function, and regulation. Pharmacol Res. 2012;66:105–43.

92. Yu H, Pardoll D, Jove R. STATs in cancer inflammation and immunity: a leading role for STAT3. Nat Rev Cancer. 2009;9:798–809.

93. Timofeeva OA, Tarasova NI, Zhang X, Chasovskikh S, Cheema AK, Wang H, et al. STAT3 suppresses transcription of proapoptotic genes in cancer cells with the involvement of its N-terminal domain. Proc Natl Acad Sci U S A. 2013;110:1267–72.

94. Schultz CW, Peer T, Dhir T, Dixon DA, Brody JR. Understanding and targeting the disease-related RNA binding protein human antigen R (HUR). Wiley Interdiscip Rev RNA. 2020;11:e1581.

95. Lee J, Kim ST, Kim K, Lee H, Kozowera L, Mortimer PG, et al. Tumor genomic profiling guides patients with metastatic gastric cancer to targeted treatment: The VICTORY umbrella trial. Cancer Discov. 2019;9:1388–405.

96. Joshi SS, Badgwell BD. Current treatment and recent progress in gastric cancer. CA Cancer J Clin. 2021;71:264–79.

97. Deng P, Sun M, Zhao WY, Hou B, Li K, Zhang T, et al. Circular RNA circVAPA promotes chemotherapy drug resistance in gastric cancer progression by regulating miR-125b-5p/STAT3 axis. World J Gastroenterol. 2021;27:487–500.

98. Zhang R, Zhao H, Yuan H, Wu J, Liu H, Sun S, et al. CircARCVFC contributes to cisplatin resistance in gastric cancer by altering miR-1205 and FGFR1. Front Genet. 2021;12:76590.

99. Zhang Q, Miao Y, Fu Q, Hu H, Chen H, Zeng A, et al. CircRNA-CDC66 regulates cisplatin resistance in gastric cancer via the miR-618/BCL2 axis. Biochem Biophys Res Commun. 2020;526:713–20.

100. Huang XX, Zhang Q, Hu H, Jin Y, Zeng AL, Xia YB, et al. A novel circular RNA circF1N1 enhances cisplatin resistance in gastric cancer via sponging miR-182-5p. J Cell Biochem. 2020;122:1009–20.

101. Yao W, Guo P, Mu Q, Wang Y. Exosome-derived circ-PVT1 contributes to Cisplatin resistance by regulating autophagy, invasion, and apoptosis via miR-30a-5p/YP1 axis in gastric cancer cells. Cancer Biother Radiopharm. 2021;36:347–59.

102. Liu S, Wu M, Peng M. Circ_0000260 regulates the development and deterioration of gastric adenocarcinoma with Cisplatin resistance by upregulating MAP1B via targeting miR-129-5p. Cancer Manag Res. 2020;12:10505–19.
125. Chen J, Li Y, Zheng Q, Bao C, He J, Chen B, et al. Circular RNA profile identifies circPVT1 as a proliferative factor and prognostic marker in gastric cancer. Cancer Lett. 2017;388:208–19.
126. Li R, Jiang J, Shi H, Qian H, Zhang X, Xu W. CircRNA: a rising star in gastric cancer. Cell Mol Life Sci. 2020;77:1661–80.
127. Liu L, Wang J, Khanabdali R, Kalionis B, Tai X, Xia S. Circular RNAs: Isolation, characterization and their potential role in diseases. RNA Biol. 2017;14:1715–21.
128. Chen L, Shan G. CircRNA in cancer: Fundamental mechanism and clinical potential. Cancer Lett. 2021;505:49–57.
129. Ng WL, Mohd Mohidin TB, Shukla K. Functional role of circular RNAs in cancer development and progression. RNA Biol. 2018;15:995–1005.
130. Zhao Q, Liu J, Deng H, Ma R, Liao JY, Liang H, et al. Targeting mitochondria-located circRNA SCAR alleviates NASH via reducing mROS output. Cell. 2020;183:76–93.
131. Li F, Yang Q, He AT, Yang BB. Circular RNAs in cancer: limitations in functional studies and diagnostic potential. Semin Cancer Biol. 2021;75:49–61.
132. Wei L, Sun J, Zhang N, Zheng Y, Wang X, Lv L, et al. Noncoding RNAs in gastric cancer: implications for drug resistance. Mol Cancer. 2020;19:62.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.