Emerging role of circular RNAs in gastric cancer: From basic biology to clinical applications (Review)

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Abstract. Despite considerable advances in cancer treatment, gastric cancer (GC) remains a formidable challenge for oncologists worldwide, especially due to the poor survival rates associated with advanced-stage cases. Circular RNAs (circRNAs) stand out as potential targets for more effective therapeutic strategies. The present review synthesizes insights into the roles of circRNAs in GC, highlighting their multifaceted influence on cancer progression and behaviors. circRNAs can regulate gene expression at multiple levels through modulating transcription, affecting alternative splicing, acting as molecular sponges for microRNAs, serving as RNA-protein complexes and even encoding functional proteins. The marked stability of circRNAs in bodily fluids has also positioned them as promising diagnostic biomarkers, with some circRNA-based tests demonstrating high accuracy. Furthermore, emerging evidence indicates that circRNAs carry out a key role in therapy resistance, affecting the therapeutic responses of patients to chemotherapy, targeted therapy and immunotherapy. Collectively, circRNA-based therapeutic strategies, even with existing challenges in delivery methods, hold considerable promise, particularly when integrated with conventional treatment modalities, offering new avenues for improving GC management.

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Contents

1. Introduction

Gastric cancer (GC) is the fifth most common cancer worldwide, imposing a notable global health challenge and a considerable burden on healthcare systems, particularly in East Asia (1). The majority of GCs are adenocarcinomas (85-90%) and this disease remains a formidable challenge despite advancements in treatment (2,3). Surgery combined with chemotherapy remains a standard therapeutic option for patients who are diagnosed early (stages IB to III), offering a substantial chance at survival (3). For those with metastatic disease, however, the outlook is far more challenging, presenting with an unfavorable survival ranging from just 3-14 months, even with treatment (4-14). In metastatic cases, chemotherapy remains the primary solution, with surgery generally limited to palliative care. Noticeably, developments in targeted therapies and immune checkpoint inhibitors have revealed encouraging results, which may contribute to improving the survival rates in patients at the advanced stage (4,15,16).

A class of non-coding RNAs, circular RNAs (circRNAs), has emerged in the rapidly evolving field of GC research (17). circRNAs were first discovered in plant viroids in 1976, but were largely ignored until RNA sequencing technologies revealed their widespread presence across species (18-22). circRNAs, different from linear RNAs, possess a closed-loop structure without the conventional 5' cap and 3' poly-A tail, exhibiting resistance to exonuclease degradation and cellular breakdown (23,24). This structural characteristic empowers them with an extended half-life and enhanced expression stability compared with their linear counterparts (19,21).

circRNAs are structures formed through back-splicing, in which a downstream 5'-splice donor is joined to a 3'-splice acceptor that is positioned upstream of the donor. While the majority originate from exons, some forms originate from

intronic sequences (19,25,26). These molecules primarily localize to the cytoplasm, where they serve multiple functions from interacting with microRNA (miRNA/miR) and proteins to acting as templates for protein synthesis (19,27-34). circRNAs reveal considerable potential, both as potential biomarkers and therapeutic targets in GC, due to their stability and diverse functions (17,35).

circRNAs have demonstrated profound relevance in both basic biology and translational medicine. One of the earliest landmark discoveries was cerebellar degeneration-related protein 1 antisense RNA, a neuronal circRNA that harbors >60 binding sites for miR-7, functioning effectively as a molecular sponge to suppress its activity (21,36,37). This interaction may also exert direct impact on multiple key pathways, such as EGFR/cyclin E1/phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit δ, v-rel reticuloendotheliosis viral oncogene homolog A and PTEN/PI3K/AKT signaling across different types of cancer, including GC, lung cancer and colorectal cancer (38-43). More broadly, circRNAs can also regulate key oncogenic pathways (such as Wnt/β-catenin, TGF-β and MYC) across various human malignancies (44-46). For example, circFBXW7 encodes a protein that antagonizes c-Myc stability, and circEIF6 activates Wnt/β-catenin signaling in breast cancer (44,45). All these existing findings support the potent modulatory roles of circRNAs in tumor behaviors at a fundamental molecular level.

Similarly, circRNAs also participate in key signaling cascades during GC. For example, circNRIP1 activates the AKT/mTOR pathway by sponging miR-149-5p, thereby promoting proliferation and epithelial-mesenchymal transition (EMT) (47). circAXIN1 facilitates Wnt signaling by producing a novel protein isoform (AXIN1-295aa) that disrupts β-catenin degradation (48). circMAP2K2 indirectly activates AKT/GSK3β signaling by degrading poly(rC) binding protein 1 (PCBP1), while circRACGAP1 may trigger drug resistance by inducing autophagy, depending on the ATG7/miR-3657 axis (49,50). Therefore, in addition to serving as biomarkers, circRNAs are also active regulators of oncogenic pathways in GC.

With respect to the aforementioned studies, the present review elucidates the latest advances in the understanding of circRNAs and their potential applications in the diagnosis and treatment of GC (Fig. 1).

2. Molecular mechanisms

Transcription control. circRNAs, working predominantly in the cytoplasm, may also carry out key roles in the nucleus by regulating gene expression levels (19,27). In GC, circRNAs can achieve transcriptional control through diverse mechanisms. circMRPS35, for example, can recruit the histone acetyltransferase, lysine acetyltransferase 7, to the promoters of FOXO1 and FOXO3a, leading to increased histone acetylation of these loci and upregulation of their expression levels, ultimately suppressing GC cell proliferation (51). Similarly, by interacting with SNF2L, circDONSON facilitates the recruitment of the nucleosome remodeling factor chromatin remodeling complex to the SOX4 promoter. This can lead to increased SOX4 expression, driving cancer cell proliferation and invasion (52,53). The Epstein-Barr virus-derived circRPMS1 can exert its effects by binding to KH domain-containing, RNA-binding, signal transduction-associated protein 1, which promotes recruitment at the methyltransferase 3, N6-adenosine-methyltransferase complex catalytic subunit (METTL3) promoter, in turn elevating METTL3 expression levels and accelerating cancer progression (54). By contrast, circGSK3B binds to enhancer of zeste homolog 2 (EZH2), a component of the polycomb repressive complex 2, and prevents its interaction with the RAR-related orphan receptor α (RORA) promoter. Eventually, this interaction upregulates RORA expression levels by inhibiting EZH2-mediated H3K27me3 modifications. In addition, increased RORA levels attenuate β-catenin signaling via protein kinase C-α-dependent phosphorylation, thereby suppressing GC cell proliferation and invasion (55,56).

Conversely, some circRNAs function as transcriptional suppressors. A notable example is circ-HuR, which binds to cellular nucleic acid binding protein and acts as a decoy to weaken its ability to bind the human antigen R (HuR) promoter (57), resulting in decreased HuR transcription. This process may ultimately restrict GC cell proliferation and metastasis given that HuR typically stabilizes mRNAs that promote tumor growth and its reduced expression, as circHuR downregulates oncogenic targets (58,59).

Alternative splicing. circRNAs may also modulate gene expression through the modulation of alternative splicing, which has more recently been recognized as a novel mechanism (60). In GC, Wang *et al* (60) demonstrated a role of circURI1 in metastasis through direct interaction with the RNA-binding protein heterogeneous nuclear ribonucleoprotein M (hnRNPM), a key regulator of alternative splicing. The study revealed that, with a specific 19-nucleotide sequence that binds to the ribonucleotide reductase catalytic subunit M1 domain of hnRNPM, the splicing patterns of a subset of genes associated with cell motility and metastasis could be altered by sequestering hnRNPM. RNA sequencing identified 22 hnRNPM-sensitive exons whose splicing was influenced by circURI1 levels. Notably, circURI1 promoted the inclusion of exon 7 in vascular endothelial growth factor (VEGF) A, producing the isoform VEGFA_e7IN, a key regulator of angiogenesis and cancer progression (61).

Further experiments revealed that knockdown of circURI1 increased hnRNPM binding to the pre-mRNAs of circURI1-sensitive genes, leading to notable changes in their splicing patterns (60). This finding highlights the underlying mechanism that circRNAs can indirectly regulate gene expression at the post-transcriptional level by modulating the activity of splicing factors, providing valuable insights into the complex roles of circRNAs in cancer biology.

circRNAs as competing endogenous RNAs (ceRNAs). A well-documented function of circRNAs is their action as ceRNAs. Specifically, circRNAs harbor miRNA response elements that bind and sequester specific miRNAs, preventing them from repressing their normal mRNA targets (28,62). By modulating miRNA activities, circRNAs can mediate key signaling pathways involved in cell growth, differentiation and tumor progression. In particular, numerous circRNA-miRNA-mRNA regulatory axes have been identified in GC (Table I) (47,63-85).

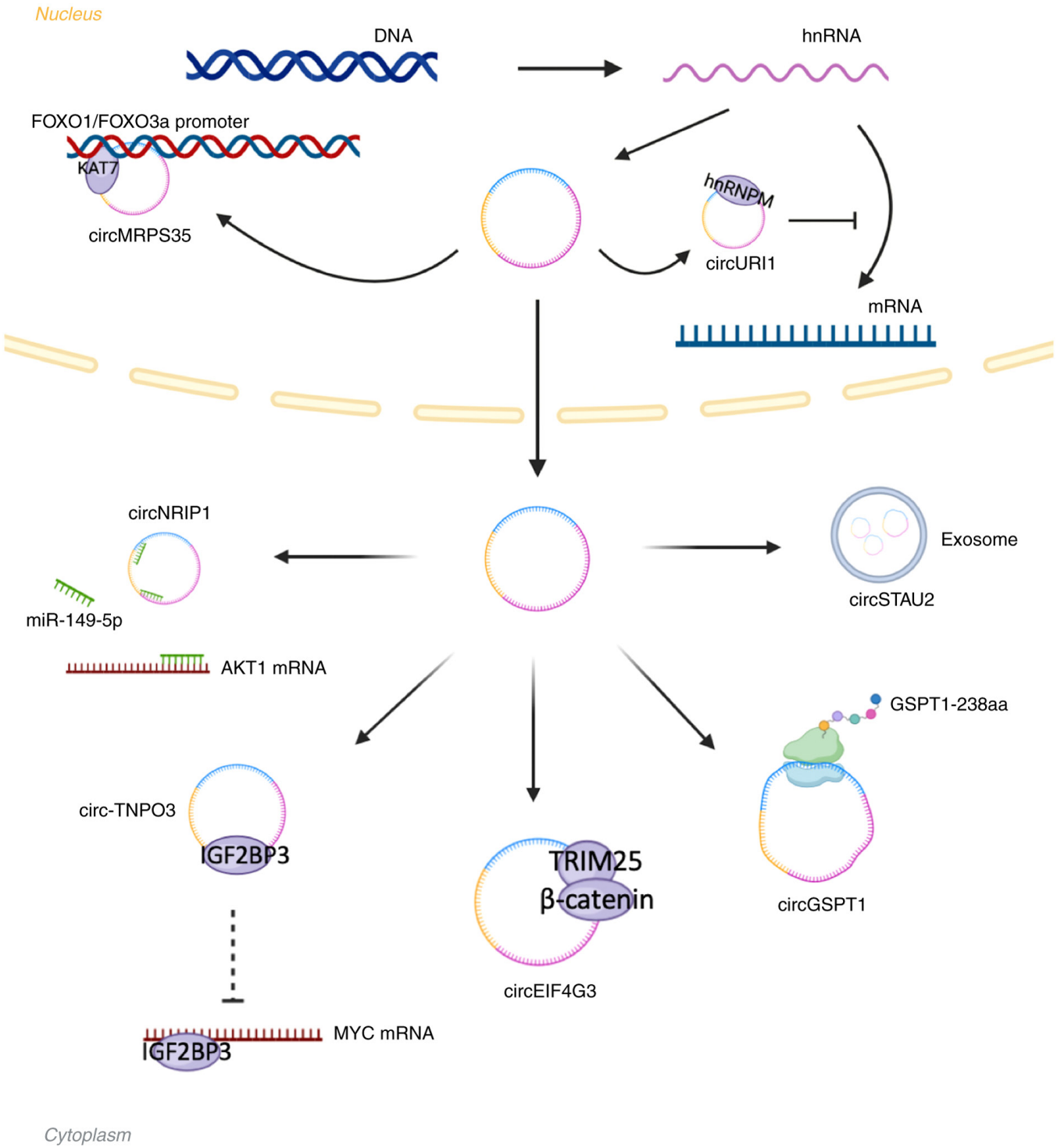

Figure 1. Comprehensive overview of the diverse mechanisms by which circRNAs function in GC. The diagram illustrates how circRNAs in GC regulate gene transcription (circMRPS35 recruits KAT7 to FOXO1/FOXO3a promoters), influence alternative splicing (circURI1 binds to hnRNPM), act as sponges for microRNAs (circNRIP1 sequesters miR-149-5p to regulate AKT1), function as protein decoys (circTNPO3 prevents IGF2BP3 from stabilizing MYC mRNA), serve as scaffolds facilitating protein-protein interactions (circEIF4G3 mediates TRIM25/β-catenin interactions), encode functional proteins that interfere with oncogenic signaling (circGSPT1 produces GSPT1-238aa) and are packaged into exosomes (circSTAU2) to modify the tumor microenvironment. GC, gastric cancer; circ, circular; KAT7, lysine acetyltransferase 7; hnRNPM, heterogeneous nuclear ribonucleoprotein M; miR, microRNA; IGF2BP3, insulin like growth factor 2 mRNA binding protein 3; hnRNA, heterogeneous nuclear RNA; eIF, eukaryotic initiation factor.

In terms of the tumor-promoting roles, circNRIP1, for instance, sponges miR-149-5p to reduce its availability (47), resulting in increased expression of AKT1, a key component of the AKT/mTOR signaling pathway, thus driving tumor progression by promoting cell proliferation, migration, invasion and EMT. Similarly, circGLIS3 sponges miR-1343-3p to block its targeting of phosphoglycerate kinase 1 (PGK1) and the resultant upregulated PGK1 could further enhance tumor growth and invasion (86). circTMC5 could promote GC progression by binding to miR-361-3p,

Table I. circRNAs as ceRNAs in GC.

First author/s, year	circRNA name	ceRNA pathway	Promote or suppress GC progression	Supplement	(Refs.)
Chen *et al*, 2024	circUGGT2	miR-186-3p/MAP3K9	Promote	Promotes cisplatin resistance.	(63)
Fang *et al*, 2022	circCPM	miR-21-3p/PRKAA2	Promote	Contributes to the activation of autophagy and 5-FU resistance.	(64)
Tang *et al*, 2024	circBIRC6	miR-488/GRIN2D	Promote	Increases CAV1 expression, thereby reducing autophagy levels.	(65)
Ma *et al*, 2024	circPTPN22	miR-6788-5p/PAK1	Promote	Inhibits autophagy via activation of the Akt and Erk phosphorylation pathways.	(66)
Yang *et al*, 2021	circUBE2Q2	miR-370-3p/STAT3	Promote	Suppresses autophagy while enhancing glycolytic metabolism.	(67)
Sang *et al*, 2022	circRELL1	miR-637/EPHB3	Suppress	Functions within exosomes to regulate autophagic processes.	(68)
Liu *et al*, 2023	circRNA_15430	miR-382-5p/ZCCHC14	Suppress	Downregulation of circRNA_15430 attenuates HP infection-induced autophagy.	(69)
Chen *et al*, 2024	circ-0075305	miR-708-5p/RPRD1A	Suppress	Involved in oxaliplatin resistance through RPRD1A-mediated inhibition of TCF4-β-catenin transcriptional complex formation, subsequently suppressing the Wnt signaling pathway.	(70)
Cai *et al*, 2019	circHECTD1	miR-137/PBX3	Promote	Diminishes sensitivity to diosbulbin-B treatment.	(71)
	circHECTD1	miR-1256/USP5	Promote	Enhances glutaminolysis and activates the β-catenin/c-Myc axis.	
Xia *et al*, 2021	circFAM73A	miR-490-3p/HMGA2	Promote	Promotes gastric cancer progression and facilitates cisplatin resistance via HNRNPK-mediated β-catenin stabilization.	(72)
Cao *et al*, 2021	circLMO7	miR-30a-3p/WNT2	Promote	Facilitates GC progression through activation of the WNT2/β-catenin signaling pathway.	(73)
Guo *et al*, 2020	circREPS2	miR-558/RUNX3	Suppress	Suppresses GC progression through inhibition of the Wnt/β-catenin signaling pathway.	(74)
Zhou *et al*, 2023	circTDRD3	miR-891b/ITGA2	Promote	Activates the AKT signaling pathway.	(75)
Peng *et al*, 2020	circCUL2	miR-142-3p/ROCK2	Suppress	Inhibits autophagy and enhance CDDP-sensitivity.	(76)
Fei *et al*, 2024	circ_0008315	miR-3666/CPEB4	Promote	Promotes CDDP resistance.	(77)
Huang *et al*, 2019	circAKT3	miR-198/PIK3R1	Promote	Promotes CDDP resistance.	(78)
Deng *et al*, 2020	circRHOBTB3	miR-654-3p/p21	Suppress	Induces G_1/S cell cycle arrest, inhibiting cellular proliferation.	(79)
Zhang *et al*, 2022	circFBXL4	miR-146a-5p/STAT1	Suppress	Upregulates FN1/CHD4 expression through STAT1-dependent mechanisms.	(80)
Miao *et al*, 2023	hsa_circ_0136666	miE-375/PRKDC	Promote	Prevents PD-L1 degradation via PRKDC, thereby facilitating immune evasion.	(81)
Song *et al*, 2020	circPIP5K1A	miR-671-5p/KRT80	Promote	Activates the PI3K/AKT signaling pathway.	(82)
Ma *et al*, 2020	hsa_circ_0004872	miR-224/Smad4	Suppress	Inhibits ADAR1 expression through Smad4-dependent mechanisms.	(83)
Xie *et al*, 2020	circSHKBP1	miR-582-3p/HUR	Promote	Enhances VEGF mRNA stability and binds to HSP90, inhibiting HSP90 ubiquitination.	(84)
Xia *et al*, 2024	circVAPA	miR-548p/TGIF2	Promote	Decreases SLIT2 transcription.	(85)
Zhang *et al*, 2019	circNRIP1	miR-149-5p/AKT1	Promote	Modulates the AKT/mTOR signaling pathway.	(47)

circRNAs, circular RNAs; ceRNA, competing endogenous RNA; GC, gastric cancer; 5-FU, 5-fluorouracil; CAV1, caveolin-1; HP, *Helicobacter pylori*; RPRD1A, regulation of nuclear pre-mRNA domain-containing protein 1A; TCF4, transcription factor 4; HNRNPK, heterogeneous nuclear ribonucleoprotein K; CDDP, cis-diamminedichloroplatinum(II); FN1, fibronectin 1; CHD4, chromodomain-helicase-DNA-binding protein 4; PD-L1, programmed death-ligand 1; PRKDC, protein kinase DNA-activated catalytic polypeptide; ADAR1, adenosine deaminase acting on RNA 1; VEGF, vascular endothelial growth factor; HSP90, heat shock protein 90; SLIT2, slit guidance ligand 2.

reducing its levels and allowing for increased expression of Rab-like protein 6 to foster cell proliferation and inhibit apoptosis (87).

Conversely, some circRNAs act as tumor suppressors. circMAPK1 sponged miR-224, increasing the expression of downstream targets Smad4 and p21 (83). This tumor-suppressive circRNA is regulated by adenosine deaminase RNA specific (ADAR1), an RNA-editing enzyme inhibiting circRNA formation by disrupting exon end linking through adenosine-to-inosine (A-to-I) editing. Moreover, Smad4 suppresses ADAR1 expression by binding to its promoter, creating a negative regulatory loop known as the circMAPK1/miR-224/Smad4/ADAR1 axis. This mechanism suppressed GC progression by reducing cell proliferation, invasion and migration, together with the circMAPK1/miR-224/p21 pathway. Similarly, circORC5, whose expression was decreased by METTL14-mediated N6-Methyladenosine (m6A) modification, sponged miR-30c-2-3p, thereby upregulating AKT1S1 and suppressing tumor growth (88).

Single circRNAs can interact with multiple miRs, forming complex ceRNA networks. For instance, circ-PRMT5 could sponge both miR-145 and miR-1304 in GC, increasing MYC expression, a key oncogene in cell proliferation and tumor progression (89). Furthermore, the understanding of these networks has increased due to advancements in bioinformatics and data mining. Specifically, on the basis of analyzing microarray and RNA-sequencing data from Gene Expression Omnibus (GEO; http://www.ncbi.nlm.nih.gov/gds/) (90), Dong *et al* (91) identified six differentially expressed circRNAs in CircInteractome (https://circinteractome.nia.nih.gov/) (92) and Circbank (https://www.circbank.cn/) (93), with the construction of miRNA-mRNA target interactions using The Cancer Genome Atlas (https://www.cancer.gov/ccg/research/genome-sequencing/tcga) and miRWalk (http://mirwalk.umm.uni-heidelberg.de/) (94) databases for analysis simultaneously. Eventually, this research plotted a comprehensive network linking 33 miRNAs and >300 mRNA targets, providing insights into key signaling pathways, including MAPK and PI3K-AKT. Additional protein-protein interaction analysis of the target genes also identified 15 hub genes, leading to the confirmation of three potential therapeutic drugs that were effective in inhibiting GC cell proliferation. These findings emphasize the potential role of the ceRNA network in the search for GC treatments.

Synthetic circRNAs have been explored as therapeutic agents (95). A notable study engineered an artificial circRNA, through enzymatic ligation, functioning as a miR-21 sponge (96), which effectively bound miR-21 and reduced its availability for targeting tumor-suppressor genes such as death-associated protein 6. The synthetic molecule outperformed linear RNA in terms of stability, while maintaining its function in the cellular environment and inhibiting the tumor-promoting effect of miR-21. The development of such synthetic circRNAs highlights the promise of leveraging engineered molecules to specifically disrupt pathogenic miRNA in cancer therapies.

circRNAs interacting with protein. circRNAs can interact with specific proteins by forming circRNA-protein complexes to exert diverse functions (29,30), such as acting as protein decoys, scaffolds that provide platforms for molecular interactions or protect proteins from degradation.

circPDIA4, as a protein decoy, can bind to DExH-box helicase 9 (DHX9) in the nucleus, preventing DHX9 from carrying out its role in repressing Alu-mediated circRNA biogenesis (97). This interaction allows hsa_circ_0001610 and other types of oncogenic circRNAs to accumulate, driving the invasive and metastatic behaviors of GC cells. Importantly, circPDIA4 sequesters DHX9, rather than altering its expression levels, limiting its function and promoting cancer progression. Notably, circFAM192A can bind protein solute carrier family (SLC)7A5, which acts as the leucine transporter, and the increased intracellular leucine concentration activates the mTOR pathway, ultimately promoting cell proliferation (98). However, in this case, circFAM192A impedes SLC7A5 degradation, further activating the mTOR pathway.

Some other circRNAs also function as scaffolds to promote protein interactions. A notable example in GC is circEIF4G3, which can inhibit β-catenin signaling by interacting with δ-catenin and tripartite motif containing 25, further suppressing GC progression (99). circRNAs can also provide a platform for protein and mRNA. For instance, circARID1A can bind insulin like growth factor 2 mRNA binding protein 3 (IGF2BP3) and SLC7A5 mRNA, and exert the function of stabilizing the mRNA of IGF2BP3, thereby stimulating GC cell proliferation (100). Similarly, circPAK2 can also interact with IGF2BPs and VEGFA mRNA forming a ternary complex to stabilize VEGFA mRNA, leading to GC vasculature formation and aggressiveness (101). circ-TNPO3 acts as a protein decoy, although it can bind to IGF2BP3, hence preventing IGF2BP3 from binding to MYC and zinc finger protein SNAI1 mRNAs, which reduces their stability and, consequently, their expression (102).

Protein-coding potential of circRNAs. circRNAs were initially considered to be non-translatable due to their lack of a cap structure and a 5' untranslated region, both of which are required for the canonical mechanism of translation initiation in eukaryotic cells. In 1979, circRNAs were reported to bind prokaryotic ribosomes but not eukaryotic ones (33), which, however, was subsequently challenged. In 1995, with the use of a rabbit reticulocyte lysate, Chen and Sarnow (32) demonstrated that artificial circRNAs containing internal ribosome entry sites (IRESs) could be translated into peptides *in vitro*. Later, in 2015, Abe *et al* (33) revealed that artificial circRNAs could be translated into peptides in human cells without IRESs, relying instead on a rolling-circle amplification mechanism. In 2017, Legnini *et al* (34) demonstrated, for the first time, a human endogenous circRNA, circ-ZNF609, containing a 753-nt open reading frame (ORF) and an IRES sequence, which encoded functional peptides, marking a paradigm shift and revealing the protein-coding potential of circRNAs.

circRNAs can be translated into proteins through three primary mechanisms (34,103-108): i) IRESs: circRNAs containing IRES sequences enable ribosomes to bind directly to the RNA, initiating translation with no requirement for a 5' cap. Generally, these sequences form complex secondary or tertiary structures to facilitate ribosome recruitment and protein synthesis (34). ii) m6A modification: Translation

can be promoted in the presence of m6A modifications on circRNAs. M6A sites act as docking points for proteins such as YTH domain family member 3, which can interact with translation initiation factors such as eukaryotic initiation factor 3 (eIF3), promoting ribosome loading at the m6A site, enabling cap-independent translation (104-106). iii) Exon junction complex (EJC): The formation of circRNAs often retains the EJC near the back-splicing junction (107). The EJC, particularly through interactions between eIF4A3 and eIF3, acts as a scaffold for ribosome recruitment, allowing translation to initiate at the circRNA junction (108).

In GC, several circRNAs have been identified as being translated into functional proteins. For example, circMAPK1 encodes a protein called MAPK1-109aa, which exerts anticancer effects by competing with MAPK1 for binding to the upstream kinase MEK1. This competition was reported to suppress MAPK1 phosphorylation and reduce the expression of downstream oncogenic genes in the MAPK signaling pathway, ultimately inhibiting GC progression (109). circGSPT1, containing two IRES sequences and a 983-nt ORF, encodes a novel protein known as GSPT1-238aa, sharing high homology with its parental protein GSPT1 but featuring a unique 12-aa peptide. Furthermore, both circGSPT1 and GSPT1-238aa were revealed to be markedly downregulated in GC tissues and were negatively associated with lymph node metastasis. Mechanistically, GSPT1-238aa could bind to Vimentin and interact with the Vimentin/Beclin1/14-3-3 complex, thereby inactivating the PI3K/Akt/mTOR pathway, eventually suppressing cell autophagy, proliferation, migration and invasion in GC cells (110). By contrast, the oncogenic circAXIN1 encodes a protein, AXIN1-295aa, which shares 293 amino acids identical to the N-terminus of the parental AXIN1 protein. While AXIN1 is part of the β-catenin destruction complex, AXIN1-295aa lacks the β-catenin binding site but retains the regulators of G protein signaling domain, which binds to adenomatous polyposis coli (APC). AXIN1-295aa could compete with AXIN1 for APC binding, preventing β-catenin degradation leading to β-catenin accumulation and activation of the Wnt/β-catenin signaling pathway, thereby promoting GC progression (48).

Exosomal circRNAs. Exosomes are nano-sized extracellular vesicles (EVs) that are secreted by the majority of eukaryotic cells. EVs can transport bioactive molecules (such as circRNAs) between cells to facilitate cell-to-cell communication (111,112). This intercellular transfer mechanism enables circRNAs to modulate the tumor microenvironment (TME) and modulate cancer progression (113). For instance, in a previous study, circSTAU2 was packaged into exosomes and transferred between GC cells, where it acted as a sponge for miR-589. By inhibiting miR-589, exosome-delivered circSTAU2 could increase the expression of capping actin protein of muscle Z-line subunit α 1 to reduce cell proliferation, migration and invasion, ultimately transmitting the inhibitory effect on GC progression by exosomes (114).

Similarly, exosome-encapsulated circGLIS3 also regulates the miR-1343-3p/PGK1 axis, thereby promoting tumor growth by upregulating PGK1, an activator of the PI3K/Akt/mTOR pathway (86). circGLIS3 reduces vimentin phosphorylation at serine 83, facilitating a more invasive cancer phenotype (115). Indirectly, circGLIS3 supports M2 macrophage polarization to develop a tumor-promoting immune environment. Expanding on this, circVAPA-rich small EVs (sEVs) from GC cells are preferentially taken up by neurons, promoting neural invasion by inhibiting SLIT2 expression levels (85). Through the miR-548p/TGIF2 axis, circVAPA downregulates SLIT2 transcription while binding to eIF4G1 to suppress SLIT2 translation. This dual mechanism drives GC cell migration and enhances tumor-neuron communication, leading to more aggressive neural invasion.

Additionally, circATP8A1, enriched in GC cell-derived exosomes, modulates the tumor immune microenvironment to promote tumor growth (116). In macrophages, circATP8A1 sponges miR-1-3p, activating the STAT6 pathway, leading to M2 macrophage polarization, and in turn, GC proliferation and metastasis. Exosomal circRNAs are valuable biomarkers for GC diagnosis given their abilities in affecting cancer progression. The stable presence of these cirRNAs in patient plasma offers notable potential for non-invasive diagnostic approaches.

3. Clinical applications of circRNAs in GC

circRNAs as diagnostic biomarkers. Over the past decades, patients diagnosed with advanced GC have experienced a poor 5-year survival rate, whereas those who have benefited from early detection have experienced survival rates as high as 97-100% (4). Therefore, when also taking into consideration the limited treatment options for advanced-stage patients, early diagnosis is key. Traditionally, tumor markers such as carcinoembryonic antigen (CEA), carbohydrate antigens (CA19-9, CA72-4, CA125, CA24-2 and CA50), pepsinogen and α-fetoprotein have been used in clinical settings for early GC detection (117,118). However, these markers suffer from low sensitivity and specificity.

Previous studies have uncovered the potential of serum-based non-coding RNAs as diagnostic tools. In 2018, Li *et al* (119) evaluated the diagnostic efficacy of hsa_circ_0001017 and hsa_circ_0061276 using reverse transcription-droplet digital PCR on plasma samples. This study, with the inclusion of 121 patients with GC and 121 healthy controls, demonstrated that detection of these two circRNAs jointly achieved an area under the curve (AUC) of 0.91, with a sensitivity of 84.7% and specificity of 96.6%, underscoring its high accuracy in distinguishing patients with GC from healthy individuals.

Roy *et al* (120) developed an 8-circRNA-based risk prediction model using serum samples sourced from two GEO datasets (GSE89143 and GSE83521) (121,122). The training cohort comprised 92 patients with GC and 46 controls, while the validation cohort included 102 patients with GC and 48 controls. In the training phase, the model achieved an AUC of 0.87, with sensitivity, specificity and accuracy all at 78%. In the validation phase, the model demonstrated a sensitivity of 89%, a specificity of 62% and an accuracy of 81%, with an AUC of 0.83, highlighting the potential of circRNAs in early-stage GC detection.

Furthermore, Xiao *et al* (123) proposed a serum-based diagnostic model that combined three EV-derived circRNAs with CEA. This approach yielded a sensitivity of 80.4%, a

specificity of 81.8% and an AUC of 0.866. Collectively, these findings accentuate the considerable potential of circRNAs as reliable biomarkers for GC diagnosis.

Prognostic value of circRNAs in GC. circRNAs can function as effective prognostic indicators for GC, with several demonstrating notable associations with patient outcomes. Measurement of circRNA levels in tumor tissues or plasma may contribute to the assessment of potential prognostic indicators that aid in stratifying patients and guiding clinical decision-making.

As a robust prognostic marker identified in GC, circMRPS35 exhibited potential utility in clinical prognostic models considering its sensitivity of 77.23% and specificity of 59.32% in predicting overall survival (51). Meanwhile, plasma levels of hsa_circ_0001017 were markedly associated with survival outcomes in patients with GC, and patients with lower plasma levels had a shorter median overall survival time compared with patients who had higher levels of hsa_circ_0001017 (60 vs. 84 months; P=0.009) (117). This underscores the value of non-invasive circRNA measurement in predicting long-term survival.

Noticeably, these markers represent a key step forward in integrating circRNAs into prognostic assessments, despite moderate accuracy stemmed from their sensitivity and specificity. Further validation and refinement of circRNA-based prognostic panels can further enhance their reliability and pave the way for personalized treatment strategies in GC.

circRNAs in treatment resistance. Chemotherapy, particularly cisplatin-based regimens, remains a cornerstone of GC treatment (124). However, the efficacy of these treatments is often compromised by the development of chemotherapy resistance. Emerging studies reveal that circRNAs are essential in modulating cisplatin resistance in GC (76-78,125-128).

For instance, hsa_circ_0081143 was upregulated in cisplatin-resistant GC tissues and enhanced the resistance by sponging miR-646, leading to the upregulation of CDK6, a key regulator of cell cycle progression (125). By contrast, silencing hsa_circ_0081143 *in vitro* markedly increased sensitivity to cisplatin, underscoring its potential as a therapeutic target to reverse resistance. Similarly, circAKT3 was markedly elevated in cisplatin-resistant cells and functioned by sponging miR-198, thereby activating the PI3K/AKT pathway through the upregulation of PIK3R1, consequently promoting DNA repair and reducing apoptosis. Based on the further clinical analysis of 105 patients, increased circAKT3 expression was demonstrated to be associated with shorter disease-free survival times and worse responses to cisplatin-based therapy. Furthermore, the predictive value of circAKT3 as a biomarker for cisplatin resistance was supported by an AUC of 0.91, indicating its potential for clinical use in identifying treatment-resistant patients.

Conversely, circCUL2 was downregulated in cisplatin-resistant cells but restored its sensitivity to cisplatin when overexpressed, depending on the inhibition of autophagy through the miR-142-3p/Rho-associated coiled-coil containing protein kinase 2 axis (76). Enhanced autophagy has been identified as a key player in cisplatin resistance during cancer treatment (126,127). Consistently, improved treatment outcomes were observed in patients with higher circCUL2 expression levels. Similarly, circMCTP2 could enhance cisplatin sensitivity by sponging miR-99a-5p and upregulating myotubularin related protein 3, which suppressed autophagy (128). Patients with elevated circMCTP2 levels revealed improved responses to cisplatin, as demonstrated by longer periods of disease-free survival. Notably, this study (128) also magnified the potential utility of circMCTP2 in guiding clinical chemotherapy decision-making, as its AUC was 0.945 for distinguishing cisplatin-resistant from cisplatin-sensitive patients.

Taken together, the aforementioned studies have revealed the diverse mechanisms by which circRNAs influence cisplatin resistance in GC. By regulating miRNA activity, autophagy and critical signaling pathways, circRNAs may represent potential therapeutic targets for overcoming chemotherapy resistance and enhancing therapeutic outcomes in patients with GC.

Targeted therapies, such as apatinib, a VEGFR-2 inhibitor, have shown promise in treating advanced GC; however, this is still challenged owing to the presence of resistance (129). circRACGAP1 has been identified as a key player in mediating resistance to apatinib (50). Ma *et al* (50) demonstrated that circRACGAP1 was upregulated in apatinib-treated GC cells and promoted drug resistance by sponging miR-3657, leading to upregulated autophagy related 7 (ATG7). Enhanced autophagy allows cancer cells to survive under apatinib-induced stress, which further weakens the effectiveness of this drug. Notably, silencing circRACGAP1 (or overexpressing miR-3657, silencing ATG7) in GC cells could suppress autophagy, and hence sensitized cells to apatinib-induced apoptosis (50). *In vivo*, GC xenograft models with circRACGAP1 knockdown demonstrated increased tumor reduction when treated with apatinib, supporting its potential as a therapeutic target to overcome apatinib resistance (50).

Immunotherapy with immune checkpoint inhibitors has become an important strategy for GC treatment, particularly for patients receiving third-line therapy (130-136). In GC, the most frequently utilized agents for immune checkpoint blockade include anti-programmed cell death protein 1 (PD-1) monoclonal antibodies (nivolumab and pembrolizumab), the anti-PD-L1 IgG1 antibody (avelumab) and anti-cytotoxic T-lymphocyte associated protein-4 antibodies (ipilimumab and tremelimumab). Resistance to anti-PD-1 therapy is also a major challenge in treating advanced GC. circDLG1 has been identified as a notable contributor to this resistance (137). Chen *et al* (137) demonstrated that circDLG1 was upregulated in GC tissues resistant to anti-PD-1 therapy, functioning by sponging miR-141-3p, thereby increasing the expression of C-X-C motif chemokine ligand 12, a chemokine known to promote immune evasion by attracting immunosuppressive cells to the TME. Moreover, high circDLG1 expression was associated with worse overall survival and progression-free survival in patients undergoing anti-PD-1 therapy. Therefore, targeting circDLG1 may enable the improvement of the effectiveness of immune checkpoint inhibitors by reducing immune evasion. Another circRNA, hsa_circ_0001947, found in sEVs, also participates in anti-PD-1 resistance (138). Wang *et al* (138) revealed elevated levels of hsa_circ_0001947 in GC-derived sEVs, where it bound miR-661 and miR-671-5p, leading to increased CD39 expression levels and subsequent

T-cell exhaustion. Inhibiting hsa_circ_0001947 reduced $CD8^+$ T cell exhaustion and improved responses to anti-PD-1 therapy *in vivo*. Consequently, targeting sEV-derived circRNAs could contribute to restoring immune function in cancer treatment.

Recently, Miao *et al* (81) also identified hsa_circ_0136666 as another key player in the immune evasion mechanisms of GC, which could bind to and inhibit miR-375, a tumor suppressor, resulting in increased DNA-dependent protein kinase catalytic subunit expression levels and increased DNA-PK protein levels. Simultaneously, DNA-PK was demonstrated to stabilize PD-L1 through phosphorylation at threonine 20 and threonine 22 sites, increasing its presence on cell surfaces. This process prompted cancer cells to evade immune detection and accelerated tumor growth, with a study revealing increased immunosuppressive cells and decreased tumor-infiltrating T cells in the affected tissue (81). Importantly, with the establishment of a mouse model, targeting hsa_circ_0136666 with siRNA-loaded lipid nanoparticles (NPs) was revealed to markedly enhance the efficacy of anti-PD-L1 immunotherapy. These findings further highlight the potential of targeting specific circRNAs, particularly in combination with existing immunotherapeutic approaches, to overcome immunotherapy resistance in cancer treatment. Taken together, these results show that circRNAs may offer a valuable solution for reducing resistance, in addition to predicting therapy resistance.

circRNAs as therapeutic targets in GC. circRNAs have emerged as potential therapeutic targets in GC, with several identified as drivers of tumor progression based on preclinical data (52). Among these, circMAP2K2, highly expressed in GC tissues, exerts oncogenic effects, manifesting as enhanced cancer cell proliferation and metastasis (49), by destabilizing PCBP1, a key RNA-binding protein (139-142). Specifically, circMAP2K2 interacts with PCBP1 to strengthen its polyubiquitination and subsequent degradation via the proteasome (49). The loss of PCBP1 further increases glutathione peroxidase 1 expression, activating the AKT/GSK3β signaling pathway, driving EMT and boosting the invasive potential of GC cells (49).

To counteract these effects, an innovative targeted delivery system was developed by utilizing epigallocatechin-3-gallate (EGCG)-lysozyme (LYS) fibrils to deliver small interfering (si)RNA-circMAP2K2 (si-circMAP2K2) into GC cells (49,143,144). These fibrils were formed through a one-step heating process under specific pH conditions, exhibiting rod-like nanostructures (length of 15-500 nm, average of 245±32 nm) that facilitated their penetration into cancer cells (49). By comparison, EGCG-LYS NPs outperformed conventional Lipofectamine 2000® in aspects of superior cellular uptake, enhanced lysosomal escape and increased siRNA delivery efficiency (49). Notably, in mouse models bearing GC xenografts, this treatment markedly reduced tumor growth, with tumor volumes shrinking by >60% compared with that in controls (49). Importantly, the use of EGCG-LYS fibrils in combination with si-circMAP2K2 was more effective in reducing tumor burden than si-circMAP2K2 alone (49). Additionally, EGCG-LYS/si-circMAP2K2 treatment markedly decreased the number of metastatic nodules in the lung, highlighting its potential to inhibit metastasis (49). A prominent feature of this therapy was its excellent safety profile supported by the absence of pronounced weight loss or damage to major organs in treated mice *in vivo*, emphasizing its non-toxic nature and potential suitability for clinical application (49).

hsa_circ_0008315, which is highly upregulated in GC tissues and cisplatin-resistant cells, is a potent target in GC treatment (77). A prior study delivered siRNA targeting hsa_circ_0008315 [PLGA-PEG(si-hsa_circ_0008315) NPs] using an innovative targeted delivery system utilizing poly(lactic-co-glycolic acid)-polyethylene glycol (PLGA-PEG) NPs (77,145,146). These NPs were prepared by employing a novel NP preparation technique of double emulsion solvent diffusion, featuring a spherical NP shape with a diameter of ~115 nm and a negative ζ potential of -19.2 mV. The encapsulation efficiency of si-hsa_circ_0008315 was 75.27±1.50%, with a polydispersity index of ~0.25 (77). These PLGA-PEG NPs demonstrated superior performance compared with naked siRNA in several key aspects. Specifically, these NPs markedly enhanced cellular uptake (fluorescence microscopy of Courmarin-6 labeled particles), reduced lysosomal degradation (decreased co-localization between NPs and lysosomes) and sustained release kinetics (cumulative siRNA release of only 44.7% after 24 h vs. 83.3% for free siRNA), enabling a prolonged therapeutic effect lasting ~1 week (77). Additionally, PLGA-PEG NPs revealed preferential accumulation in tumor tissues via the enhanced permeability and retention (EPR) effect, confirmed by *in vivo* biodistribution experiements (77). This delivery system markedly inhibited tumor growth and metastasis in both cell and animal models. In patient-derived xenograft models, the administration of PLGA-PEG(si-hsa_circ_0008315)NPs effectively reduced tumor volume and weight (77). Importantly, this NP-based approach demonstrated dual therapeutic effects of suppressing tumor progression and reversing cisplatin resistance (77). Furthermore, systemic toxicity assessment through H&E staining of major organs and blood biochemical examinations confirmed the biocompatibility of these NPs, without notable hepatotoxicity or renotoxicity (77). Collectively, this innovative NP-based approach exhibited adequate biocompatibility, in addition to antitumor and anti-metastasis properties.

The proposed nanotherapeutic approach, integrating high stability, low toxicity and potent antitumor efficacy, provides a viable strategy for GC. By leveraging nanotechnology to enhance the delivery of siRNA, this approach can exert anti-GC effects and offer a safer alternative to conventional therapies, potentially improving outcomes for patients with advanced GC.

4. Discussion

Metastatic GC can only be treated by chemotherapy and palliative surgery at present, resulting in a poor prognosis, with an overall survival time of only 3-5 months without treatment (4-14). Clinical trials report a median overall survival time of just 6-14 months in certain patients even with chemotherapy (4-14), underscoring the urgent need for more effective interventions. circRNAs have been shown to carry out key roles in different types of cancer, both as biomarkers for early diagnosis and as therapeutic targets, providing valuable insights and inspiration for exploring their potential in GC

management (147-149). As investigations in this field progress, continued refinement of detection methodologies, delivery platforms and circRNA engineering will be essential for fully realizing both the diagnostic and therapeutic applications of these molecules in GC.

circRNAs are a new and promising tool for cancer treatment, being very stable, resistant to breakdown and able to produce proteins for longer periods of time based on their unique structures (23,24,32-34). This inherent stability empowers them with potential as reliable biomarkers in various types of cancer. In colorectal cancer, a panel of three serum circRNAs achieved an AUC of 0.969 for distinguishing early-stage patients from healthy controls, outperforming conventional biomarkers such as CEA and CA19-9 (150). Similarly, a combination of three plasma circRNAs reached an AUC of 0.919 for early detection in non-small cell lung cancer (151). Nevertheless, several limitations hamper the clinical translation of circRNAs as diagnostic biomarkers. First, there is still a lack of standardized methodologies for the identification, validation and detection of circRNAs clinically. Reliable detection methods for circRNAs in bodily fluids are essential for maintaining consistent results across different laboratories and healthcare settings. Second, the majority of circRNAs, expressed at low levels, cannot be detected accurately with current technologies, necessitating the improvement of the sensitivity and accuracy of existing circRNA detection methods (152). Finally, there is inadequate validation and clinical translation considering that the majority of studies on circRNAs have been single-center and retrospective. Carrying out prospective validation and controlled clinical trials in future is warranted to establish circRNAs as reliable biomarkers that can impact clinical decision-making.

Concerning therapeutic potential, circRNAs have demonstrated considerable promise in various other types of cancer, offering potential approaches to treat patients with GC (153-158). In hepatocellular carcinoma, circRNA-based neoantigen vaccines effectively triggered antitumor immune responses through enhanced dendritic cell activation and T cell responses; and the inherent stability of circRNA enabled more sustained protein expression levels compared with traditional linear mRNA vaccines (153). Hu *et al* (157) revealed that chimeric antigen receptor (CAR)-encoding circRNA resulted in increased and more durable CAR expression on T cells compared with linear mRNA approaches; moreover, circRNA-based CAR-T cells demonstrated superior cell-killing activities and cytokine release *in vitro*, as well as improved antitumor efficacy *in vivo* (157). Importantly, the successful administration of the first circRNA drug (HM2002) for cardiac conditions marks the first-in-human clinical trial of a circRNA therapeutic (NCT06621576).

circRNAs provide new potential avenues of treatment for patients with GC, especially those at advanced stages with limited options available (4-14). At this stage, chemotherapy can only extend patient survival by a few months, demonstrating the need for new treatments. circRNAs have been utilized in other types of cancer, suggesting their potential of providing more stable and long-lasting effects, whether by activating the immune system or targeting cancer cells directly (153-157). circRNA vaccines may be a feasible direction to target specific proteins in GC to enhance the efficiency of treatments. For direct circRNA targeting applications, PLGA-PEG NP delivery systems have demonstrated their particular promise due to their biocompatibility, biodegradability and established Food and Drug Association approval status (147,146,159,160). However, the delivery of circRNA-based therapeutics remains a great challenge to be addressed. In particular, the gastrointestinal environment is one of the most intricate and complicated systems in the body, including highly acidic conditions (pH, 1-3) and abundant digestive enzymes that can degrade therapeutic agents. Another issue is that the majority of current delivery approaches rely on the EPR effect for passive tumor targeting, but this mechanism varies considerably, depending on patients and tumor types, which may potentially compromise the therapeutic consistency. In addition, there may be potential off-target effects, as circRNAs frequently share sequence homology with their linear RNA counterparts, necessitating selective approaches that target the characteristic back-splice junctions of circRNAs.

In conclusion, circRNAs have unique properties and potential in both diagnostic and therapeutic applications, warranting continued investigation in translational research to address the notable unmet needs in GC management. Future efforts should emphasize the exploration of their interactions within complex signaling networks, understanding their roles in TME modulation and optimizing delivery systems. By acquiring mechanistic insights and establishing rigorous evaluation, circRNAs are anticipated to emerge as valuable tools in the evolving landscape of precision oncology for patients with GC.

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Authors' contributions

LW contributed to investigating and writing. PZ, ZY and YL contributed to literature collection and writing summarization. HQ and NW contributed by provided guidance and revising the manuscript. JX contributed by provided guidance, and revising and editing the manuscript. All authors read and approved the final manuscript. Data authentication not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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