Molecular Cancer

REVIEW

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Non-coding RNAs in gastric cancer: mechanisms and therapeutic prospects

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Abstract

Gastric cancer is the fifth most common cancer and the third leading cause of cancer-related deaths worldwide. It is associated with high molecular and phenotypic heterogeneity. Early-stage gastric cancer can be treated with endoscopic resection and surgery, whereas at its advanced stage, sequential chemotherapy presents the only treatment option, which starts with first-line platinum and fluoropyrimidine-based dual drugs, supporting a median survival period of less than one year. Targeted monoclonal antibodies approved for the treatment of gastric cancer are effective for a limited subset of patients. Furthermore, painless and precise markers for the early detection of gastric cancer and new targets for its treatment are unavailable. Interestingly, many non-coding RNAs (ncRNAs), such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), play key roles in the development of gastric cancer. Multiple pieces of evidence suggest that ncRNAs play a crucial role in the treatment of gastric cancer using chemotherapy and targeted therapy drugs. In this article, we systematically reviewed the important roles of ncRNAs in chemotherapy resistance, immune escape, metabolism, and angiogenesis of gastric cancer, and systematically elucidated the relevant molecular mechanisms. In addition, we also proposed the potential clinical significance of ncRNA as a new therapeutic target and prognostic biomarker for gastric cancer.

Keywords Gastric cancer, Non-coding RNAs, Biomarker, Chemotherapy, Drug resistance

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Introduction

Gastric cancer (GC) presents one of the most aggressive malignancies worldwide, ranking as the fifth most common cancer (4.9%) and fifth leading cause of cancer-related mortality (6.8%) according to the GLOBOCAN database [1]. In 2017, nearly half of the world's new GC cases were reported in China, with more than 80% being advanced GC [2, 3]. Despite advancements in diagnostic and therapeutic strategies, including surgery, chemotherapy, targeted therapy, and immunotherapy, the prognosis of advanced-stage patients remains poor, with a 5-year survival rate < 30% [4]. Chemoresistance, metastasis, and tumor heterogeneity pose major challenges to effective treatment, particularly in cases of recurrent or metastatic disease [5, 6]. The molecular complexity in GC, which is driven by genetic and epigenetic alterations, underscores the urgent need to identify novel biomarkers and therapeutic targets to improve clinical outcomes.

Non-coding RNAs (ncRNAs), previously considered as transcriptional noise, have recently been recognized as pivotal regulators of gene expression and cellular processes [7, 8]. Circular RNAs (circRNAs) and long non-coding RNAs (lncRNAs) represent two prominent classes of ncRNAs with distinct biogenic and functional mechanisms [9, 10]. CircRNAs, characterized by covalently closed loops, are stable, exhibit tissue-specific expression, and function as microRNA sponges, RNA-binding protein scaffolds, or templates for peptide translation [11, 12]. Each lncRNA molecule comprises > 200 nucleotides. LncRNAs regulate chromatin remodeling, transcriptional regulation, and post-transcriptional modifications through interactions with epigenetic complexes, transcription factors, or mRNA stability machineries [13, 14]. The dysregulation of these lncRNAs has been implicated in oncogenesis, metastasis, and resistance to therapy across several cancer types, suggesting their potential as promising candidates for diagnostic and therapeutic innovations.

Recently, a profound interplay between ncRNAs and GC progression, which is associated with chemotherapy resistance, immune evasion, angiogenesis, and metabolic reprogramming, has been reported. For instance, circRNAs such as circAKT3 and circFAM73A regulate cisplatin resistance by sponging tumor-suppressive miR-198 and miR-490-3p and activate oncogenic pathways PI3K/AKT and Wnt/β-catenin axis, respectively [15, 16]. Similarly, lncRNAs such as HOTAIR and SNHG7 recruit miR-34a to promote the malignant progression of GC [17, 18]. Furthermore, these ncRNAs orchestrate the tumor microenvironment by regulating immune checkpoint proteins, macrophage polarization, and the activation of endothelial cells. The dynamic roles of ncRNAs in GC highlight their potential as prognostic biomarkers, predictors of therapeutic responses, and targets for RNA-based interventions. This review summarizes the current knowledge on the mechanisms underlying ncRNA-mediated GC chemoresistance, resistance to immunotherapy, angiogenesis, and metabolism, providing insights into their translational applications in precision oncology.

Overview of non-coding RNA

Sources and detection methods of non-coding RNA

CircRNAs are mainly generated through the reverse splicing of precursor mRNA. In this process, downstream splicing donors connect with upstream splicing receptors to form a closed-loop structure [19, 20], and involves reverse complementary sequences in introns (such as Alu elements) or RNA binding proteins (such as QKI, FUS) [21–23]. CircRNA detection requires several complementary technologies. Among these strategies, RNA sequencing (RNA-seq) involves whole transcriptome sequencing and algorithms (such as CIRCexplorer) to identify reverse splicing sites and discover novel molecules; however, it requires high-level data and RNase R preprocessing to eliminate linear RNA interference [24–26]. Microarrays target known circRNAs through predesigned probes and are suitable for large-scale screening; however, restricted coverage limits the effectiveness of this strategy [27]. RT qPCR, used during the validation phase, involves divergent primers for amplification of specific circular structures and RNase R digestion for improved accuracy [28, 29]. Moreover, digital PCR (ddPCR) achieves absolute Quantification through droplet partitioning, with a sensitivity of 0.001%, and is suitable for low-abundance samples, such as plasma exosomes [30]. NanoString nCounter relies on probe hybridization for direct counting, with no amplification step; it supports analysis of degraded samples (such as FFPE tissue) [31].

LncRNAs are mainly encoded by the non-coding genome sequences, including intergenic regions, antisense strands, and intron regions of protein-coding genes [13]. Intergene lncRNAs (such as HOTAIR) are transcribed by independent promoters that often harbor histone modification markers [17]. Antisense lncRNAs (such as XIST) overlap with the coding gene antisense strand, and chromatin silencing occurs through the recruitment of epigenetic modification complexes (such as PRC2) [32]. Intron-derived lncRNAs, such as MALAT1, are produced through variable splicing or transcriptional reading [33]. Multi-technology collaboration aids in the detection of lncRNAs: RNA sequencing (RNA-seq) combined with strand-specific library construction (such as dUTP labeling) can distinguish between sense/antisense transcripts and discover novel lncRNAs; however, it requires long-read long sequencing (e.g., PacBio) to resolve full-length isoforms [34]. Microarrays achieve

high-throughput screening involving probes targeting known lncRNA exons or splice sites, but are limited by database coverage [35]. RT-qPCR requires primers spanning the exon-intron boundary region to eliminate genomic DNA interference, and is combined with nuclear-cytoplasmic separation experiments for verifying subcellular localization [35]. Digital PCR (ddPCR) can reveal low-abundance lncRNAs supporting absolute quantification; hence, it is effective for liquid biopsy [36]. NanoString nCounter, which can directly detect lncRNAs using probes, without involving amplification, is compatible with degraded samples (such as FFPE tissue); however, its probe design relies on known sequences [37, 38]. In functional studies, CRISPR interference (CRISPRi) and RNA FISH techniques are frequently used to analyze the spatial localization of lncRNAs and regulatory networks [39–41].

Biological functions of non-coding RNA

A multidimensional regulatory role of circRNAs in gene expression is associated with their unique circular structure and dynamic regulatory networks. CircRNAs are competitive endogenous RNA (ceRNA); these molecules can adsorb specific miRNAs, acting as miRNA sponges, block the inhibitory effect of miRNAs on target mRNA, and enhance the translation efficiency of target genes [42, 43]. Meanwhile, circRNAs harboring RNA-binding protein (RBP) interaction motifs can act as molecular baits and regulate the splicing or stability of downstream target mRNA by isolating RBP (such as QKI or FUS) [21–23]. Specifically, base pairing between inverted repeat elements or the dimerization of RBPs brings a downstream splice-donor site (SD) into close proximity with an upstream splice-acceptor site (SA). This association may lead to backsplicing that is facilitated by the canonical splicing machinery (Fig. 1). During backsplicing, an upstream branch point (BP) attacks a downstream SD site, which subsequently attacks an upstream SA site to result in the formation of exon–intron circRNAs (EIcircRNAs) or exonic circRNAs (that is, circRNAs in which the internal intron is spliced out) (Fig. 1). Contrastingly, circRNAs interact with specific proteins, such as RNA polymerase II, to enhance their functions [44]. Interestingly, circRNAs containing internal ribosome entry sites (IRES), such as circZNF609 and circFNDC3B, can initiate non-classical translation under hypoxic or stress conditions, generating short peptides with unique functions and further expanding the role of circRNAs in proteomic regulation [45–47]. These molecular interactions collectively reveal the global regulatory roles of circRNAs from the epigenetic to translational level, which provides a new perspective for analyzing disease mechanisms and targeted therapy.

LncRNAs play multi-level roles in the regulation of gene expression through their complex primary structure and dynamic chromatin interaction networks. LncRNAs, the core mediators of epigenetic regulation, can recruit the polycomb inhibitory complex (PRC2) or DNA methyltransferase to specific genomic regions, mediating histone modification or DNA methylation, which leads

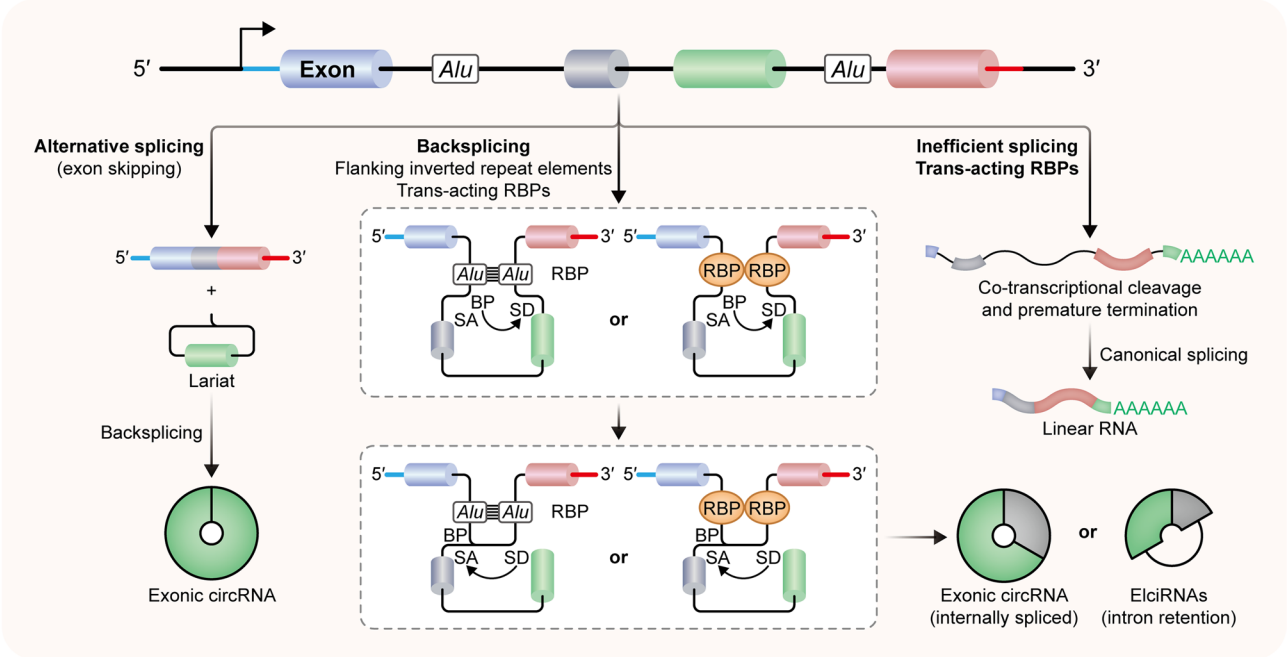

Fig. 1 The biogenesis of LncRNAs and circRNAs. Canonical splicing of mRNAs produces linear transcripts but back-splicing produces stable circular RNAs (circRNAs) consisting of non-sequential exon–exon junctions. BP, branch point; SA, splice-acceptor site; SD, splice-donor site

to the silencing of the entire chromosome or tumor suppressor gene cluster (Fig. 1) [48–50]. Meanwhile, lncRNAs can serve as molecular scaffolds or signaling hubs, dynamically coordinating the balance between transcriptional activation and inhibition by binding to transcription factors or regulating mRNA stability [51–53]. Moreover, some lncRNAs directly contribute to precursor mRNA splicing or nuclear-cytoplasmic transport through antisense complementary pairing, which are associated with the fine regulation of the post-transcriptional processes [54, 55]. Notably, certain lncRNAs encode functional micropeptides through hidden short open reading frames, overturning the traditional definition of non-coding RNAs. These processes reflect the global regulatory functions of lncRNAs in chromatin remodeling, transcriptional regulation, and post-translational modification, and provide innovative pathways for the development of lncRNA-based molecular diagnostic tools and targeted therapies.

Non-coding RNA in the resistance to GC chemotherapy

Platinum drugs comprise a class of cell cycle non-specific drugs that contain platinum elements, and are mainly used for cancer treatment. They promote cancer cell death by binding to the DNA of the cancer cells and inhibiting their replication and cell division. Common platinum drugs include first-generation cisplatin (CDDP), second-generation carboplatin, third-generation oxaliplatin, and lobaplatin, which are widely used in the treatment of gastric, ovarian, lung, and colorectal cancers [56–58]. Furthermore, 5-fluorouracil (5-FU) is the core drug used in GC chemotherapy as a first-line treatment, postoperative adjuvant, and neoadjuvant treatment (such as the FLOT scheme) in cases of locally advanced/metastatic gastric cancer [59, 60]. It can interfere with cancer cell metabolism by simulating the structure of uracil; it is widely used in colorectal, breast, and head and neck cancers [61, 62]. Trastuzumab, a humanized monoclonal antibody, targets and blocks the HER2 signaling pathway, and regulates antibody-dependent cytotoxicity (ADCC), inhibiting cancer cell growth. It is primarily used to treat HER2-positive breast and gastric cancers. It is frequently used in combination with chemotherapy drugs such as docetaxel and carboplatin [63–65]. Doxorubicin is an anthracycline antibiotic that destroys cancer cells by embedding double-stranded DNA, inhibiting topoisomerase II, and producing liver oxygen free radicals. It presents a nonspecific, broad-spectrum chemotherapeutic drug widely used in breast cancer, lymphoma, leukemia, and GC [66–68].

CircRNA and resistance to chemotherapy drugs

Recent studies revealed that circRNAs form a dynamic regulatory network associated with the resistance to GC chemotherapy through epigenetic regulation, metabolic reprogramming, and cell death signaling (Fig. 2). Its closed-loop structure endows it with high stability by adsorbing miRNAs through the ceRNA mechanism or by directly binding to protein complexes, which reshape the resistance-related pathways [69, 70]. Partial circRNAs are transmitted through exosomes and regulate the microenvironment across cells or mediate m6A modifications to modulate the drug resistance phenotype. These findings highlight the translational potential of circRNAs as key targets for reversing drug resistance and as prognostic markers (Fig. 2).

Several oncogenic circRNAs can promote the resistance of GC cells to platinum. In terms of platinum-based drug resistance (Tables 1 and 2), circAKT3 promotes the expression of PIK3R1 (a regulatory subunit of PI3K) by sponging miR-198 to enhance CDDP resistance of GC cells [15]. Circ _0008315 regulates the characteristics of stem cells in GC through the miR-3666/CPEB4 signaling pathway, promoting CDDP resistance and malignant progression of GC cells [71]. Furthermore, CircFAM73A promotes CDDP resistance by regulating miR-490-3p/HMGA2 through a positive feedback loop and recruiting HNRNPK to promote β-catenin stability [16]. Circ_0081143 acts as an endogenous sponge by directly binding to miR-646; the downregulation of miR-646 effectively reverses the inhibition of CDK6 induced by circ_0081143 knockdown, which promotes CDDP resistance in GC cells [72]. Autophagy, a fundamental cellular self-degradation process, plays a critically context-dependent role in cancer, functioning as both a tumor-suppressing mechanism during early carcinogenesis and a pro-survival pathway that fosters therapy resistance in established tumors. For example, circPOFUT1 directly sponges miR-488-3p, activating the expression of PLAG1 and ATG12; thus, it enhances the malignant phenotype and autophagy-related CDDP resistance in GC cells [73]. The exosomal transfer of M2 macrophage-derived circTEX2 enhances CDDP resistance in GC cells via the miR-145/ABCC1 axis [74]. CircVAPA was reported to promote CDDP resistance and malignant progression of GC via the miR-125b-5p/STAT3 signaling pathway [75]. CircLDLRAD3 promotes CDDP resistance in GC cells by regulating the miR-588/SOX5 pathway [76]. CircFN1 promotes CDDP resistance in GC cells via miR-182-5p [77]. CircARVCF enhances CDDP resistance in GC cells by increasing FGFR1 expression by sponging miR-1205 [78]. Circ_0026359 promotes CDDP resistance by regulating the miR-1200/POLD4 pathway [79]. CircDONSON promotes CDDP resistance in GC cells by regulating the miR-802/BMI1 axis [80]. Helicobacter

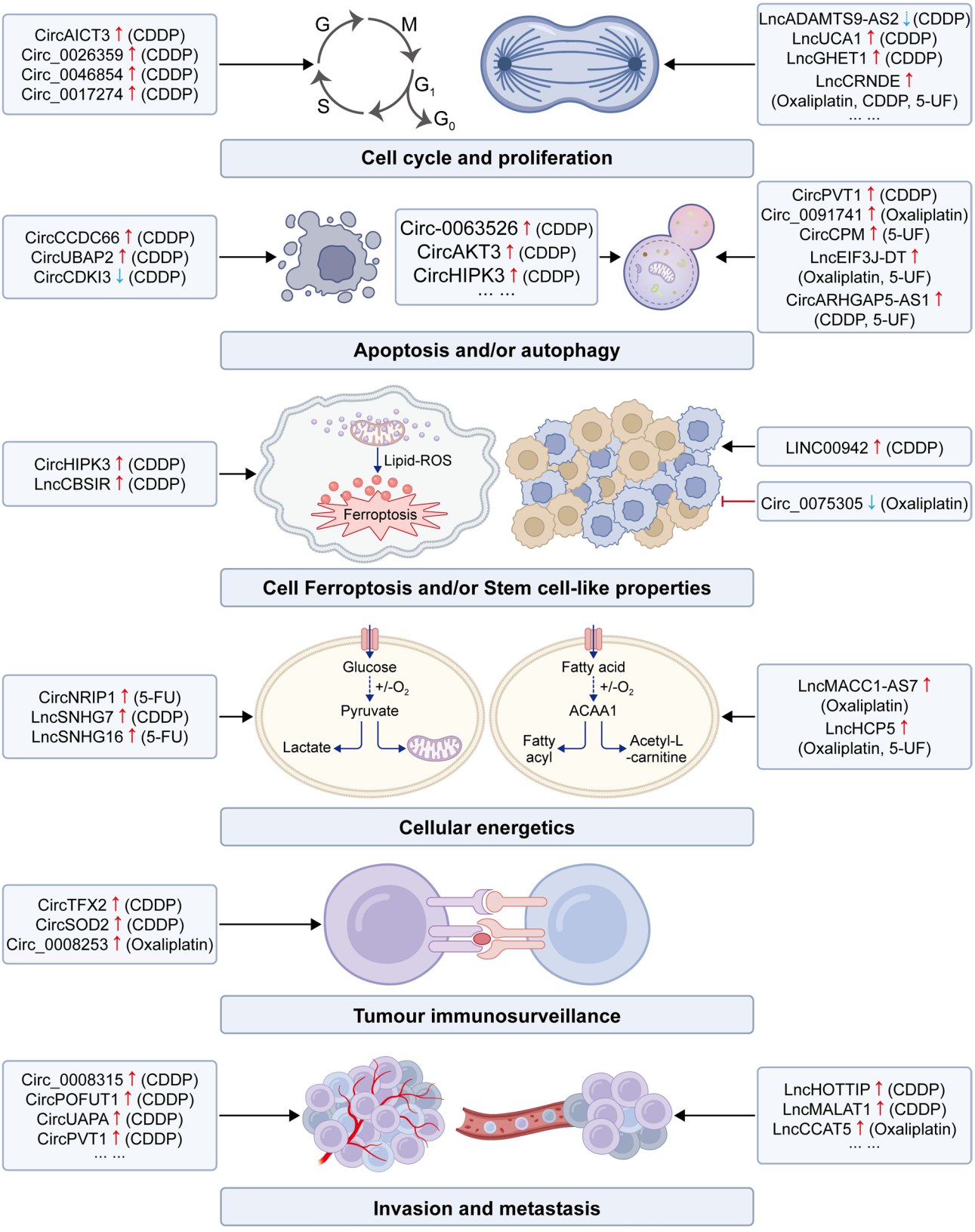

Fig. 2 Summary diagram of ncRNAs participated in the chemotherapy resistance of GC. Several ncRNAs are involved in GC chemotherapy resistance by influencing the gene alterations of cell cycle and proliferation, apoptosis, autophagy, cell ferroptosis, stem cell-like propertiies, cellular energetics, tumour immunosurveillace, invasion and metastasis through regulating expression of potential target genes and related signalling pathway

Table 1 Specific NcRNAs regulating cisplatin resistance in gastric cancer

Non-coding RNAs	Expression	Drugs	Functions	Genes and Signaling Pathways	Biomarkers	Reference
circAKT3	↑	cisplatin	promoting DNA damage repair; inhibiting autophagy	miR-198/PIK3R1	Therapeutic biomarker	[15]
circFAM73A	↑	cisplatin	promoting cell proliferation and migration	miR-490-3p/HMGA2/HNRNPK/β-catenin	Therapeutic biomarker	[16]
circ_0008315	↑	cisplatin	promoting cell proliferation, mobility and EMT	miR-3666/CPEB4	Prognostic biomarker	[71]
circ_0081143	↑	cisplatin	promoting cells viability and invasion ability	miR-646/CDK6	Therapeutic biomarker	[72]
circPOFUT1	↑	cisplatin	promoting cell proliferation, migration, invasion; inhibiting autophagy	miR-488-3p/PLAG1/ATG12	Therapeutic biomarker	[73]
circTEX2	↑	cisplatin	promoting M2 macrophage polarization	miR-145/ABCC1	Therapeutic biomarker	[74]
circVAPA	↑	cisplatin	promoting cell proliferation, migration and invasion; inhibiting cell apoptosis	miR-125b-5p/STAT3	Therapeutic biomarker	[75]
circLDLRAD3	↑	cisplatin	promoting cell proliferation, survival and invasion	miR-588/SOX5		[76]
circFN1	↑	cisplatin	promoting cell viability; inhibiting cell apoptosis	miR-182-5p	Therapeutic biomarker	[77]
circARVCF	↑	cisplatin	promoting colony formation and metastasis; inhibiting cell apoptosis	miR-1205/FGFR1		[78]
circ_0026359	↑	cisplatin	promoting cell proliferation	miR-1200/POLD4	Therapeutic biomarker	[79]
circDONSON	↑	cisplatin	promoting cell viability; inhibiting cell apoptosis	miR-802/BMI1	Therapeutic biomarker	[80]
circ_0046854	↑	cisplatin	promoting cell growth	miR-511-3p/CSF1		[81]
circ_0110805	↑	cisplatin	promoting cell viability, migration and invasion; inhibiting apoptosis	miR-299-3p/ENDOPDI		[82]
circ_0017274	↑	cisplatin	promoting cell growth	miR-637/CDX2		[83]
circ_0063526	↑	cisplatin	promoting cell migration, invasion and autophagy	miR-449a/SHMT2		[84]
circPVT1	↑	cisplatin	regulating cell autophagy, invasion and apoptosis	miR-30a-5p/YAP1	Therapeutic biomarker	[85]
		paclitaxel	promoting cell proliferation and migration; inhibiting apoptosis	miR-124-3p/ZEB1	Therapeutic biomarker	[86]
circPDSS1	↑	cisplatin	promoting cell proliferation, migration and invasion; inhibiting cell apoptosis	miR-515-5p/ITGA11		[87]
circASAP2	↑	cisplatin	promoting cell proliferation, migration; inhibiting apoptosis	miR-330-3p/NT5E		[88]
circHIPK3	↑	cisplatin	inhibiting autophagy-dependent ferroptosis	miR-508-3p/Bcl-2/beclin1/SLC7A11	Diagnostic/ Therapeutic biomarker	[89]
circCCDC66	↑	cisplatin	inhibiting cell apoptosis	miR-618/BCL2	Therapeutic biomarker	[90]

Table 1 (continued)

Non-coding RNAs	Expression	Drugs	Functions	Genes and Signaling Pathways	Biomarkers	Reference
circSOD2	↑	cisplatin	promoting M1 macrophage polarization	miR-1296/STAT1	Therapeutic biomarker	[102]
circUBAP2	↑	cisplatin	promoting cell apoptosis; inhibiting cell viability	miR-300/KAT6B	Therapeutic biomarker	[103]
circMCTP2	↓	cisplatin	inhibiting cell proliferation, apoptosis and autophagy	miR-99a-5p/MTMR3	Therapeutic biomarker	[104]
circUGGT2	↑	cisplatin	inhibiting cell growth and metastasis	METTL14/miR-186-3p/MAP3K9	Prognostic biomarker	[105]
circCUL2	↓	cisplatin	inhibiting malignant transformation and autophagy	miR-142-3p/ROCK2	Therapeutic biomarker	[27]
circ_0001017	↓	cisplatin	inhibiting cell growth, metastasis; enhancing cell apoptosis	miR-543/PHLPP2		[106]
circCDK13	↓	cisplatin	promoting cell apoptosis	MR/EIF4A3		[107]
LncRNA HOTAIR	↑	cisplatin	promoting cell proliferation	miR-34a	Therapeutic biomarker	[17]
LncRNA SNHG7	↑	cisplatin	promoting glycolysis	miR-34a/LDHA-glycolysis		[18]
LncRNA CBSLR	↑	cisplatin	regulating ferroptosis	m6A-YTHDF2	Therapeutic biomarker	[113]
LINC00942	↑	cisplatin	impairing cell apoptosis and inducing stemness	MSI2/c-Myc	Therapeutic biomarker	[114]
LncRNA UCA1	↑	cisplatin	promoting cell proliferation; inhibiting cell apoptosis	EZH2/PI3K/AKT	Therapeutic biomarker	[115]
			promoting cell proliferation; inhibiting cell apoptosis	miR-513a-3p/CYP1B1	Therapeutic biomarker	[116]
LncRNA HOTTIP	↑	cisplatin	promoting cell proliferation, migration, invasion and EMT	HMGA1/miR-218	Therapeutic biomarker	[117]
LncRNA GHET1	↑	cisplatin	promoting cell proliferation; inhibiting cell apoptosis	Bax, Bcl-2, MDR1, MRP1		[118]
LncRNA CRNDE	↑	cisplatin	promoting cell proliferation	NEDD4-1/PTEN		[119]
		oxaliplatin, 5-FU	inhibiting cell autophagy	SRSF6/PICALM	Prognostic/ Therapeutic biomarker	[120]
LncRNA MALAT1	↑	cisplatin	promoting cell proliferation, migration and invasion; inhibiting cell apoptosis	PI3K/AKT	Prognostic biomarker	[121]
			regulating cell apoptosis and autophagy	miR-30e/ATG5		[122]
			promoting cell viability; regulating autophagy	miR-30b/ATG5	Therapeutic biomarker	[123]
LncRNA BANCR	↑	cisplatin	inhibiting cell proliferation and viability	ERK1/2	Therapeutic biomarker	[124]
LOC101928316	↑	cisplatin	promoting cell activity, cell invasion and migration	PI3K-Akt-mTOR	Therapeutic biomarker	[125]
LncRNA ADAMTS9-AS2	↓	cisplatin	inhibiting cell viability and motility	miR-223-3p/NLRP3		[141]

Table 1 (continued)

Non-coding RNAs	Expression	Drugs	Functions	Genes and Signaling Pathways	Biomarkers	Reference
LncRNA HULC	↓	cisplatin	inhibiting cell autophagy	METase/FoxM1		[142]
LncRNA FGD5-AS1	↑	cisplatin	promoting cell proliferation; inhibiting cell senescence and DNA damage	YBX1/ROS		[140]
		5-FU	promoting cell proliferation	miR-153-3p/CITED2		[130]

Table 2 Specific NcRNAs regulating oxaliplatin resistance in gastric cancer

Non-coding RNAs	Expression	Drugs	Functions	Genes and Signaling Pathways	Biomarkers	Reference
circ_0075305	↑	oxaliplatin	reducing stem cell-like properties	RPRD1A/Wnt/β-catenin	Therapeutic biomarker	[108]
circ_0091741	↑	oxaliplatin	promoting cell autophagy	miR-330-3p/TRIM14/Dvl2/Wnt/β-catenin	Therapeutic biomarker	[91]
circ_0008253	↑	oxaliplatin	promoting M2 macrophage polarization; inhibiting apoptosis	M2-polarized macrophages		[92]
circ_0006089	↑	oxaliplatin	promoting cell proliferation, migration and invasion	miR-217/NRP1	Therapeutic biomarker	[93]
circLRCH3	↑	oxaliplatin	promoting cell proliferation, migration and invasion; inhibiting cell apoptosis	miR-383-5p/FGF7	Therapeutic biomarker	[94]
circ_0000144	↑	oxaliplatin	inhibiting cell proliferation and metastasis	miR-502-5p/ADAM9	Therapeutic biomarker	[95]
circ_0032821	↑	oxaliplatin	promoting cell proliferation, migration and invasion	miR-515-5p/SOX9	Therapeutic biomarker	[96]
LncCCAT5	↑	oxaliplatin	promoting cell growth and metastasis	Wnt/β-Catenin/STAT3	Therapeutic biomarker	[126]
LncDLGAP1-AS2	↑	oxaliplatin	promoting cell viability, proliferation, and metastasis; inhibiting cell apoptosis	Bax, Bcl-2, Caspase-3, p53, MMP-2, CD44	Therapeutic biomarker	[127]
LncMACC1-AS1	↑	oxaliplatin	promoting fatty acid oxidation and stemness	miR-145-5p/TGF-β1/SMAD2/3	Therapeutic biomarker	[128]
LncZNF674-AS1	↓	oxaliplatin	inhibiting cell viability and colony formation; promoting cell apoptosis	EZH2/CHST7	Therapeutic biomarker	[129]

pylori induces circ_0046854 to regulate the microRNA-511-3p/CSF1 axis, and enhances CDDP-resistance in GC cells [81]. Circ-0110805 enhances CDDP resistance in GC cells via the miR-299-3p/ENDOPDI axis [82]. Circ_0017274 promotes CDDP resistance by regulating the miR-637/CDX2 pathway in gastric cancer [83]. Exosomal circ_0063526 enhances CDDP resistance in GC cells via the regulation of the miR-449a/SHMT2

axis [84]. CircPVT1 promotes resistance of GC cells to CDDP and paclitaxel through the regulation of the miR-30a-5p/YAP1 and miR-124-3p/ZEB1 axes, respectively [85, 86]. CircPDSS1 promotes CDDP resistance in GC cells through the miR-515-5p/ITGA11 pathway [87]. CircASAP2 promotes CDDP resistance in GC cells by regulating the miR-330-3p/NT5E pathway [88]. CircHIPK3 enhances ferroptosis through the miR-508-3p/Bcl-2/beclin1/SLC7A11 axis, promoting CDDP resistance in GC cells [89]. CircCCDC66 enhances CDDP resistance in GC cells via the miR-618/BCL2 axis [90]. Exosomal circ_0091741 promotes resistance of GC cells to autophagy and oxaliplatin through miR-330-3p/TRIM14/Dvl2/Wnt/β-catenin axis [91]. Exosomal circ_0008253 derived from M2 macrophages regulates oxaliplatin resistance in GC cells [92]. Circ_0006089 promotes progression of GC and oxaliplatin resistance via miR-217/NRP1 [93]. CircLRCH3 promotes oxaliplatin resistance in GC cells by regulating the miR-383-5p/FGF7 axis [94]. Circ_0000144 promotes oxaliplatin resistance in GC cells by modulating the miR-502-5p/ADAM9 axis [95]. Circ_0032821 promotes oxaliplatin resistance in gastric cancer cells via miR-515-5p/SOX9 [96]. Furthermore, circCPM promotes 5-FU resistance in GC cells by activating PRKAA2-mediated autophagy (Table 3) [97]. CircNRIP1, serving as a miR-138-5p sponge, enhances hypoxia-induced 5-FU resistance in gastric cancer cells by regulating HIF-1α-dependent glycolysis [98]. Circ_0004650 enhances 5-FU resistance in GC cells by sponging miR-145-5p [99]. In terms of doxorubicin drug resistance, circ_0081143 enhances YES1 expression by targeting miR-129-2-3p, thereby promoting the malignant development of gastric cancer and doxorubicin resistance [100]. Exosomal circPRRX1 enhances doxorubicin resistance in gastric cancer cells by regulating the miR-3064-5p/PTPN14 pathway [101].

Contrastingly, a few circRNAs alleviate the resistance of GC cells to chemotherapeutic drugs. For instance, circSOD2 polarizes macrophages to the M1 phenotype by targeting the miR-1296/STAT1 axis to alleviate cisplatin resistance in GC cells [102]. CircUBAP2 inhibits CDDP resistance in GC cells via the miR-300–KAT6B axis [103]. CircMCTP2 upregulates MTMR3 expression by sponging miR-99a-5p and promoting the sensitivity of GC cells to CDDP [104]. CircUGGT2 suppresses METTL14-dependent m6 modification to inhibit gastric cancer progression and cisplatin resistance via the miR-186-3p/MAP3K9 axis [105]. CircCUL2 induces autophagy through miR-142-3p/ROCK2, thereby inhibiting malignant transformation and CDDP resistance in GC [27]. Circ_0001017 inhibits CDDP resistance in GC cells via the miR-543/PHLPP2 axis [106]. Methionine restriction promotes CDDP sensitivity in gastric cancer cells by down-regulating circCDK13 levels [107]. Overexpression of Circ-0075305 can effectively reduce stem cell-like characteristics and enhance the sensitivity of GC cells to oxaliplatin via the RPRD1A/Wnt/β-catenin axis [108]. Circ_0000520 enhances the sensitivity of gastric cancer

Table 3 Specific NcRNAs regulating 5-FU resistance in gastric cancer

Non-coding RNAs	Expression	Drugs	Functions	Signaling Pathways	Biomarkers	Reference
circCPM	↑	5-FU	promoting cell autophagy	miR-21-3p/PRKAA2	Prognostic/Therapeutic biomarker	[97]
circNRIP1	↑	5-FU	regulating glucose metabolism	miR-138-5p/HIF-1α	Therapeutic biomarker	[98]
circ_0004650	↑	5-FU	inhibiting cell apoptosis	miR-145-5p	Therapeutic biomarker	[99]
LncSNHG16	↑	5-FU	promoting glycolysis	miR-506-3p-PTBP1	Therapeutic biomarker	[131]
LncFEZF1-AS1	↑	5-FU	promoting cell proliferation; inhibiting cell autophagy	ATG5		[132]
LINC02323	↑	5-FU	promoting cell proliferation and motility; inhibiting cell apoptosis	miR-139-3p	Prognostic biomarker	[133]
LncHNF1A-AS1	↑	5-FU	promoting cell viability, proliferation and EMT; inhibiting cell apoptosis	miR-30b-5p/EIF5A2	Therapeutic biomarker	[134]
LncMIR155HG	↑	5-FU, cisplatin,	promoting cell proliferation and migration	NF-κB/STAT3	Therapeutic biomarker	[135]
LncEIF3J-DT	↑	5-FU, oxaliplatin,	promoting cell autophagy	miR188-3p/ATG14	Prognostic biomarker	[136]
LncHCP5	↑	5-FU, oxaliplatin,	promoting stemness and fatty acid oxidation	miR-3619-5p/AMPK/PGC1α/CEBPB	Therapeutic biomarker	[137]

cells to trastuzumab via the PI3K-AKT signaling pathway (Table 4) [109].

LncRNA and resistance to chemotherapy drugs

Recently, lncRNAs was reported to mediate complex molecular networks associated with resistance to GC chemotherapy through epigenetic modifications, metabolic reprogramming, and the regulation of programmed cell death (Fig. 2). These lncRNAs adsorb miRNAs through the ceRNA mechanism as well as directly interact with protein complexes to dynamically regulate resistance-related signaling pathways, making them potential targets for reversing chemotherapy resistance [110–112].

Several lncRNAs can promote chemotherapy resistance in GC (Table 2). In the context of platinum drug resistance (Tables 1 and 2), hypoxia-inducible lncRNA CBSLR was reported to promote CDDP resistance in GC cells by inhibiting ferroptosis [113]. LINC00942 promotes CDDP resistance in gastric cancer cells by inhibiting MSI2 degradation, which enhances the stability of c-Myc mRNA [114]. UCA1 promotes GC cell resistance to CDDP via the EZH2/PI3K/AKT and miR-513a-3p/CYP1B1 axes [115, 116]. The exon-mediated transfer of HOTTIP promotes CDDP resistance in GC cells by regulating the HMGA1/miR-218 axis [117]. The lncRNAs SNHG7 and HOTAIR interfere with miR-34a to desensitize gastric cancer cells to CDDP [17, 18]. The lncRNA GHET1 promotes the resistance of gastric cancer cells to CDDP by downregulating Bax expression and upregulating the expression of Bcl-2, MDR1, and MRP1 [118]. CRNDE promotes CDDP resistance via the NEDD4-1/PTEN axis, and alleviates oxaliplatin and 5-FU resistance via SRSF6/PICALM in GC cells [119, 120]. The lncRNA MALAT1 promotes CDDP resistance via three pathways, including the PI3K/AKT, miR-30b/ATG5, and miR-30e/ATG5 axes [121–123]. BANCR promotes CDDP resistance in gastric cancer cells by activating the ERK1/2 pathway [124]. HDAC3-mediated expression of lncRNA LOC101928316 activates the PI3K Akt mTOR pathway, inducing CDDP resistance in GC cells [125]. Moreover, CCAT5 promotes oxaliplatin resistance in metastatic GC cells with high Wnt activity via the crosstalk between Wnt/β-Catenin and STAT3 signaling [126]. DLGAP1-AS2 promotes oxaliplatin resistance in gastric cancer cells by regulating the expression of Bax, Bcl-2, Caspase-3, p53, MMP-2, and CD44 genes [127]. The MSC-regulated lncRNA MACC1-AS1 expression promotes stemness and oxaliplatin resistance in GC via fatty acid oxidation [128]. LncRNA ZNF674-AS1 enhances oxaliplatin resistance in GC cells by regulating EZH2-mediated CHST7 methylation [129]. LncRNA FGD5-AS1 promotes 5-FU resistance in GC cells through the miR-153-3p/CITED2 axis (Table 3) [130]. LncRNA SNHG16 desensitizes GC cells to 5-FU by targeting the miR-506-3p-PTBP1-mediated glucose metabolism [131]. The lncRNA FEZF1-AS1 promotes 5-FU resistance in GC cells by regulating autophagy via the FEZF1-AS1/ATG5 axis [132]. LINC02323 promotes 5-FU resistance in GC cells via miR-139-3p and predicts adverse outcomes of neoadjuvant chemotherapy in patients with GC [133]. HNF1A-AS1 serves as a ceRNA for miR-30b-5p and facilitates the EMT process in EIF5A2-induced GC to promote 5-FU resistance [134]. Previous research focusing on the multidrug resistance revealed that lncRNA MIR155HG induces the resistance of GC cells to CDDP and 5-FU via the NF-κB/STAT3 axis [135]. The lncRNA EIF3J-DT induces oxaliplatin and 5-FU resistance in GC via the miR188-3p/ATG14 axis, which regulates autophagy [136]. MSC-induced lncRNA HCP5 drives fatty acid oxidation through the miR-3619-5p/AMPK/PGC1α/CEBPB axis, promoting gastric cancer stemness and oxaliplatin and 5-FU resistance [137]. Specifically, lncRNA ARHGAP5-AS1 enhances cisplatin, 5-FU, and doxorubicin resistance in GC cells via SQSTM1/METTL3, thereby promoting cell autophagy [138]. LncRNA LINC00665 promotes tumorigenesis and

Table 4 Specific NcRNAs regulating doxorubicin and trastuzumab resistance in gastric cancer

Non-coding RNAs	Expression	Drugs	Functions	Genes and Signaling Pathways	Biomarkers	Reference
circ_0081143	↑	doxorubicin	promoting cell proliferation, migration and invasion	miR-129-2-3p/YES1	Therapeutic biomarker	[100]
circPRRX1	↑	doxorubicin	promoting cell proliferation, migration and invasion	miR-3064-5p/PTPN14	Therapeutic biomarker	[101]
circ_0000520	↓	trastuzumab	promoting cell apoptosis; inhibiting cell viability	PI3K/Akt		[109]
LncARHGAP5-AS1	↑	doxorubicin	promoting cell autophagy	SQSTM1/METTL3	Therapeutic biomarker	[138]
LINC00665	↑	trastuzumab	promoting cell migration and invasion	miR-199b-5p/SERPINE1/PI3K/AKt		[139]

trastuzumab resistance in GC through the miR-199b-5p/SERPINE1 axis (Table 4) [139].

In contrast, some lncRNAs enhance the sensitivity of GC cells to chemotherapy. For example, the lncRNA FGD5-AS1 stabilizes YBX1, inhibiting cell aging and ROS production, and suppresses CDDP resistance [140]. The lncRNA ADAMTS9-AS2 inhibits the development of gastric cancer and sensitizes chemotherapy-resistant GC cells to cisplatin by regulating the miR-223-3p–NLRP3 axis [141]. METases inhibit autophagy via the HULC/FoxM1 pathway to reduce CDDP resistance in drug-resistant gastric cancer cells [142].

Non-coding RNAs and immunotherapy for gastric cancer

Immunotherapy has become an important breakthrough in the treatment of GC owing to its unique mechanism associated with recognizing and clearing tumor cells by activating the patient's immune system [143, 144]. However, immune escape remains a major obstacle to effective immunotherapy [145]. Research has shown that immune escape in GC is significantly correlated to multiple molecular mechanisms, involving circRNAs that promote tumor cell escape from the immune system by regulating the PD-L1/PD-1 signaling pathway, immune cell function, and remodeling of the tumor microenvironment (TME). Specifically, circRNAs can enhance the immune escape ability in GC cells by regulating the key signaling axes and metabolic reprogramming (Table 5). These findings validate that circRNAs are novel molecular targets for GC immunotherapy and have significant clinical translational potential (Fig. 3).

Previous research on PD-L1/PD-1 signaling regulation indicates that Circ_0136666 drives PD-L1 phosphorylation through the miR-375/PRKDC axis, promoting TME formation and immune escape [146]. CircRHBDD1 and circ_0073453 either directly upregulate PD-L1 expression or enhance PD-L1-mediated $CD8^+$T cell inhibition through the miR-146a-5p/IL-8 pathway, respectively. LncRNAs UCA1, SNHG15, and PROX1-AS1 competitively bind to miRNAs, including miR-141 and miR-877-5p, to release miRNA-mediated inhibition of PD-L1, and form a multilevel regulatory network [147–151]. In T cell depletion and functional inhibition, CircDLG1 induces resistance to PD-1 therapy through the miR-141-3p/CXCL12 axis, while Circ_0001947 accelerates $CD8^+$T cell depletion via the miR-661/miR-671-5p-CD39 pathway [152, 153]. Circ_0001479 promotes immune escape by inhibiting $CD8^+$ T cell infiltration and is associated with immune checkpoints via the miR-661/miR-671-5p/CD39 pathway [154]. In addition, metabolic reprogramming and TME remodeling are key mechanisms: Circ_0008035 regulates pyruvate metabolism through EXT1-mediated PKM2 nuclear translocation, whereas Circ_0008287 induces $CD8^+$ T-cell apoptosis through the miR-548c-3/CLIC1 axis, concomitantly establishing an immunosuppressive microenvironment [155, 156]. CircSOD2 targets miR-1296/STAT1 to promote M1 polarization and enhance cisplatin efficacy, while Circ_102191 and exosomal circ_0017252 regulate M2 polarization through miR-493-3p/XPR1 and miR-17-5p, respectively, revealing the bidirectional role of circRNA in immune cell phenotype regulation [102, 157, 158]. These interactions suggest the circRNA-driven immune escape in GC through multi-target and multidimensional mechanisms and its important translational value as a prognostic marker or molecular target for combination immunotherapy.

Non-coding RNA and angiogenesis in gastric cancer

Angiogenesis is crucial for the malignant progression of cancer, which directly promotes proliferation, invasion, and distant dissemination by providing oxygen and nutrition to the tumor, and establishing metastatic pathways [159–162]. Non-coding RNA plays crucial roles in angiogenesis through multilevel molecular interactions and signaling regulatory networks. Additionally, non-coding RNA-mediated angiogenesis synergizes with processes such as EMT and immune escape, enhancing tumor invasiveness and providing a "vicious cycle" support for metastasis by promoting vascular leakage (Table 6). Hence, targeting these RNA molecules can simultaneously inhibit angiogenesis and tumor evolution. Overall, these roles of ncRNAs highlight their dual intervention value in suppressing cancer progression.

CircRNAs are involved in the regulation of tumor angiogenesis through various molecular mechanisms. For instance, circSHKBP1 and circ_0044366 activate VEGF by sponging miR-582-3p and miR-29a, respectively, thereby significantly promoting tumor cell angiogenesis [163, 164]. Circ_0006089 upregulates TGFB1 by inhibiting miR-361-3p, driving cell growth, metastasis, and glycolysis, and enhancing angiogenesis [165]. Similarly, circFCHO2 promotes tumor invasion and stem cell characteristics through the miR-194-5p/JAK1/STAT3 axis, while circLMP2A upregulates VEGFA through the KHSRP/VHL/HIF1α pathway, which directly enhances endothelial cell tube formation and cell migration [166, 167]. Notably, some circRNAs, such as circ_0005758, inhibit angiogenesis and tumor proliferation and invasion through the miR-1229-3p/GCNT4 axis, indicating their potential as anticancer molecules [168]. Moreover, circPAK2 and circDONSON promote lymphangiogenesis and radiation resistance by regulating the IGF2BPs/VEGFA or miR-149-5p/LDHA pathways, respectively, further expanding the multifunctional role of circRNAs in the tumor microenvironment [169, 170]. Circ_0001190

Table 5 Non-coding RNAs regulating immune resistance in gastric cancer

Non-coding RNAs	Target cell	Expression	Genes and Signaling Pathways	Mechanism	Immune effect	Reference
circ_0136666	CD8 + T cells	↑	miR-375/PRKDC/PD-L1	regulating immune checkpoint proteins and prompting phosphorylation of PD-L1	promoting TME formation and immune escape	[146]
circRHBDD1	CD8 + T cells	↑	GF2BP2/PD-L1	upregulating of PD-L1 expression and reprogramming of T cell-mediated immune response	promoting immune escape	[147]
circ_0073453	CD8 + T cells	↑	miR-146a-5p/IL-8/PD-L1	regulating secretion of IL-8; enhancing PD-L1 expression and resisting cytotoxic CD8 + T cell killing	promoting immune escape	[148]
circDLG1	CD8 + T cells, MDSCs	↑	miR-141-3p/CXCL12/PD-1	acting as miRNA sponge and promoting resistance to anti-PD-1-based therapy	promoting immune escape	[152]
circ_0001947	CD8 + T cells	↑	miR-661/miR-671-5p/CD39	acting as miRNA sponge and CD8 + T cells depletion	promoting immune resistance	[153]
circ_0001479	CD8 + T cells	↑	miR-133a-5p/DEK/Wnt/β-catenin	inhibiting CD8 + T cells infiltration and associated with immune checkpoints	promoting immune escape	[154]
circ_0008035	CD8 + T cells	↑	EXT1/PKM2	promoting EXT1-mediated nuclear translocation of PKM2 and regulating pyruvate metabolism	promoting immune escape	[155]
circ_0008287	CD8 + T cells	↑	miR-548c-3/CLIC1	impairing the function of CD8 + T cells and promoting CD8 + T cells apoptosis	promoting immune escape	[156]
circSOD2	M1 macrophage	↑	miR-1296/STAT1	acting as miRNA sponge and regulating target gene	promoting M1 macrophage polarization	[102]
circ_102191	M2 macrophage	↑	miR-493-3p/XPR1	acting as miRNA sponge and regulating target gene	promoting M2 macrophage polarization	[157]
circ_0017252	M2 macrophage	↓	miR-17-5p/DUSP2	acting as miRNA sponge	inhibiting M2 macrophage polarization	[158]
LncRNA UCA1	-	↑	miR-26a/b/miR-193a/miR-214/PDL1	interacting with miRNA directly and regulating PD-L1 expression	immune escape	[149]
LncRNA PROX1-AS1	-	↑	miR-877-5p/PD-L1	interacting with miRNA directly and regulating PD-L1 expression	immune escape	[150]
LncRNA SNHG15	-	↑	miR141/PD-L1	interacting with miRNA directly and regulating PD-L1 expression	immune escape	[151]

and circ_0008035 were reported to promote angiogenesis in gastric cancer via the miR-586/SOSTDC1 and miR-429/SMAD2 axis, respectively [171, 172]. Hence, circRNA is associated with a potentially important switch in angiogenesis through dynamic regulatory molecules such as VEGF and HIF1α, and its expression level is closely related to tumor progression and prognosis.

LncRNAs play a bidirectional role in tumor angiogenesis through epigenetic regulation and signaling pathways. Most lncRNAs that promote angiogenesis drive tumor

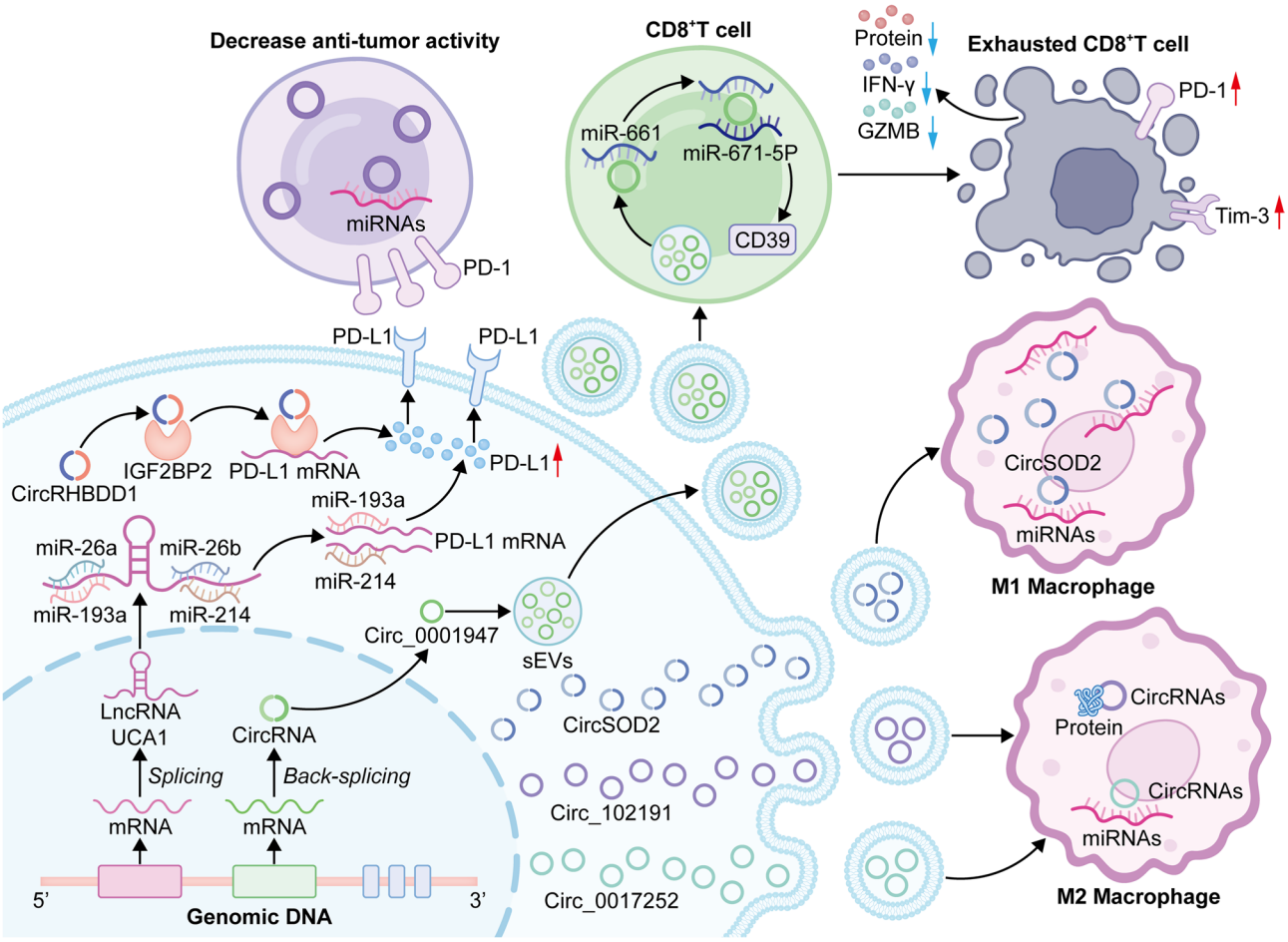

Fig. 3 The role of tumor-derived ncRNAs in immune cells, including T cell and macrophage

development by activating the pro-angiogenic signaling axis. For instance, HNF1A-AS1 promotes tumor invasion and lymph-angiogenesis through the miR-30b-3p/PI3K/AKT pathway [173]. MALAT1 enhances cell migration, tumorigenicity, and metastasis through the ERK/MMP and FAK/paxillin pathways and induces angiogenesis [174]. The STAT3/VEGFA pathway comprises another key node regulated by lncRNAs, and PVT1 significantly promotes tumor growth and angiogenesis by activating this pathway [175]. Some lncRNAs directly target angiogenesis-related factors, such as NKX2-1-AS1, which promotes tumor proliferation through the SERPINE1/VEGFR-2 axis and is associated with poor prognosis. NEAT1 enhances endothelial cell migration and angiogenesis through miR-17-5p/TGFβR2 [176, 177]. Notably, a few lncRNAs can inhibit angiogenesis. WT1-AS reduces cell proliferation, EMT, and stem cell characteristics by inhibiting the WT1 gene and induces apoptosis [178]. LINC01314 inhibits tumor invasion and angiogenesis by blocking the KLK4/Wnt/β-catenin pathway [179]. Additionally, CRART16 promotes tumor proliferation through the miR-122-5p/FOS/VEGFD axis and mediates bevacizumab resistance, revealing the potential role of lncRNAs in treatment resistance [180]. H3K27 acetylation upregulates lncRNA LINC00501 via EMT activation and angiogenesis to promote GC metastasis via the hnRNPR/SLUG pathway [181]. These reports indicate that lncRNAs play complex roles in the spatiotemporal dynamics of angiogenesis through various pathways such as VEGFR and Wnt/β- catenin, and their functional diversity provides new targets for developing antiangiogenic therapeutic strategies.

Non-coding RNA and metabolism of gastric cancer

Metabolic reprogramming is an important feature of malignant tumors and provides a major basis for the rapid proliferation, invasion, metastasis, and treatment resistance of cancer cells by modulating energy supply, biosynthesis, and redox balance. Recent research has revealed that metabolic pathway abnormalities drive the malignant behavior of tumors and participate in the multidimensional process of onset and development of tumors by regulating the TME, epigenetic modifications, and cell fate determination [182–184]. Especially

Table 6 Non-coding RNAs regulating angiogenesis of gastric cancer

Non-coding RNAs	Expression	Genes and Target genes and pathways	Functions	Angiogenesis	Reference
circSHKBP1	↑	miR-582-3p/HUR/VEGF/HSP90	promoting cell proliferation, migration and invasion	promoting angiogenesis	[163]
circ_0044366	↑	miR-29a/VEGF	promoting cell proliferation and migration,	promoting angiogenesis	[164]
circ_0006089	↑	miR-361-3p/TGFB1	promoting cell growth, metastasis and glycolysis	promoting angiogenesis	[165]
circFCHO2	↑	miR-194-5p/JAK1/STAT3	promoting cell proliferation, invasion and stem cell characteristics	promoting angiogenesis	[166]
circLMP2A	↑	KHSRP/VHL/HIF1α/VEGFA	promoting tube formation and migration	promoting angiogenesis	[167]
circ_0005758	↓	miR-1229-3p/GCNT4	promoting cell proliferation, migration and invasion	inhibiting angiogenesis	[168]
circPAK2	↑	IGF2BPs/VEGFA	promoting cell migration, invasion, lymph angiogenesis, EMT and metastasis	promoting angiogenesis	[169]
circDONSON	↑	miR-149-5p/LDHA	promoting cell proliferation and metastasis; inhibiting cell apoptosis and radiosensitivity	promoting angiogenesis	[170]
circ_0001190	↓	miR-586/SOSTDC1	promoting cell vitality, proliferation, migration and invasion	promoting angiogenesis	[171]
circ_0008035	↑	miR-429/SMAD2	promoting cell proliferation and metastasis; inhibiting cell apoptosis	promoting angiogenesis	[172]
LncRNA HNF1A-AS1	↑	miR-30b-3p/PI3K/AKT	promoting cell invasion, metastasis and lymphangiogenesis	promoting angiogenesis	[173]
LncRNA MALAT1	↑	ERK/MMP; FAK/paxillin	promoting cell migration, invasion, tumorigenicity and metastasis	promoting angiogenesis	[174]
LncRNA PVT1	↑	STAT3/VEGFA	promoting tumor growth	promoting angiogenesis	[175]
LncRNA NKX2-1-AS1	↑	SERPINE1/VEGFR-2	promoting cell proliferation and poor prognosis	promoting angiogenesis	[176]
LncRNA NEAT1	↑	miR-17-5p/TGFβR2	promoting cell proliferation, migration and tube formation ability of endothelial cells	promoting angiogenesis	[177]
LncRNA WT1-AS	↑	WT1	inhibiting cell proliferation, migration, EMT and stemness; promoting cell apoptosis	inhibiting angiogenesis	[178]
LncRNA LINC01314	↓	KLK4/Wnt/β-catenin	inhibiting cell migration and invasion	inhibiting angiogenesis	[179]
LncRNA CRART16	↑	miR-122-5p/FOS/VEGFD	promoting cell proliferation, colony formation and bevacizumab resistance	promoting angiogenesis	[180]
LncRNA LINC00501	↑	hnRNPR/SLUG	promoting EMT and gastric cancer metastasis	promoting angiogenesis	[181]

in gastric cancer, an imbalance in metabolic pathways, such as glycolysis, glutamine metabolism, and fatty acid oxidation, is significantly correlated to chemotherapy resistance, immune escape, and poor prognosis [185, 186]. Revealing key nodes in the metabolic regulatory network is considered crucial for overcoming treatment bottlenecks. NcRNAs, a precise regulator of tumor metabolism, dynamically integrate metabolic activity of enzymes, substrate utilization, and energy sensing systems through the "molecular sponge" effect, epigenetic modifications, and signal pathway interactions, presenting a complex metabolic regulatory axis [187].

Recently, multiple studies have shown that circRNAs are involved in the malignant progression of gastric cancer by regulating multiple metabolic pathways (Table 7; Fig. 4). For instance, circNRIP1 acts as a microRNA-149-5p sponge, promoting cancer progression through the AKT1/mTOR pathway, enhancing lactate metabolism [188]. CircLMO7 and circDYRK1A act as microRNA-30a-3p and microRNA-889-3p sponges, promoting glutamine metabolism and gastric cancer progression through the WNT2/β-catenin pathway and miR-889-3p/FBXO4 axis, respectively [189, 190]. Circ_0008035 regulates immune escape in GC via the pyruvate metabolism by promoting EXT1-mediated PKM2 nuclear translocation [155]. Circ_0088300-mediated upregulation of BOLL promotes growth and metastasis in GC through mitochondrial metabolic reprogramming [191]. Furthermore, circ_0003159 upregulates LIFR expression by competitively binding to miR-221-3p/miR-222-3p, which inhibits glycolysis and blocks gastric cancer development [192]. Conversely,

Table 7 Non-coding RNAs regulating metabolism in gastric cancer

Non-coding RNAs	Expression	Genes and Target genes and pathways	Functions	Metabolic pathway	Reference
circ_0008035	↑	EXT1/PKM2	inhibiting CD8 + T cell number and function	pyruvate metabolism	[155]
circNRIP1	↑	miR-149-5p/AKT1/mTOR	promoting cell proliferation, migration and invasion	glycolysis metabolism	[188]
circLMO7	↑	miR-30a-3p/WNT2/β-catenin	promoting cell proliferation, migration and invasion	glutamine metabolism	[189]
circDYRK1A	↓	miRNA-889-3p/FBXO4	inhibiting cell proliferation, migration and invasion	glutamine metabolism	[190]
circ_0088300	↑	BOLL	promoting cell growth and metastasis	mitochondrial metabolism	[191]
circ_0003159	↓	miR-221-3p/miR-222-3p/LIFR	inhibiting cell viability, migration and invasion; promoting cell apoptosis	glycolysis metabolism	[192]
circUBE2Q2	↑	miR-370-3p/STAT3	promoting cell proliferation, migration and invasion; inhibiting cell autophagy	glycolysis metabolism	[193]
LncRNA SNHG7	↑	miR-34a/LDHA-glycolysis	promoting DDP resistance	glycolysis metabolism	[18]
LncRNA SNHG16	↑	miR-506-3p-PTBP1	inhibiting cell growth; promoting cell apoptosis	glycolysis metabolism	[131]
LncRNA MACC1-AS1	↑	miR-145-5p/TGF-β1/SMAD2/3	promoting cell stemness	fatty acid metabolism	[128]
LncRNA HCP5	↑	miR-3619-5p/AMPK/PGC1α/CEBPB	promoting cell stemness	fatty acid metabolism	[137]
LncRNA AC012181.2	↑	HERPUD1	promoting cell proliferation, migration and invasion	metabolic reprogramming	[187]
LncRNA SNHG26	↑	NCL/c-Myc/HK2	promoting cell proliferation and EMT	glycolysis metabolism	[194]
LncRNA VAL	↑	PKM2-Parkin	promoting cell proliferation and invasion	glycolysis metabolism	[195]
LncRNA NRAV	↑	electron transport chain	promoting cell proliferation; inhibiting cell apoptosis	glycolysis metabolism	[196]
LncRNA CCAT1	↑	PTBP1/PKM2	promoting cell proliferation, migration and invasion	glycolysis metabolism	[197]
LncRNA MACC1-AS1	↑	AMPK/Lin28	promoting cell proliferation and inhibiting cell apoptosis	glycolysis metabolism	[198]
LncRNA NEAT1	↑	c-Jun/c-Fos/SREBP1	promoting lymph node metastasis and poor prognosis	fatty acid metabolism	[199]
LncRNA LINC00924	↑	hnRNPC/Mnk2	promoting peritoneal metastasis	fatty acid metabolism	[200]
LncRNA NR_033928	↑	IGF2BP3/HUR/GLS mRNA	promoting cell proliferation; inhibiting cell apoptosis	glutamine metabolism	[201]

circUBE2Q2 regulates STAT3-mediated autophagy and glycolysis and promotes the malignant progression of GC [193].

Similarly, lncRNAs participate in GC progression by regulating GC cell metabolism (Table 7; Fig. 3). For instance, lncRNA SNHG7 mediates cisplatin resistance in GC cells through the miR-34a/LDHA glycolysis axis [18]. SNHG16 induces 5-FU resistance in GC cells by targeting miR-506-3p-PTBP1-mediated glycolysis metabolism [131]. The lncRNA SNHG26 promotes GC progression and metastasis by inducing the expression of c-Myc and the glycolytic metabolism positive feedback loop [194]. LncRNA VAL promotes PKM2 enzyme activity and enhances glycolysis in GC and malignant progression [195]. NRAV promotes glycolysis by regulating the electron transport chain [196]. CCAT1 promotes glycolysis via the PTBP1/PKM2 pathway [197]. The lncRNA MACC1-AS1 promotes glycolysis in GC cells through AMPK/Lin28-mediated MACC1 mRNA stability [198]. Additionally, lncRNA MACC1-AS1 can be regulated by MSC to promote stemness and oxaliplatin resistance through fatty acid oxidation in GC [128]. HCP5 can also be induced by MSC, which drives fatty acid oxidation through the miR-3619-5p/AMPK/PGC1α/CEBPB axis and promotes stemness and chemo-resistance in GC [137]. LncRNA NEAT1-induced RPRD1B stability promotes fatty acid metabolism and lymph node metastasis in GC through the c-Jun/c-Fos/SREBP1 axis [199]. LINC00924-induced reprogramming of fatty acid metabolism promotes gastric cancer peritoneal metastasis via

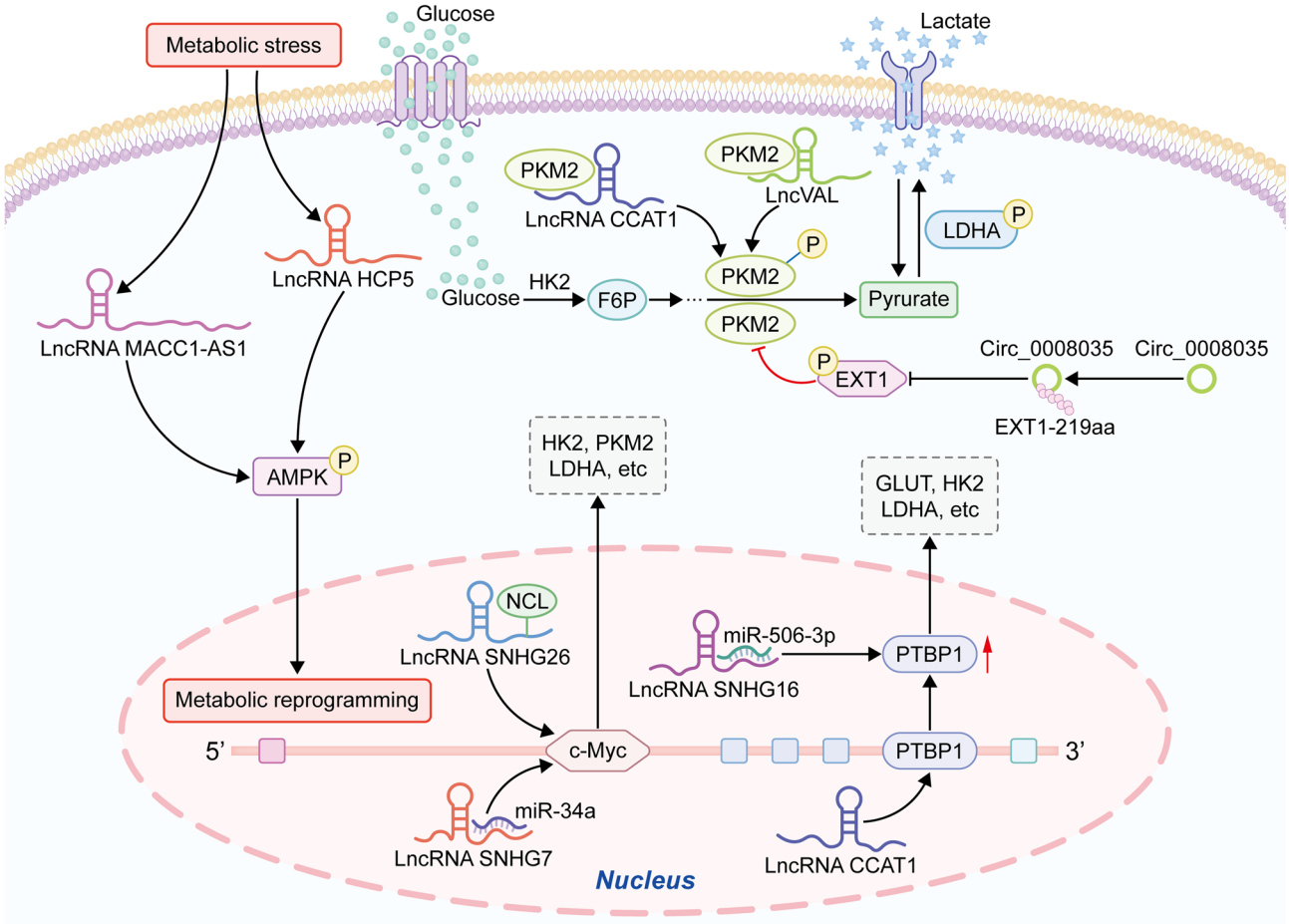

Fig. 4 LncRNA and/or circRNA-mediated posttranslational modification of cellular metabolism. LncRNA and/or circRNA-mediated posttranslational modifications directly affect metabolic enzymes to reprogram glucose metabolism. Examples are phosphorylation of PKM2 by LncRNA CCAT1, LncVAL, and circ_0008035. LncRNA and/or circRNA -mediated posttranslational modification of transcription factors regulates aerobic glycolysis-related genes. Examples are hydroxylation, phosphorylation of PTBP1 by LncRNA CCAT1 and SNHG16, respectively; ubiquitination of c-Myc by LncRNA SNHG7, and SNHG26. LncRNA and/or circRNA -mediated posttranslational modifications of metabolic pathways include phosphorylation of AMPK signalling pathway components by LncRNA MACC1-AS1, and HCP5. LncRNA: long noncoding RNA; PKM2: pyruvate kinase muscle isozyme M2; LDHA: lactate dehydrogenase A; P, phosphorylation; GLUT: glucose transporter isoform; HK2: Hexokinase 2; F6P: fructose 6-phosphate; HK2: Hexokinase 2; AMPK: adenosine monophosphate-activated protein kinase

hnRNPC-regulated Mnk2 alternative splicing [200]. The M5C methylated lncRNA NR_033928 promotes cell proliferation in GC through stabilization of GLS mRNA and glutamine metabolism reprogramming [201].

CircRNA therapeutics in cancer

Recently, circRNA-based cancer treatment strategies have demonstrated significant potential in preclinical studies and early clinical trials (Table 8). Based on clinical trial data, researchers have developed various circRNA treatment platforms, primarily focusing on vaccine development and gene expression regulation in tumors and infectious diseases (supplementary Fig. 1) [202–207].

Lipid nanoparticles (LNP) present an emerging mainstream technology for drug delivery, with several advantages such as high efficiency in nucleic acid delivery and modification, especially in siRNA-mediated gene silencing (such as circFAM53B-219aa targeted therapy) and cytokine coding (such as IL-12 anti-tumor therapy) [71, 146]207– [210]. The dendritic cell (DC) vaccine, as a traditional immunotherapy carrier, has been explored as a combination therapy scheme with a PD-1 inhibitor (camrelizumab) in breast cancer and pancreatic cancer by combining with a circRNA epitope (supplementary Fig. 2) [211, 212].

Notably, the current research is still in the preclinical stage, and only one phase I clinical trial involving HER2-negative advanced breast cancer has entered the phase of human study [211]. Three major trends in treatment strategies are reported: (1) Personalized vaccines encoding tumor neoantigens activate specific immune responses. (2) Gene regulatory tools (such as siRNAs) target oncogenic circRNAs. (3) Cytokine-engineered circRNA platforms involve the remodeling of the local

Table 8 Comprehensive overview of published circrna therapeutics in cancer

Registration Number/NCT number	Start date	Tumor type	Categorization	Delivery vector	Product	Study phase	Clinical application	Reference
NCT06530082	2024	Breast cancer	Vaccine	DC vaccine	circRNA	Phase 1	CircFAM53B-219aa DC vaccine monotherapy and its combination with camrelizumab in the treatment of HER2-negative advanced breast cancer	[212]
	2023	Gastric cancer	Gene expression modulation	PLGA-PEG nanoparticles	siRNA	preclinical	anti-tumor therapeutics	[71]
	2023	Gastric cancer	Gene expression modulation	LNP	siRNA	preclinical	anti-tumor therapeutics combined with anti-PDL1 drugs	[146]
	2025	Prostate cancer	Gene expression modulation	LNP	siRNA	preclinical	anti-tumor therapeutics	[208]
	2024	Lung cancer	Cytokine	LNP	IL-12	preclinical	Drug candidate encoding IL-12 for anti-tumor therapeutics	[209]
	2024	Intrahepatic Cholangiocarcinoma	Gene expression modulation	LNP	circRNA	preclinical	anti-tumor therapeutics	[211]
	2024	Hepatocellular carcinoma	Vaccine	LNP	antigens	preclinical	neoantigen immunotherapy in solid tumors	[210]
	2025	Pancreatic cancer	Vaccine	DC vaccine	antigens	preclinical	circRNA vaccine combined with low-dose gemcitabine in pancreatic cancer	[213]

immune microenvironment [209]. These advances provide new ideas for overcoming tumor heterogeneity and treatment resistance; however, further research can validate their long-term safety and in vivo stability.

Discussion

The complex mechanisms underlying the role of non-coding RNAs in cancer progression highlight their significant role as drivers of malignant tumors and the potential therapeutic targets. Resistance to chemotherapy poses the major challenge to GC treatment; it is strongly influenced by ncRNAs, such as circAKT3 and HOTAIR, which interact with miR-198 and miR-34a to activate survival pathways, such as PI3K/AKT, and inhibit cell apoptosis [15, 17]. Furthermore, immune escape is coordinated by ncRNA-mediated PD-L1 regulation (circRHBDD1 and lncRNA UCA1) and metabolic reprogramming (circ_0008035), which synergistically create an immunosuppressive tumor microenvironment [147, 149, 155]. These molecular mechanisms highlight the dynamic adaptability of ncRNAs in GC cells to cope with therapeutic stress. Therefore, the development of strategies to disrupt the ncRNA-mRNA protein axis is required to restore drug sensitivity and immune recognition.

Angiogenesis and metabolic reprogramming further demonstrate the multifaceted role of ncRNAs in promoting the invasiveness of gastric cancer. CircSHKBP1 and lncRNA MALAT1 enhance VEGF-driven angiogenesis, whereas circNRIP1 and lncRNA SNHG16 reconnect glycolysis and fatty acid oxidation to promote tumor growth and chemotherapy resistance [131, 188]. Notably, certain non-coding ncRNAs (circ_0005758 and lncRNA WT1-AS) inhibit these processes and facilitate therapeutic development [168, 178]. The preclinical prospects of targeting these pathways using siRNA-loaded nanoparticles or circRNA-based vaccines (e.g., circSOD2 polarized macrophages) have been reported; however, tissue-specific delivery and avoiding off-target effects remain challenging [102].

Translating the discovery of ncRNAs into clinical practice requires overcoming tumor heterogeneity and improving delivery systems. Previous trials (NCT06530082) explored circRNA vaccines and lipid nanoparticles (LNPs); however, integrated multiomics data are essential to identify patient-specific ncRNA profiles and establish scalable solutions [211]. Further studies based on advanced models (patient-derived organoids) can validate the function of ncRNAs in specific environments and develop combination therapies that combine ncRNA-targeted therapy with immunotherapy or chemotherapy. Mechanistic research combined with innovative technologies can potentially support ncRNA-mediated

transformation of transcriptional noise into precise targets for gastric cancer diagnosis and treatment.

While this review synthesizes compelling evidence for ncRNAs as pivotal regulators in gastric cancer pathogenesis and therapy resistance, several limitations warrant acknowledgment. First, the tumor microenvironment heterogeneity and dynamic ncRNAs interactions across different GC subtypes complicate the establishment of universal therapeutic targets. Second, most mechanistic insights derive from in vitro or preclinical models, which may not fully recapitulate the complexity of human disease progression and drug resistance in vivo. Third, clinical translation is hindered by challenges in efficient ncRNA-targeted delivery systems, including stability, tissue-specific targeting, and potential off-target effects of RNA-based interventions (e.g., siRNA, circRNA vaccines). Additionally, the functional redundancy among ncRNAs and their crosstalk with multiple signaling pathways necessitate combinatorial targeting strategies, which require further validation in advanced clinical trials. Future studies integrating multi-omics profiling of patient-derived samples and spatially resolved transcriptomics will be essential to overcome these limitations and refine ncRNA-based precision therapies.

Conclusions

Gastric cancer therapy is challenged by molecular heterogeneity and resistance. Non-coding RNAs critically drive tumor progression through orchestrating chemoresistance, immune evasion, angiogenesis, and metabolic reprogramming. They offer dual clinical value as prognostic biomarkers and therapeutic targets via RNA-based interventions. Despite the significant translational barriers posed by tumor heterogeneity and targeted delivery, our work has paved the way for a clinically feasible roadmap to curb the malignant progression of gastric cancer by discovering and altering ncRNAs that play a critical role in gastric cancer, while innovating lipid nanoparticle (LNP) platforms to achieve precise ncRNA regulation. It is crucial that we demonstrate that combining these ncRNA targeting strategies with conventional therapies can synergistically improve treatment efficacy and drive clinically feasible outcomes in personalized oncology.

Abbreviations

5-FU	5-Fluorouracil
ADAM9	A Disintegrin And Metalloproteinase 9
ADAMTS9-AS2	ADAM Metallopeptidase With Thrombospondin Type 1 Motif 9 Antisense RNA 2
ADCC	Antibody-dependent cellular cytotoxicity
AKT	Protein kinase B (PKB)
AMPK	AMP-activated protein kinase
ATG5/ATG12/ATG14	Autophagy related 5/12/14
Bax	BCL2 associated X, apoptosis regulator
Bcl-2	B-cell lymphoma 2
BCL2	B-cell lymphoma 2
BMI1	B lymphoma Mo-MLV insertion region 1 homolog
ceRNA	Competitive endogenous RNA
circRNA	Circular RNA
CRISPRi	CRISPR interference
CDDP	Cisplatin
ddPCR	Droplet digital PCR
EMT	Epithelial-mesenchymal transition
ERK1/2	Extracellular signal-regulated kinases 1/2
EZH2	Enhancer of zeste homolog 2
FISH	Fluorescence in situ hybridization
GC	Gastric Cancer
GLOBOCAN	Global Cancer Observatory (IARC database)
HER2	Human epidermal growth factor receptor 2
HIF-1α	Hypoxia-inducible factor 1-alpha
HOTAIR	HOX transcript antisense RNA (lncRNA)
IRES	Internal ribosome entry site
LNP	Lipid nanoparticle
lncRNA	Long non-coding RNA
miRNA/miR	MicroRNA
mTOR	Mechanistic target of rapamycin
ncRNA	Non-coding RNA
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PI3K	Phosphoinositide 3-kinase
RBP	RNA-binding protein
RT-qPCR	Reverse transcription quantitative polymerase chain reaction
siRNA	Small interfering RNA
STAT1/3	Signal transducer and activator of transcription 1/3
TAM	Tumor-associated macrophage
TGF-β	Transforming growth factor beta
TME	Tumor microenvironment
VEGFA/D	Vascular endothelial growth factor A/D
Wnt	Wingless-type MMTV integration site family

Supplementary Information

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Supplementary Material 1

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Authors' contributions

Han Zhifei: Conceptualization, Formal analysis, Investigation, Writing – original draft. Liu Wenjuan: Conceptualization, Formal analysis, Investigation, Writing – original draft. Yigao Zhu: Investigation, Writing – review and editing. Sun Yinggang: Investigation, Writing – review and editing. Sun Dong: Supervision, Writing – review and editing. Ruyue Jia: Investigation, Writing – review and editing. Yanting Yang: Investigation, Writing – review and editing. Houbao Qi: Investigation, Writing – review and editing. Long Zhang: Investigation, Writing – review and editing. Yanfei Huo: Investigation, Writing – review and editing. Nasha Zhang: Funding acquisition, Project administration, Investigation, Writing – review and editing. Chai Jie: Funding acquisition, Project administration, Supervision, Validation, Writing – review and editing. Yang Ming: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – review and editing.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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