Biological functions of circRNA in regulating the hallmarks of gastrointestinal cancer (Review)

MENGJUN QIU, YOUXIANG CHEN and CHUNYAN ZENG

Department of Gastroenterology, Digestive Disease Hospital, The First Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi 330006, P.R. China

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Abstract. Circular RNA (circRNA) was first observed in the cytoplasm of eukaryotic cells in 1979, but it was not characterized in detail until 2012, when high-throughput sequencing technology was more advanced and available. Consequently, the mechanism of circRNA formation and its biological function have been progressively elucidated by researchers. circRNA is abundant in eukaryotic cells and exhibits a certain degree of organization, timing and disease-specificity. Additionally, it is poorly degradable, meeting the characteristics of an ideal clinical biomarker. In the present review, the recent research progress of circRNAs in digestive tract malignant tumors was primarily discussed. This included the roles, biological functions and clinical significance of circRNA, providing references for its research value and clinical potential in gastrointestinal cancer.

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Correspondence to: Dr Chunyan Zeng, Department of Gastroenterology, Digestive Disease Hospital, The First Affiliated Hospital, Jiangxi Medical College, Nanchang University, 17 Yongwaizheng Street, Donghu, Nanchang, Jiangxi 330006, P.R. China
E-mail: zcy896@163.com and zengcy896@ncu.edu.cn

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1. Introduction

Circular RNA (circRNA) is a type of non-coding RNA composed of a covalently closed cyclic structure that lacks a 5' cap and 3' polyadenylate tail, and typically forms through the back-splicing of a single pre-mRNA. Due to the nature of its structure, circRNA is resistant to RNase R-mediated degradation and exhibits stable expression in multiple tissues and organs, such as the brain (1,2). Nearly 10% of transcribed genes in cells are potential sources of circRNA. Based on the different looping sequences of parent genes, circRNAs can be classified into four broad categories: Exon circRNA (ecRNA), intron circRNA (ciRNA), exon-intron circRNA (elciRNA) and others, including viruses, tRNA, rRNA and small nuclear RNA (3-6). The functions of circRNA are diverse, including: i) Acting as microRNA (miRNA) sponges, typically inhibiting miRNA activity (7-9); ii) binding to RNA binding proteins (RBPs) and regulating their interaction with target RNA molecules (10-13); iii) being translated into peptide segments (14-17); iv) influencing the transcription of host genes (4,5); and v) impacting gene splicing processes (18-20). A large number of circRNAs have been shown to play important regulatory roles in the occurrence and development of tumors, with some serving as potential clinical serum markers that can provide meaningful information for clinical treatment and prognosis.

Gastrointestinal cancers include esophageal cancer (EC), gastric cancer (GC), hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA), pancreatic cancer (PC) and colorectal cancer (CRC). EC is among the most fatal cancer types, ranking as the sixth leading cause of cancer-related death globally and exhibiting a higher prevalence in men (21). In total, ~90% of EC is esophageal squamous cell carcinoma (ESCC), which is mainly induced by drinking and smoking. Being overweight and gastroesophageal reflux are recognized as the principal risk factors for esophageal adenocarcinoma (21). GC ranks as the third leading cause of cancer-related death globally, with >1 million estimated new cases annually (22). Infection with *Helicobacter pylori* remains a significant risk factor for GC. Liver cancer is the sixth most common cancer and the fourth leading cause of cancer-related mortality worldwide, including HCC (~80% of cases), intrahepatic CCA (ICC; ~10% of cases), combined hepatocellular and CCA, as well as other types (21). Long-term infection of hepatitis B and C viruses, heavy

drinking, smoking and extended periods of consumption of foods containing aflatoxin are all risk factors for liver cancer. PC is a highly malignant digestive tract tumor, typically presenting with non-specific symptoms such as abdominal pain and weight loss, as the first clinical manifestation (23). Most patients with PC are diagnosed at an advanced stage soon after the symptoms appear, missing the optimal timing for surgical intervention and resulting in an extremely poor prognosis (24). The triggers for PC are complex but smoking and a family history of chronic pancreatitis are considered to be the main factors (25). The incidence rate of CRC is typically related to the lower development level or low economic level of the country, mainly due to differences in living standards and dietary patterns (26).

Numerous studies have shown that circRNA is abundantly expressed in digestive system tumors, and its unique a loop structure, resistance to degradation and ability to enter body fluids make it a potential target for effective cancer treatment (27-29). A comprehensive understanding of current research progress on circRNA in gastrointestinal cancer will therefore help to further explore its potential and establish a foundation for the clinical translation of technologies that target circRNA.

2. Biogenesis of circRNA

circRNAs from individual genes are mostly produced in the form of multiple isomers, through a process termed 'reverse splicing', which involves spliceosome machinery. Certain genes can generate a greater variety of circRNAs than linear RNAs, such as CAMSAP1, CYP24A1 and CRIM1 (30). ecRNA is primarily located in the cytoplasm and is formed by connecting the 5' donor site downstream of the exon to the 3' splice acceptor site through a single or multi-level jump. This process forms a lasso-driven cyclization model, followed by intron removal via splicing (6,31). ciRNA is predominantly located in the nucleus and is an intron that depends on cleavage-catalyzed cyclization, involving the insertion of the lariat tail (32). elciRNA is a double-stranded RNA composed of introns located on both sides of an exon, which have complementary sequences and ultimately produce a circRNA containing both introns and exons through variable splicing (31). Thus far, the formation process of circRNA has not been fully understood. For instance, the specific mechanisms of catalyzing the cyclization of cord tail insertion have not yet been completely elucidated and further research is needed.

3. Biological function of circRNA

circRNA as a competitor for endogenous mRNA. circRNA is a common competing endogenous RNA (ceRNA), which can act as an miRNA sponge to regulate the expression of miRNA target genes through complementary base pairing. For instance, exosomal circUHRF1 has been shown to inhibit natural killer cell-derived IFN-γ and TNF-α secretion through the miR-449c-5p/T cell immunoglobulin and mucin-domain containing-3 axis and promotes the malignant progression of HCC (33). In CRC, circCAMSAP1 acts as a sponge for miR-328-5p, thus abrogating its ability to suppress the expression of the transcription factor, E2F1 (34). In addition, circNRIP1 acts as an miR-149-5p sponge to promote GC progression via the AKT1/mammalian target of rapamycin (mTOR) pathway (35). Thus, the miRNA sponge functionality of circRNAs can have important implications for cancer. Moreover, a single circRNA may contain multiple different miRNA binding sites and may even target multiple conserved sites of a single miRNA (8,36). circRNAs that act as miRNA sponges are primarily ecRNA and elciRNA. In fact, miRNA sponge activity is currently the most widely studied biological function of circRNAs.

Interaction between circRNA and RBPs. circRNA can promote protein stability and transportation by binding to multiple RBPs and even forming intricate circular and linear complexes. For instance, cerebellar degeneration-related protein 1 antisense RNA (also known as ciRS-7) acts as a molecular miRNA sponge by forming the RNA-induced silencing complex with miR-7 and Argonaute2 proteins (9). Furthermore, circCTNNB1, an intronic circRNA derived from the CTNNB1 gene, has been shown to bind to DEAD-box polypeptide 3 and facilitate its interaction with transcription factor Yin Yang 1 (YY1), triggering the transactivation of YY1 and promoting β-catenin activity (37). Additionally, the expression level of circFoxo3 can regulate the formation of ternary complexes with p21 and CDK2, thereby controlling cell cycle progression (38).

circRNA participation in protein translation. Eukaryotic protein-coding mRNAs typically require a 5'-terminal cap structure. However, growing evidence suggests that circRNAs that contain an internal ribosome entry site (IRES) can be translated into polypeptides *in vivo*, through the IRES cis-regulatory element (16,39-41). circZNF609 contains an open reading frame (ORF) at the start codon with an in-frame stop codon, allowing its translation into a protein product (12). In addition to mediating circRNA translation through IRESs and ORFs, RNA methylation can also mediate the initiation of circRNA-encoded protein translation (17). The peptides/proteins encoded by circRNAs are typically <100 amino acids, and these functional proteins may play an important role in the progression of diseases. FBXW7-185aa, a functional protein encoded by circ-FBXW7, has been shown to inhibit the proliferation and cell cycle progression in glioblastoma by degrading c-Myc (14). CircPPP1R12A-73aa, a protein encoded by circPPP1R12A, has been reported to promote colon cancer progression through the modulation of the Hippo-yes-associated protein (YAP) pathway (42).

Regulation of gene transcription. Due to the nuclear localization of ciRNA and elciRNA, these types of circRNA can effectively regulate the transcription of parental genes. For instance, ci-ankrd52, which is formed from an intron of ankyrin repeat domain 50, can localize at the transcription start site of the parent gene, exerting positive regulation on RNA polymerase II (Pol II) and promoting gene transcription (5). elciRNAs can also enhance gene transcription by binding to Pol II nucleosides upstream of the transcription start site of the gene (4).

Impact of gene splicing. The specific cyclization process of circRNA inevitably affects the linear splicing of precursor mRNA (43). In both humans and fruit flies, the Muscleblind (Mbl) protein binds to specific sites within the introns that flank its own pre-mRNA. This interaction directly competes with the splicing of the precursor mRNA, influencing the balance between the production of linear mRNA and the formation of circMbl, a circular RNA derived from the Mbl gene (18). During the formation of cDNA in mice, Fmn, a new type of circRNA containing transcription initiation sites, has been identified (19). This circRNA causes 'mRNA traps' by separating transcription initiation sites, leading to the loss of functional protein products. However, this circRNA may partially reverse this physiological phenomenon post-translation.

4. Biological function and clinical significance of circRNAs in gastrointestinal cancer

circRNA and EC

Upregulation of circRNAs in EC. Among circRNAs that are upregulated in EC, circGSK3β promotes the malignant progression of ESCC via direct inhibition of GSK-3β. Furthermore, plasma circGSK3β levels can serve as a biomarker for the detection of early-stage ESCC (44). circLPAR3 upregulates MET gene expression through sponging miR-198 and activates the RAS/MAPK and PI3K/AKT pathways, promoting ESCC cell migration, invasion and metastasis *in vitro* and *in vivo* (45). circ-141539 upregulation is positively associated with advanced TNM staging, low histological grade and poor prognosis in patients with ESCC. Furthermore, circ-141539 promotes the malignant progression of EC by sponging miR-4469 and activating CDK3 expression (46). circPVT1 is significantly upregulated in EC tissues and cancer cell lines and can reverse the inhibitory effect of miR-4663 on tumors (47). ciRS-7 is significantly upregulated in ESCC tissue and is associated with poor patient survival. Furthermore, ciRS-7 adsorbs miR-7 and reactivates its downstream homeobox B13-mediated NF-κB/p65 pathway, which promotes the malignant progression of ESCC (48). High expression of circ-0006168 is positively associated with lymph node metastasis and an advanced TNM stage in patients with ESCC, and it promotes the expression of mTOR through sponging miR-100 (49). In addition, circ-0006168 can also facilitate Taxol resistance in ESCC by regulating the miR-194-5p/jumonji domain containing 1C axis (50). circNRIP1 promotes proliferation and invasion of ESCC cells by targeting the miR-595/semaphorin 4D axis and inhibiting the PI3K/AKT signaling pathway (51). circCYP24A1 binds pyruvate kinase M2 (PKM2) to regulate NF-κB-induced C-C motif ligand 5 secretion in the progression of ESCC (52). Insulin-like growth factor 2 (IGF2BP2) mediates circRUNX1-enhanced FOXP3 expression by acting as a competitive miRNA sponge to inhibit miR-449b-5p activity, thus promoting ESCC cell proliferation and metastasis *in vitro* and *in vivo* (53). circCD44 functions as a sponge for miR-23b-5p, activating TGF-β-activated kinase 1/NF-κB signaling and promoting ESCC cell migration, invasion and proliferation (54). circ-0026611 is highly expressed in ESCC cells and exosomes, and exosomal circ-0026611 promotes ESCC lymphangiogenesis by interacting with N-α-acetyltransferase 10 and inhibiting prospero homeobox 1 acetylation and ubiquitination (55). High circABCA13 expression predicts a poor prognosis in patients with ESCC as it upregulates sulfiredoxin 1 and subsequently activates the Wnt/β-catenin pathway by acting as a sponge for miR-4429 in ESCC (56). Functional artificial circRNAs prevent miRNA binding to downstream target genes by adsorbing endogenous prooncogenic miRNAs, significantly inhibiting the growth and migration of EC cells, allowing a new avenue for the construction of therapeutic circRNAs (57).

Downregulation of circRNAs in EC. In a study, compared with matched adjacent normal tissues, circCNTNAP3 was more significantly downregulated in three pairs of ESCC tissues (58). circCNTNAP3 promotes expression of the tumor suppressor gene, p53, through sponging miR-513a-5p and, in turn, p53/RNA binding motif protein 25 mediates the regulation of circCNTNAP3 biosynthesis, resulting in a positive feedback loop for the expression of circCNTNAP3 and p53 in ESCC (58). circVRK1 is downregulated in ESCC tissues and cell lines, exerting its tumor suppressor effect. circVRK1 acts as a molecular sponge for miR-624-3p, inactivating the PI3K/AKT signaling pathway by positively regulating PTEN expression and ultimately reversing the radiation resistance of ESCC (59). Zinc finger E-box binding homeobox 1 inhibits eukaryotic translation initiation factor 4A3 (EIF4A3) promoter activity, thereby repressing the biogenesis of circDOCK5. Downregulated circDOCK5 expression enhances the migration and invasion of ESCC cells by forming a positive feedback loop with TGF-β, altering the miR-627-3p/TGFB2 signaling pathway (60). Tissue microarray analysis identified that circTRPS1-2 was downregulated in ESCC tissues, which was correlated with poor prognosis. Furthermore, circTRPS1-2 inhibits the progression of ESCC by decreasing ribosome biogenesis (61). The downregulation of circTNRC6B expression in ESCC tissue is an independent risk factor for poor prognosis. circTNRC6B exerts a tumor-suppressing effect in ESCC by regulating the miR-452-5p/dystroglycan 1 axis (62). Downregulation of circFAM120B expression in cancer tissues and patient plasma is associated with poor prognosis and tumor progression in ESCC. However, circFAM120B inhibits the tumorigenicity of ESCC by adsorbing miR-661 to stabilize the expression of protein phosphatase 1L (63). In addition, circFAM120B decreases the stability of protein kinase R by binding to it and promoting its polyubiquitination and degradation, ultimately inhibiting the p38 MAPK-mediated epithelial-mesenchymal transition (EMT) pathway (63).

The relationship between circRNA and the malignant hallmarks of EC is summarized in Table I. circRNAs play a significant role in the development and progression of EC. Upregulated circRNAs such as circGSK3β, circLPAR3, circ-141539, circPVT1, ciRS-7, circ-0006168, circNRIP1, circ-0026611 and circABCA13, promote malignant progression by competitive inhibition of miRNAs and the consequent activation of various signaling pathways. Conversely, downregulated circRNAs, including circCNTNAP3, circVRK1, circTRPS1-2, circTNRC6B and circFAM120B, act as tumor suppressors by regulating miRNA targets and inhibiting key signaling pathways. Understanding the dysregulation of circRNAs in EC may provide valuable insights for identifying potential biomarkers and therapeutic strategies in the future.

Table I. Relationship between circRNA and the malignant hallmarks of esophageal cancer.

First author, year	Main cell lines	circRNA name	Expression	Main malignant hallmarks	Potential clinical value	(Refs.)
Hu *et al*, 2019	TE1 and KYSE180	circGSK3β	Up	Migration, invasion and EMT	Diagnosis and prognosis	(44)
Shi *et al*, 2020	KYSE450 and TE13	circLPAR3	Up	Migration, invasion and metastasis	Treatment and diagnosis	(45)
Liu *et al*, 2021	KYSE510 and EC9706	circ-141539	Up	Proliferation and invasion	Diagnosis, prognosis and treatment	(46)
Zhong *et al*, 2019	TE10	circPVT1	Up	Proliferation and invasion	Treatment and diagnosis	(47)
Li *et al*, 2018	Eca109 and KYSE150	ciRS-7	Up	Proliferation, migration and invasion	Treatment and diagnosis	(48)
Shi *et al*, 2019	KYSE450 and TE13	circ-0006168	Up	Proliferation, migration and invasion	Treatment and diagnosis	(49)
Qu *et al*, 2021	Eca109 and KYSE150	circ-0006168	Up	Proliferation, invasion, migration, apoptosis and Taxol resistance	Treatment	(50)
Zhou *et al*, 2021	KYSE30 and KYSE450	circNRIP1	Up	Proliferation, invasion, migration and inhibition of apoptosis	Diagnosis	(51)
Gu *et a*l, 2022	KYSE30, KYSE150, KYSE170 and TE1	circCYP24A1	Up	Proliferation, migration and invasion	Treatment and diagnosis	(52)
Wang *et al*, 2022	KYSE150 and TE1	circRUNX1	Up	Proliferation and metastasis	Treatment and diagnosis	(53)
Meng *et al*, 2023	KYSE510 and TE1	circCD44	Up	Proliferation, invasion and migration	Treatment	(54)
Yao *et al*, 2023	KYSE30 and Eca109	circ-0026611	Up	Migration, invasion and lymphangiogenesis	Treatment	(55)
Luo *et al*, 2023	KYSE30 and KYSE410	circABCA13	Up	Proliferation, migration, invasion, anchorage-independent and growth	Treatment and prognosis	(56)
Wang *et al*, 2020	Eca109, KYSE450 and TE1	circCNTNAP3	Down	Proliferation and apoptosis	Treatment	(58)
He *et al*, 2019	KYSE150 and KYSE450	circVRK1	Down	Proliferation, migration, EMT and radioresistance	Treatment	(59)
Meng *et al*, 2021	TE1, KYSE150 and KYSE170	circDOCK5	Down	Invasion, migration and EMT	Treatment	(60)
Zhao *et al*, 2023	KYSE150 and Eca109	circTRPS1-2	Down	Proliferation and migration	Treatment and prognosis	(61)
Xu *et al*, 2023	TE1, KYSE150 and KYSE170	circTNRC6B	Down	Proliferation, migration and invasion	Treatment	(62)
Song *et al*, 2022	TE1 and KYSE150	circFAM120B	Down	Proliferation, metastasis and invasion	Treatment	(63)

circRNA, circular RNA; Down, downregulated; EMT, epithelial-mesenchymal transition; Up, upregulated.

CircRNA and GC

Upregulation of circRNAs in GC. The expression of circSHKBP1 in GC tissues is significantly higher than that in normal tissues, and increased expression of circSHKBP1 is related to advanced TNM stage, vascular infiltration and poor survival. The level of circSHKBP1 in the serum exosomes of patients with GC is ~6 times higher than that in tumors (64). Exosomal circSHKBP1 can regulate the miR-582-3p/HuR/VEGF pathway and directly interact with HSP90 to inhibit the ubiquitination of HSP90 by STIP1 homology and U-box containing protein 1, ultimately accelerating GC progression (64). The expression of circAKT3 is significantly increased in cisplatin-resistant GC tissues and cells, which can serve as a biomarker of cisplatin resistance. Mechanistically, circAKT3 promotes phosphoinositide-3-kinase regulatory subunit 1 (PIK3R1) expression and activates the PI3K/AKT signaling pathway through sponging miR-198, ultimately promoting cisplatin resistance in GC cells (65). Heterogeneous nuclear ribonucleoprotein L (HNRNPL) can bind to the flanking introns of circLMO7 exons to promote the self-cyclization of circLMO7 in GC. circLMO7 then promotes the development of GC through the circLMO7/miR-30a-3p/WNT2 axis (66). High expression of circFAM73A indicates a poor prognosis in patients with GC. circFAM73A, as a sponge for miR-490-3p, relieves the inhibition of high mobility group A2 (HMGA2), and HMGA2 can further enhance the activities of E2F1 and HNRNPL, which in turn promote circFAM73A expression and form a positive feedback loop (67). Additionally, circFAM73A can also directly interact with heterogeneous nuclear ribonucleoprotein K (hnRNPK) to facilitate β-catenin stabilization, ultimately promoting the cancer stem cell-like properties and malignancy of GC cells (67). circARID1A is upregulated in GC tissues, promoting the interaction between IGF2BP3 and solute carrier family 7 member 5 (SLC7A5) by directly binding to IGF2BP3 (68). This forms a circARID1A-IGF2BP3-SLC7A5 RNA-protein ternary complex to increase SLC7A5 mRNA stability and activate the AKT/mTOR pathway, ultimately promoting GC proliferation. circ-0007967 upregulates the expression of mastermind-like transcriptional coactivator 3 through sponge adsorption of miR-411-5p, promoting the proliferation of GC cells (69). circ-0044301 is significantly upregulated in GC tissues compared with non-cancerous tissues and is positively correlated with poor patient prognosis. circRNA-0044301 participates in the progression of GC by regulating the miR-188-5p/death domain associated protein/MAPK axis (70). circABCA5 upregulates SPI1 expression and promotes nuclear translocation by directly binding to EIF4A3, promoting the proliferation, invasion and migration of GC cells by activating IL6/janus kinase 2 (JAK2)/STAT3 signaling (71). C-E-Cad is significantly upregulated in GC tissues compared with adjacent benign tissues. circ-E-Cad encodes the C-E-Cad protein, while the TGF-β/SMAD pathway enhances the expression level of C-E-Cad, ultimately promoting the malignant progression of GC cells by upregulating the PI3K/AKT pathway (72). circTDRD3 is upregulated in GC tissues and is correlated with tumor progression and poor prognosis. circTDRD3 promotes GC cell progression by regulating the miR-891b/integrin (ITG)A2 axis and the AKT signaling pathway (73).

Downregulation of circRNAs in GC. circCUL2 has low expression in GC tissues and cells. circCUL2 inhibits the growth and metastasis of GC through the miR-142-3p/Rho associated coiled-coil containing protein kinase 2 axis, while mediating the autophagy activation of GC cells and increasing their sensitivity to cisplatin (74). circMRPS35 is significantly downregulated in GC tissues compared with normal tissues, and high expression of circMRPS35 is negatively correlated with advanced TNM staging, lymph node metastasis and tumor size in GC. circMRPS35 is mainly located in the nucleus of GC cells and can recruit lysine acetyltransferase 7 to the promoters of FOXO1 and FOXO3a genes, increase the acetylation level of H4K5 in the promoter region of these genes, activate the transcription of FOXO1/3a and trigger downstream target gene expression responses, including p21, p27 and E-cadherin, inhibiting GC cell proliferation and invasion (75). circ-0004872 is significantly downregulated in GC tissue, and sponges miR-224 to regulate the expression of p21 and SMAD4, thus inhibiting the proliferation, invasion and migration of GC cells. SMAD4 can also promote the expression of circ-0004872 by directly binding to the adenosine deaminase RNA specific 1 promoter region, forming a negative regulatory loop (76). circDIDO is considered beneficial in GC and is formed by the reverse splicing of exons 2-6 of DIDO1. circDIDO encodes a 529 amino acid tumor suppressor protein, which interacts with poly (ADP-ribose) polymerase 1 and inhibits its activity (77). circDIDO1 also specifically binds to peroxiredoxin 2 (PRDX2), promoting RBX1-mediated ubiquitination and degradation of PRDX2, leading to the inactivation of its downstream pathways to exert tumor inhibitory effects (77). circMAPK1 in GC tissue encodes a novel protein, MAPK1-109aa, which inhibits the phosphorylation of MAPK1 by competitively binding to MEK1, thereby suppressing the activation of MAPK1 and its downstream factors in the MAPK pathway and inhibiting the malignant biological behavior of GC cells (78). circEIF4G3 is downregulated in GC tissues compared with adjacent normal tissues. Notably, lower circEIF4G3 expression predicts poor survival in patients with GC. circEIF4G3 binds to δ-catenin protein to promote tripartite motif containing (TRIM)25-mediated δ-catenin ubiquitin degradation and inactivates β-catenin signaling in GC cells. In addition, circEIF4G3 can interact with miR-4449 to upregulate salt inducible kinase 1 expression and also inhibit β-catenin signaling (79). Ultimately, circEIF4G3 inhibits the progression of GC. circST3GAL6 expression levels are negatively associated with tumor stage and size. circST3GAL6, as the ceRNA of miR-300, alleviates the inhibitory effect of miR-300 on its target gene, FOXP2, which transcriptionally inhibits MET and regulates the AKT/mTOR pathway, thereby promoting apoptosis and autophagy of GC (80). circSTAU2 and Mbl-like splicing regulator 1 (MBNL1) colocalize in the cytoplasm, and MBNL1 promotes the expression of circSTAU2. Exosome-delivered circSTAU2 promotes the expression of capping actin protein muscle Z-line α1 via sponge adsorption of miR-589 and suppresses GC cell proliferation, invasion and migration *in vitro* and *in vivo* (81). As a tumor suppressor, circMTHFD2L RNA-encoded CM-248aa competitively targets the acidic domain of SET nuclear oncogene, which restores the activity of protein phosphatase 2A and further mediates the dephosphorylation and inactivation of AKT, ERK and p65

in GC (82). Low expression of circIPO7 is an independent risk factor for poor prognosis in GC. Overexpressed circIPO7 directly binds to captin-1, reducing the interaction between captin-1 and Ras GTPase-activating protein-binding protein 1 (G3BP1), dissociating captin-1 from the ribosome and suppressing the translation of its target mRNA, and reducing the activation of the PI3K/AKT/mTOR pathway (83).

The relationship between circRNA and the malignant hallmarks of GC is summarized in Table II. The expression levels of circSHKBP1, circAKT3, circLMO7, circFAM73A, circARID1A, circ-0007967, circ-0044301, circABCA5, circ-E-Cad and circTDRD3 are significantly increased in GC tissues, and circCUL2, circMRPS35, circ-0004872, circDIDO, circMAPK1, circEIF4G3, circST3GAL6, circ-STAU2, circMTHFD2L and circIPO7 are downregulated in GC tissues. Hence, circRNAs play various roles in promoting or inhibiting GC progression through different mechanisms. Certain circRNAs can accelerate GC progression by promoting cancer stem cell-like properties, enhancing mRNA stability or activating proliferation and invasion. Conversely, other circRNAs inhibit tumor formation and progression by influencing autophagy, gene transcription, protein degradation and protein phosphorylation.

CircRNA and HCC

Upregulation of circRNAs in HCC. High expression of exosomal circRNA-100338 in serum was considered an adverse factor for metastasis and poor prognosis in patients with HCC who underwent curative hepatectomy. circ-100338 can affect the angiogenesis and vasculogenic mimicry formation ability of human umbilical vein endothelial cells, ultimately promoting the proliferation and metastasis of HCC (84). circSORE is highly expressed in sorafenib-resistant HCC cells and is modified with N^6-methyladenosine (m^6A). circSORE is a sponge for miR-103a-2-5p and miR-660-3p, which can competitively activate the WNT2b/β-catenin pathway, thus inducing the resistance of HCC to sorafenib treatment, laying a theoretical foundation for clinical research of sorafenib resistant HCC (85). Histone writers, E1A binding protein p300 (EP300) and WD repeat domain 5, bind to the circSOD2 promoter and trigger its promoter H3K27ac and H3K4me3 modification, respectively, which further activates circSOD2 expression in HCC. circSOD2 sponges miR-502-5p to upregulate the expression of DNA methyltransferase 3a (DNMT3a) in HCC cells. Upregulated DNMT3a decreases suppressor of cytokine signaling 3 (SOCS3) expression by increasing SOCS3 promoter DNA methylation and accelerates JAK2/STAT3 signaling pathway activation (86). circRHOT1 is mainly distributed in the nucleus and interacts directly with TIP60, recruiting TIP60 to the nuclear receptor subfamily 2 group F member 6 (NR2F6) promoter and initiating the transcription of NR2F6, promoting the growth, migration and invasion of HCC cells (87). circMAT2B promotes glycolysis and malignant progression of HCC by activating the miR-338-3p/PKM2 axis under hypoxia (88). In HCC tissues, CXC motif chemokine ligand 11 secreted by cancer-associated fibroblasts (CAFs) upregulates the expression of circUBAP2, competitively upregulating interferon induced protein with tetratricopeptide repeats (IFIT)1/IFIT3 levels and promoting the expression of IL-17 and IL-1β via sponge adsorption of miR-4756, promoting the progression of HCC (89). m^6A-modified circCPSF6 competitively interacts with poly(rC)-binding protein 2 to prevent its conjugation to YAP mRNA, resulting in enhanced YAP1 mRNA stability and increased HCC malignancy (90). circMRPS35 is highly expressed in patients with HCC and upregulates the expression of syntaxin 3 through sponging miR-148a, thereby promoting the ubiquitination and degradation of PTEN (91). Upon cisplatin treatment, circMRPS35-168aa is significantly upregulated, contributing to enhanced cell survival and reduced apoptosis in HCC cells. This phenomenon underscores the pivotal role of the peptide in mediating chemoresistance, thereby advancing understanding of the molecular intricacies involved in HCC progression and the development of therapeutic resistance (91). Upregulation of circFOXK2 indicates poor prognosis of HCC. However, circFOXK2-encoded FOXK2-142aa interacts with lactate dehydrogenase A (LDHA) to activate its phosphorylation (92). The phosphorylation of LDHA plays a pivotal role in reprogramming glucose metabolism towards the Warburg effect, facilitating HCC progression and highlighting the potential of targeting this pathway for therapeutic intervention. In addition, circFOXK2 can also induce mitochondrial fission by regulating the miR-484/Fis1 pathway, promoting tumor progression and activating the Warburg effect in HCC cells (92). Upregulation of circPRDM4 in patients with HCC treated with anti-programmed cell death protein-1 therapy facilitates tumor growth and immune escape. Mechanistically, circPRDM4 recruits hypoxia-inducible factor (HIF)-1α to the CD274 promoter to boost programmed death-ligand 1 (PD-L1) expression and inhibit the $CD8^+$ T cell-mediated antitumor immune response under hypoxic conditions (93). circ-0007429 is aberrantly upregulated in HCC tissues and is positively correlated with poor clinical outcomes. circ-0007429 acts as a sponge targeting the tumor suppressor, miR-637, to promote TRIM71 expression and affect the expression of its downstream molecule, argonaute-2, which promotes HCC progression and aerobic glycolysis *in vitro* and *in vivo* (94).

Downregulation of circRNAs in HCC. The RNA-splicing protein, Quaking (QK) 5, regulates the low expression of circ-ZKSCAN1 in HCC, and circZKSCAN1 blocks the binding between fragile X mental retardation protein (FMRP) and cell division cycle and apoptosis regulator 1 mRNA by competitively binding FMRP, subsequently restraining the transcriptional activity of the Wnt/β-catenin signaling pathway and negatively regulating cell stemness, which inhibits the malignant behavior of HCC (95). Downregulation of circTRIM33-12 expression is an independent risk factor for the overall survival and recurrence free survival rates of patients with HCC after surgery. circTRIM33-12 significantly reduces the level of 5-hydroxymethylcytosine (5hmC) in HCC cells by sponging miR-191 and enhancing Tet methylcytosine dioxygenase 1 (TET1) expression, resulting in the impairment of tumor immune evasion (96). circMEMO1 is significantly downregulated in HCC tissues and can modulate the promoter methylation and gene expression of transcription factor 21; it regulates EMT through the miR-106b-5p/TET1/5hmC axis, resulting in negative regulation of HCC progression and increased sensitivity of HCC cells to sorafenib treatment (97). circPABPC1 not only inhibits cell adhesion and migration by downregulating ITGB1 but also directly connects ITGB1 to the 26S proteasome,

Table II. Relationship between circRNA and the malignant hallmarks of gastric cancer.

First author, year	Main cell lines	circRNA name	Expression	Main malignant hallmarks	Potential clinical value	(Refs.)
Xie *et al*, 2020	BGC823 and HGC27	circSHKBP1	Up	Proliferation, migration, invasion and angiogenesis	Diagnosis, prognosis and treatment	(64)
Huang *et al*, 2019	SGC7901 and BGC823	circAKT3	Up	Cisplatin resistance, DNA damage repair and apoptosis	Treatment	(65)
Cao *et al*, 2021	SGC7901 and BGC823	circLMO7	Up	Proliferation, migration, invasion and glutamine metabolism	Diagnosis	(66)
Xia *et al*, 2021	SGC7901 and BGC823	circFAM73A	Up	Proliferation, migration, cisplatin resistance and cancer stemness	Treatment and diagnosis	(67)
Ma *et al*, 2022	SGC7901 and BGC823	circARID1A	Up	Proliferation	Treatment	(68)
Zha *et al*, 2022	SGC7901 and BGC823	circ-0007967	Up	Proliferation	Diagnosis and treatment	(69)
Jiang *et al*, 2022	HGC-27 and MKN-28	circ-0044301	Up	Proliferation, migration and invasion	Treatment	(70)
Hou *et al*, 2023	MKN-45 and SGC7901	circABCA5	Up	Proliferation, invasion and migration	Prognosis, diagnosis and treatment	(71)
Li *et al*, 2023	MGC-803, BGC-823 and AGS	circ-E-Cad	Up	Proliferation, migration and EMT	Treatment	(72)
Zhou *et al*, 2023	HGC27 and MKN45	circTDRD3	Up	Proliferation and metastasis	Treatment	(73)
Peng *et al*, 2020	AGS and SGC7901	circCUL2	Down	Cisplatin sensitivity, proliferation, migration and invasion	Treatment	(74)
Jie *et al*, 2020	MKN28, MGC803 and SGC7901	circMRPS35	Down	Proliferation and invasion	Diagnosis and treatment	(75)
Ma *et al*, 2020	SGC7901 and BGC823	circ-0004872	Down	Proliferation, migration and invasion	Treatment	(76)
Zhang *et al*, 2021	HGC27 and MGC803	circDIDO1	Down	Proliferation, migration and invasion	Prognosis and treatment	(77)
Jiang *et al*, 2021	SGC7901, MGC803 and MKN45	circMAPK1	Down	Proliferation and invasion	Treatment	(78)
Zang *et al*, 2022	AGS and HGC-27	circEIF4G3	Down	Proliferation, migration, invasion and apoptosis	Prognosis and treatment	(79)
Xu *et al*, 2022	SGC7901 and BGC823	circST3GAL6	Down	Apoptosis, autophagy and EMT	Treatment	(80)
Zhang *et al*, 2023	MKN45 and BGC823	circSTAU2	Down	Proliferation, invasion and migration	Treatment	(81)
Liu H *et al*,2023	MGC803, HGC-27, SGC7901 and AGS	circMTHFD2L	Down	Metastasis and proliferation	Prognosis and treatment	(82)
Liu J *et al*, 2023	SNU-1 and MKN-45	circIPO7	Down	Proliferation and tumor growth	Treatment	(83)

circRNA, circular RNA; Down, downregulated; EMT, epithelial-mesenchymal transition; Up, upregulated.

resulting in ubiquitin-independent ITGB1 degradation (98). Decreased circRPN2 expression in HCC is correlated with poor prognosis. circRPN2 binds to enolase 1 (ENO1) and accelerates ubiquitin/proteasome-dependent ENO1 degradation, activating the AKT/mTOR pathway to regulate aerobic glycolysis reprogramming in HCC cells. circRPN2 also upregulates FOXO1 expression by sponging miR-183-5p to suppress HCC glycolysis and metastasis (99). As a potential therapeutic target for HCC, circVAMP3 has been found to bind to the cell cycle-associated protein 1 (CAPRIN1) and G3BP1 complex by directly interacting with CAPRIN1, promoting stress granule formation in cells and negatively regulating the proliferation and metastasis of HCC cells *in vitro* and *in vivo* (100). As a newly identified tumor suppressor circRNA in HCC, low expression of circPTTG1IP is associated with the number of tumors, tumor encapsulation, microvascular invasion and TNM stage, and is an independent factor of overall survival and recurrence in patients with HCC (101). Mechanistic studies have determined that downregulation of circPTTG1P sequesters miR-16-5p by acting as a miRNA sponge. This competitively regulates the ring finger protein 125 (RNF125) expression level, and RNF125 interacts with and degrades JAK1 protein to inhibit the JAK1/STAT3 pathway (101). In addition, the study also demonstrated that the JAK1-selective inhibitor, Figotinib, can markedly inhibit the recruitment of tumor-associated macrophages and M2 polarization triggered by the circPTTG1IP/JAK1 axis, to remodel the tumor microenvironment and improve patient prognosis. Patients with HCC with low circDHPR expression have shorter overall survival and disease-free survival times. circDHPR acts as a ceRNA for miR-3194-5p, which increases RasGEF domain family member 1B expression to promote tumor growth and metastasis (102). Sorafenib-resistance in HCC is a challenging clinical problem. As such, elucidating the underlying mechanism of sorafenib treatment is crucial for identifying new therapeutic targets for HCC. Sorafenib regulates the expression of circZKSCAN1 via upregulation of QKI-5. circZKSCAN1 can enhance the anti-tumorigenesis effect of sorafenib in HCC cells by encoding the circZKSaa peptide. circZKSCAN1 can also interact with F-box and WD repeat domain containing 7 to promote the ubiquitination of mTOR, thereby inhibiting activation of the PI3K/AKT/mTOR pathway and making HCC cells sensitive to sorafenib (103).

The relationship between circRNA and the malignant hallmarks of HCC is summarized in Table III. Overall, several circRNAs are dysregulated in HCC, either upregulated or downregulated, and have critical roles in HCC progression and sensitivity to treatment. Upregulated circRNAs such as circ-100338, circSORE, circSOD2, circRHOT1, circMAT2B, circUBAP2, circCPSF6, circMRPS35, circFOXK2, circPRDM4 and circ-0007429, are associated with various adverse factors, including metastasis, resistance to treatment and poor prognosis. By contrast, downregulated circRNAs such as circZKSCAN1, circTRIM33-12, circMEMO1, circPABPC1, circRPN2, circVAMP3, circPTTG1IP and circZKSCAN1 are involved in inhibiting malignant behavior, immune evasion, HCC progression and promoting sensitivity to sorafenib treatment. Understanding the dysregulation of circRNAs in HCC may provide valuable insights into the molecular mechanisms underlying HCC development and potentially guide the development of new therapeutic strategies for this disease.

CircRNA and CCA

Upregulation of circRNAs in CCA. circCCAC1 levels are increased in cancerous bile-resident extracellular vesicles and tissues. circCCAC1 upregulates YY1 through sponge adsorption of miR-514a-5p, and YY1 directly binds to the promoter of calcium modulating ligand to activate its transcription, ultimately promoting the proliferation and invasion of CAA. Meanwhile, circCCAC1 in extracellular vesicles can enter human umbilical vein endothelial cells to disrupt the vascular endothelial barrier and induce angiogenesis (104). In addition, circCCAC1 enhances endothelial cell monolayer permeability by regulating the SH3 domain containing GRB2 like-2, endophilin A1/ZO-1/Occludin signaling pathway, accelerating occurrence and metastasis of CCA (104). circ-0000284 not only promotes the progression of CCA through the miR-637/lymphocyte antigen 6 family member E axis but also directly transfers from CCA cells to surrounding normal cells through exosomes, stimulating the migration and proliferation of surrounding normal cells (105). Microarray analysis was used to identified 171 differentially expressed circRNAs in six paired distal CCA tumor and adjacent normal tissue samples, including 132 upregulated and 39 downregulated circRNAs. Upregulated circ-0000673 expression was associated with tumor invasion, poor cell differentiation and residual tumor. The area under the receiver operating characteristic (ROC) curve of circ-0000673 was 0.85, demonstrating a good ability to distinguish distal CCA from normal tissue (106). circ-0005230 is highly expressed in CCA tissues and cells, promoting the growth and metastasis of CCA cells through sponging miR-1238 and miR-1299 (107). circLAMP1 is upregulated in CCA and is associated with poor prognosis. circLAMP1 upregulates YY1 expression via sponging miR-556-5p and miR-567, playing a tumorigenic role in CCA (108). circ-0021205 expression is enhanced in CCA tissues and is correlated with tumor size and advanced TNM stage. circ-0021205 upregulates RAB22A expression by targeting miR-204-5p, thereby facilitating CCA progression (109). circACTN4 is upregulated in ICC tissues and upregulates YAP1 expression by acting as a molecular sponge for miR-424-5p. circACTN4 also transcriptionally activates frizzled class receptor 7 by interacting with Y-box binding protein 1 (YBX1). Furthermore, circACTN4 enhances the interaction between YAP1 and β-catenin and activates the Wnt/Hippo signaling pathways, ultimately promoting the proliferation and metastasis of ICC (110). circEIF3C promotes ICC progression and immune evasion through the miR-34a-5p/B7-H4 axis (111). circGGNBP2 induced by IL-6 can encode cGGNBP2-184aa protein, which directly interacts with STAT3 and promotes $STAT3^{Tyr705}$ phosphorylation, nuclear translocation and activation of the JAK/STAT pathway in ICC (112). circMBOAT2 is an upregulated circRNA associated with lipid metabolism in ICC and is correlated with an unfavorable prognosis. CircMBOAT2 interacts with polypyrimidine tract binding protein 1 (PTBP1) in ICC cells and protects PTBP1 from ubiquitin/proteasome-dependent degradation, promoting PTBP1-mediated cytoplasmic export of fatty acid synthase (FASN) mRNA (113). Overall, circMBOAT2 promotes lipid metabolism reprogramming in ICC via the circMBOAT2/PTBP1/FASN axis, especially unsaturated lipids, ultimately affecting cell membrane composition, energy metabolism and redox homeostasis, leading to the progression

Table III. Relationship between circRNA and the malignant hallmarks of hepatocellular carcinoma.

First author, year	Main cell lines	circRNA name	Expression	Main malignant hallmarks	Potential clinical value	(Refs.)
Huang *et al*, 2020	Hep3B and MHCC97H	circ-100338	Up	Angiogenesis, proliferation and invasion	Diagnosis and treatment	(84)
Xu *et al*, 2020	HepG2, Skhep1 and Huh7	circSORE	Up	Sorafenib resistance and apoptosis	Treatment	(85)
Zhao *et al*, 2020	HepG2 and Huh7	circSOD2	Up	Proliferation, metastasis and cell-cycle	Treatment	(86)
Wang *et al*, 2019	Hep3B and Huh7	circRHOT1	Up	Proliferation, invasion, migration and apoptosis	Diagnosis	(87)
Li *et al*, 2019	Huh7 and HepG2	circMAT2B	Up	Glycolysis, proliferation, invasion and migration	Treatment	(88)
Liu *et al*, 2021	MHCC97H and Huh7	circUBAP2	Up	Migration and metastasis	Treatment	(89)
Chen *et al*, 2022	MHCC97H, Huh7 and HCCLM3	circCPSF6	Up	Proliferation, apoptosis, migration and invasion	Treatment	(90)
Li *et al*, 2021	HCCLM3 and Huh7	circMRPS35	Up	Proliferation, invasion, migration and cell-cycle	Diagnosis, treatment and prognosis	(91)
Zheng *et al*, 2023	HepG2 and Huh7	circFOXK2	Up	Proliferation, apoptosis and invasion	Treatment and prognosis	(92)
Chen *et al*, 2023	MHCC97H and HCCLM3	circPRDM4	Up	Immune escape	Treatment and prognosis	(93)
Fan *et al*, 2023	Huh7 and Hep3B	circ-0007429	Up	Proliferation, migration, invasion, apoptosis and aerobic glycolysis	Treatment	(94)
Zhu *et al*, 2019	SMMC7721 and HCCLM3	circZKSCAN1	Down	Cancer stemness and proliferation	Treatment	(95)
Zhang *et al*, 2019	SMMC7721, HCCLM3 and Huh7	circTRIM33-12	Down	Proliferation, invasion, migration and immune evasion	Prognosis and treatment	(96)
Dong *et al*, 2021	HCCLM3 and Huh7	circMEMO1	Down	Sorafenib sensitivity, EMT and cancer stemness	Diagnosis	(97)
Shi *et al*, 2021	HA22T, HCCLM3 and Huh7	circPABPC1	Down	Invasion and migration	Treatment	(98)
Li *et al*, 2022	MHCC97H and HCCLM3	circRPN2	Down	Proliferation, migration, invasion and glycolysis	Prognosis and treatment	(99)
Chen *et al*, 2022	SMMC7721 and Huh7	circVAMP3	Down	Proliferation and metastasis	Prognosis	(100)
Peng *et al*, 2022	PLC/PRF/5 and MHCC97H	circPTTG1IP	Down	Proliferation, migration and invasion	Treatment	(101)
Guo *et al*, 2023	SMMC7721 and Hep3B	circDHPR	Down	Proliferation and metastasis	Treatment	(102)
Song *et al*, 2023	HCCLM3 and Hep3B	circZKSCAN1	Down	Proliferation, apoptosis and cell cycle	Treatment	(103)

circRNA, circular RNA; Down, downregulated; EMT, epithelial-mesenchymal transition; Up, upregulated.

of ICC (113). circZNF215 expression is notably increased in ICC tissues, and high circZNF215 expression predicts a poor prognosis. circZNF215 promotes oxidation-induced inactivation of PTEN and $AKT^{Ser473/Thr308}$ phosphorylation by blocking the interaction between peroxiredoxin 1 (PRDX1) and PTEN through competitively binding to PRDX1 (114).

Downregulation of circRNAs in CCA. circNFIB is downregulated in ICC tissues and is associated with a worse prognosis. circNFIB competitively interacts with MEK1, which induces the dissociation between MEK1 and ERK2, thereby inhibiting ERK phosphorylation and suppressing ICC growth and metastasis. Moreover, circNFIB serves as a promising therapeutic molecule in ICC as it has been shown to enhance the antitumor effects of trametinib *in vitro* and *in vivo* (115). circ-0059961 is downregulated in CCA tissues and carcinoma cells, such as CCLP-1 and QBC939, and overexpressed circ-0059961 inhibits CCA proliferation, migration and invasion. Mechanistically, circ-0059961 acts as a sponge for miR-629-5p to upregulate secreted frizzled related protein 2 (116). circSMARCA5 is downregulated in CCA, and mechanistic investigations have demonstrated that circSMARCA5 inhibits cell growth and promotes apoptosis by sponging miRNA-95-3p to regulate the expression of TNF receptor associated factor 3 (117).

The relationship between circRNA and the malignant hallmarks of CCA is summarized in Table IV. In CCA, upregulated or downregulated circRNAs influence the progression of the disease. Upregulated circRNAs such as circCCAC1, promote the growth and invasion of CCA cells, disrupt blood vessels and induce the formation of new blood vessels. Other upregulated circRNAs such as circ-0000284, circ-0005230, circLAMP1, circ-0021205, circACTN4, circEIF3C, circGGNBP2, circMBOAT2 and circZNF215, also contribute to CCA progression via various mechanisms. However, certain circRNAs are downregulated in CCA such as circNFIB, circ-0059961 and circSMARCA5, which inhibit the growth and metastasis of CCA cells. Understanding the role of these circRNAs in CCA could aid with finding new biomarkers for the prognosis and treatment of CCA.

CircRNA and PC

Upregulation of circRNAs in PC. circIARS in the plasma exosomes of patients with metastatic PC can enter human microvascular vein endothelial cells and upregulate RhoA and RhoA-GTP levels through the miR-122/ZO-1 signaling axis, ultimately enhancing endothelial monolayer permeability and promoting tumor invasion and metastasis (118). circFOXK2 not only acts as a sponge for miR-942 to promote the expression of ankyrin 1, glial cell line-derived neurotrophic factor and paired box 6, but it can also enhance the expression of oncogene NUF2 and pyridoxal kinase through interaction with YBX1 and hnRNPK, ultimately promoting the progression of pancreatic ductal adenocarcinoma (PDAC) (119). circBFAR is positively correlated with lymph node metastasis and advanced TNM stage in PDAC, indicating a poor prognosis in patients. circBFAR upregulates the expression of MET and activates the PI3K/AKT signaling pathway by sponging miR-34b-5p, ultimately promoting the malignant progression of PDAC (120). circ-0000069 is markedly upregulated in PC tissues and cell lines, and its area under the ROC curve in cancer tissues is 0.8944, demonstrating diagnostic value. circ-000069 can promote the growth of PC cells through the miR-144/STIL axis, and circ-0000069 in exosomes can be transferred from SW1990 cells to human pancreatic duct epithelial cells, thereby enhancing the malignant transformation of PC (121). circMBOAT2 is highly expressed in PC tissues and cells and modulates tumor development and glutamine catabolism through the miR-433-3p/glutamic-oxaloacetic transaminase 1 axis (122). circEYA3 is elevated in PDAC tissues and cells, and high expression of circEYA3 is associated with advanced lymph node invasion and tumor metastasis, predicting a poor prognosis in patients. Mechanistically, circEYA3 exerts a carcinogenic effect on PDAC by increasing ATP synthesis through the miR-1294/c-Myc axis (123). circZNF91 in hypoxic exosomes of PC cells competitively binds to miR-23b-3p, upregulates sirtuin 1 expression and enhances the deacetylation-dependent stability of HIF-1α, leading to glycolysis and gemcitabine chemoresistance in recipient PC cells. Meanwhile, transcription of HIF-1α also increases the expression of circZNF91 in hypoxic exosomes, forming a positive feedback loop (124). circPDK1 is upregulated in PC tissues and serum exosomes and is associated with poor prognosis. Exosomal circPDK1 is activated by HIF-1α at the transcriptional level during hypoxia and upregulates bromodomain PHD finger transcription factor expression by competitively binding to miR-628-3p (125). In addition, circPDK1 may serve as a scaffold to enhance the binding of ubiquitin conjugating enzyme E2 O (UBE2O) and bridging integrator 1 (BIN1), thus facilitating the effects of UBE2O on the ubiquitination and degradation of BIN1 (125). circATG7 in the cytoplasm of PC cells increases the autophagy related 7 (ATG7) mRNA level by sponging miR-766-5p, and nuclear circATG7 increases the stability of ATG7 mRNA by recruiting HuR, which promotes the proliferation, metastasis and autophagy of PC (126). circFARP1 expression in CAFs is positively correlated with gemcitabine chemoresistance in advanced PDAC. In addition, circFARP1 enhances leukemia inhibitory factor (LIF) expression by functioning as a miR-660-3p sponge in CAFs. circFARP1 also directly interacts with caveolin 1 (CAV1) and blocks the interaction of CAV1 and E3 ubiquitin-protein ligase zinc and ring finger 1 to inhibit CAV1 degradation, which enhances LIF secretion. Overall, circFARP1 enhances the expression and secretion of LIF in CAFs to induce chemoresistance (127). circMYO1C mediated by the m^6A methyltransferase, methyltransferase 3 N6-adenosine-methyltransferase complex catalytic subunit (METTL3), is highly expressed in PDAC tissues. circMYO1C targets the m^6A site of PD-L1 mRNA to enhance PD-L1 mRNA stability by cooperating with the m^6A reader, IGF2BP2, thereby accelerating PDAC immune escape (128). Upregulation of circ-0014784 promotes the invasion, proliferation, EMT and angiogenesis of PC by regulating miR-214-3p/YAP1 signaling (129).

Downregulation of circRNAs in PC. circNFIB1 is downregulated in PDAC tissues and is negatively correlated with lymph node metastasis in patients. circNFIB1 inhibits the PI3K/AKT pathway and decreases the expression of VEGF-C by sponging miR-486-5p and upregulating PIK3R1 expression, ultimately suppressing lymphangiogenesis and lymph node metastasis in PDAC (130). The expression level of circ-000864 is lower in PC tumor tissues compared with adjacent tissues.

Table IV. Relationship between circRNA and the malignant hallmarks of cholangiocarcinoma.

First author, year	Main cell lines	circRNA name	Expression	Main malignant hallmarks	Potential clinical value	(Refs.)
Xu *et al*, 2021	CCLP1 and QBC939	circCCAC1	Up	Angiogenesis, proliferation, invasion and apoptosis	Diagnosis, treatment and prognosis	(104)
Wang *et al*, 2019	RBE and HuCCT1	circ-0000284	Up	Proliferation, invasion, migration and apoptosis	Diagnosis	(105)
Xu *et al*, 2019	HuCCT1 and KMBC	circ-0005230	Up	Proliferation, invasion, migration and apoptosis	Treatment	(107)
Xu *et al*, 2021	RBE and KMBC	circLAMP1	Up	Invasion and migration	Treatment	(108)
Tu *et al*, 2021	HuCCT1 and KMBC	circ-0021205	Up	Proliferation, invasion and migration	Treatment and diagnosis	(109)
Chen *et al*, 2022	RBE and FRH0201	circACTN4	Up	Proliferation, migration and invasion	Treatment and prognosis	(110)
Zhong *et al*, 2023	RBE and QBC939	circEIF3C	Up	Immune evasion, invasion and cell viability	Treatment	(111)
Li *et al*, 2022	RBE and HuCCT1	circGGNBP2	Up	Proliferation, cell cycle and invasive	Treatment	(112)
Yu *et al*, 2023	RBE and HCCC9810	circMBOAT2	Up	Proliferation, apoptosis, cell cycle and lipid metabolism reprogramming	Treatment	(113)
Liao *et al*, 2023	HuCCT1, HCCC9810 and RBE	circZNF215	Up	Proliferation, cell cycle, migration and invasion	Prognosis and treatment	(114)
Du *et al*, 2022	HuCCT1, HCCC9810 and RBE	circNFIB	Down	Proliferation, cell cycle, migration, invasion and trametinib resistance	Treatment	(115)
Zhang *et al*, 2022	CCLP1 and QBC939	circ-0059961	Down	Proliferation, migration, invasion and apoptosis	Treatment	(116)
Wang *et al*, 2023	TFK1	circSMARCA5	Down	Proliferation and apoptosis	Treatment	(117)

circRNA, circular RNA; Down, downregulated; Up, upregulated.

circ-000864 inhibits the migration and invasion of PC cells by upregulating the expression of BTG anti-proliferation factor 2 through sponging miR-361-3p (131). The expression of circ-0013587 is significantly decreased in erlotinib-resistant AsPC-1 cells, and circ-0013587 can reverse erlotinib resistance in PC cells by increasing the levels of E-cadherin through suppressing the expression of miR-1227 (132). Cytoplasmic circ-0092367 sponges miR-1206 and decreases its expression and increases the expression of epithelial splicing regulatory protein 1 (a target gene of miR-766-5p), thereby inhibiting EMT and enhancing the sensitivity of PC cells to gemcitabine treatment (133). circANAPC7, a tumor suppressor, promotes the expression of PH domain and leucine rich repeat protein phosphatase 2 (PHLPP2) by binding to miR-373. circANAPC7 is involved in the ZIP4-mediated cAMP response element-binding protein/miR-373/PHLPP2 feed-forward loop, leading to AKT dephosphorylation and downregulation of cyclin D1 and TGF-β, suppressing tumor growth and muscle wasting in PC (134). circ-0000994 inhibits the proliferation, migration and invasion of PC cells through spongingmiR-27a and miR-27b (135). circACTR2 is significantly downregulated in gemcitabine-resistant PC cell lines, and high expression of circACTR2 is associated with improved survival in patients with PC. circACTR2 directly represses miR-221-3p levels and thus upregulates the expression of PTEN, thereby inhibiting the PI3K/AKT signaling pathway and enhancing the sensitivity of PC cells to gemcitabine treatment (136).

The relationship between circRNA and the malignant hallmarks of PC is summarized in Table V. Several circRNAs such as circIARS, circFOXK2, circBFAR, circ-0000069, circMBOAT2, circEYA3, circZNF91, circPDK1, circATG7, circFARP1, circMYO1C and circ-0014784, have been found to be upregulated in PC and contribute to tumor progression by regulating various pathways and molecules. Conversely, circNFIB1, circ-000864, circ-0013587, circ-0092367, circANAPC7, circ-0000994 and circACTR2 are downregulated in PC and function as tumor suppressors by inhibiting proliferation and invasion and by promoting drug sensitivity via their interaction with specific miRNAs. These findings suggest that circRNAs have a critical role in the development and progression of PC.

circRNA and CRC

Upregulation of circRNAs in CRC. circNSUN2 is significantly upregulated in the tumor tissue and serum samples of patients with CRC with liver metastasis. The m^{6}A modification of circNSUN2 promotes the formation of a ternary complex with IGF2BP2 and HMGA2 in the cytoplasm, enhancing the stability of HMGA2 mRNA and promoting the progression of liver metastasis in CRC (137). As a novel CRC-derived exosomal circRNA, circPACRGL is significantly upregulated in CRC cells. circPACRGL serves as a sponge for miR-142-3p/miR-506-3p to enhance the expression of TGF-β1, which promotes the proliferation, migration and invasion of CRC cells, as well as differentiation of neutrophils from N1 to N2 (138). circERBIN enhances the expression of eukaryotic initiation factor 4E-binding protein 1 (4EBP-1) by sponging miR-125a-5p and miR-138-5p and increases HIF-1α protein expression via 4EBP-1, significantly promoting the angiogenesis of CRC (139). circ-0000392 distinguishes CRC cases from healthy controls with an area under the curve (AUC) of 0.713, and the expression of circ-0000392 is significantly correlated with pathological stage, lymph node metastasis and distant metastasis. circ-0000392 acts as a ceRNA against miR-193a-5p, which directly targets PIK3R3, affecting activation of the AKT-mTOR pathway in CRC cells (140). The expression level of circ1662 is positively correlated with the malignant progression of CRC and is associated with poor survival. METTL3 promotes the expression of circ1662 by binding to its flanking sequences and installing m^{6}A modifications. circ1662 directly binds to YAP1 and accelerates its nuclear accumulation to inhibit the expression of SMAD3, enhancing CRC invasion and migration (141). circSPARC is highly abundant in CRC tumor tissues and plasma and shows promising diagnostic performance in distinguishing CRC from normal tissues (AUC=0.8613). circSPARC serves as a sponge for miR-485-3p to facilitate JAK2 expression and promote the accumulation of phosphorylated (p)-STAT3. In addition, circSPARC can recruit FUS and promote nuclear translocation of p-STAT3, ultimately enhancing the proliferation and migration of CRC (142). circQSOX1 is highly expressed and predicts poor prognosis in patients with CRC. m^{6}A-modified circQSOX1 facilitates CRC tumorigenesis by sponging miR-326 and miR-330-5p to upregulate phosphoglycerate mutase 1, thereby activating glycolysis and inactivating the anti-cytotoxic T-lymphocyte associated protein-4 therapy response of CRC (143). circREEP3 is frequently upregulated in tumor tissues from patients with CRC and predicts poorer patient survival. circREEP3 interacts with chromodomain helicase DNA binding protein 7 to activate FKBP prolyl isomerase 10 transcription and promote the proliferation and metastasis of CRC cells. In addition, circREEP3 can restrict antitumor immunity via suppression of retinoic acid-inducible gene 1 signaling (144). circCAPRIN1 is upregulated in the tissues of patients with CRC. Furthermore, high expression of circCAPRIN1 is associated with advanced TNM stage and poor survival. Mechanistically, circCAPRIN1 interacts with STAT2 to transcriptionally activate acetyl-CoA carboxylase 1, thereby promoting lipid synthesis and facilitating CRC tumorigenesis (145). Exosomal circTUBGCP4 can induce the tip cell formation, angiogenesis and tumor metastasis of CRC cells. circTUBGCP4 sponges miR-146b-3p to upregulate pyruvate dehydrogenase kinase isoform 2 expression and ultimately contribute to the accumulation of p-AKT (146).

Downregulation of circRNAs in CRC. circTADA2A is significantly downregulated in CRC compared with normal adjacent tissues and cell lines. circTADA2A inhibits glycolysis and the cell cycle and potentiates the apoptosis of CRC cells by acting as a sponge for miR-374a-3p and increasing Krüppel-like factor 14 expression (147). circGALNT16 is downregulated in CRC tissues and can significantly inhibit the proliferation, invasion and migration of CRC cells. Mechanistically, circGALNT16 inhibits the progression of CRC by specifically binding to the KH3 domain of hnRNPK, and it can also enhance the interaction between hnRNPK and p53 by inhibiting SUMO specific peptidase 2-mediated hnRNPK deSUMOylation. circGALNT16 attenuates serpin family E member 1 and enhances the p21 mRNA expression level by regulating the sequence-specific DNA-binding ability of the hnRNPK-p53 complex (148). circRHOBTB3

Table V. Relationship between circRNA and the malignant hallmarks of pancreatic cancer.

First author, year	Main cell lines	circRNA name	Expression	Main malignant hallmarks	Potential clinical value	(Refs.)
Li *et al*, 2018	Hs 766 T and Aspc1	circIARS	Up	Invasion and metastasis	Diagnosis and prognosis	(118)
Wong *et al*, 2020	CFPAC1 and PANC1	circFOKX2	Up	Proliferation, invasion, migration, cell cycle and apoptosis	Diagnosis	(119)
Guo *et al*, 2020	PANC1 and Bxpc3	circBFAR	Up	Proliferation, invasion and migration	Treatment and prognosis	(120)
Ye *et al*, 2020	MiaPaCa2 and SW1990	circ-0000069	Up	Proliferation, invasion, migration, cell cycle and apoptosis	Treatment	(121)
Zhou *et al*, 2021	PANC1 and SW1990	circMBOAT2	Up	Proliferation, invasion, migration and glutamine catabolism	Treatment	(122)
Rong *et al*, 2021	PANC1 and MiaPaCa2	circEYA3	Up	Proliferation, invasion, migration and apoptosis	Treatment	(123)
Zeng *et al*, 2021	Bxpc3 and SW1990	circZNF91	Up	Chemoresistance and glycolysis	Treatment	(124)
Lin *et al*, 2022	PANC1 and MiaPaCa2	circPDK1	Up	Glycolysis, proliferation and migration	Diagnosis, prognosis and treatment	(125)
He *et al*, 2022	PANC1 and MiaPaCa2	circATG7	Up	Autophagy, proliferation and migration	Treatment	(126)
Hu *et al*, 2022	PANC1 and MiaPaCa2	circFARP1	Up	Gemcitabine resistance, proliferation, sphere formation and apoptosis	Treatment	(127)
Guan *et al*, 2023	PANC1 and Capan2	circMYO1C	Up	Proliferation, migration and immune escape	Treatment	(128)
Liu *et al*, 2023	PANC1 and SW1990	circ-0014784	Up	Proliferation, invasion, angiogenesis and EMT	Treatment	(129)
Kong *et al*, 2020	PANC1 and Capan2	circNFIB1	Down	Lymphangiogenesis, lymphatic metastasis and migration	Treatment	(130)
Huang *et al*, 2020	Aspc1	circ-000864	Down	Proliferation, migration, invasion, cell cycle and apoptosis	Treatment	(131)
Xu *et al*, 2021	Aspc1	circ-0013587	Down	Proliferation, invasion, EMT and erlotinib resistance	Treatment	(132)
Yu *et al*, 2021	Aspc1 and MiaPaCa2	circ-0092367	Down	EMT and gemcitabine resistance	Treatment	(133)
Shi *et al*, 2022	Aspc1 and MiaPaCa2	circANAPC7	Down	Muscle wasting and proliferation	Treatment	(134)
Liu *et al*, 2022	PANC1 and SW1990	circ-0000994	Down	Proliferation, migration, invasion and apoptosis	Treatment	(135)
Xu *et al*, 2023	PANC1 and SW1990	circACTR2	Down	Gemcitabine resistance, cell cycle and apoptosis	Treatment	(136)

circRNA, circular RNA; Down, downregulated; EMT, epithelial-mesenchymal transition; Up, upregulated.

Table VI. Relationship between circRNA and the malignant hallmarks of colorectal cancer.

First author, year	Main cell lines	circRNA name	Expression	Main malignant hallmarks	Potential clinical value	(Refs.)
Chen *et al*, 2019	HCT116 and DLD1	circNSUN2	Up	Invasion, migration and EMT	Treatment and prognosis	(137)
Shang *et al*, 2020	HCT116 and SW480	circPACRGL	Up	Proliferation, invasion and migration	Treatment	(138)
Chen *et al*, 2020	HCT116 and RKO	circERBIN	Up	Proliferation, invasion, metastasis, migration and angiogenesis	Treatment	(139)
Xu *et al*, 2020	RKO and SW620	circ-0000392	Up	Proliferation and invasion	Treatment	(140)
Chen C *et al*, 2021	HCT116 and SW480	circ1662	Up	EMT, invasion and migration	Treatment and prognosis	(141)
Wang *et al*, 2021	HCT116 and DLD1	circSPARC	Up	Proliferation, migration and invasion	Diagnosis, treatment and prognosis	(142)
Liu *et al*, 2022	HCT116 and HT29	circQSOX1	Up	Immune escape and glycolysis	Treatment	(143)
Chen *et al*, 2022	HCT116 and LoVo	circREEP3	Up	Invasion, metastasis and sphere formation	Prognosis	(144)
Yang *et al*, 2023	LoVo and RKO	circCAPRIN1	Up	Proliferation, migration, EMT and adipogenesis	Diagnosis and treatment	(145)
Chen *et al*, 2023	HCT116 and SW480	circTUBGCP4	Up	Angiogenesis, metastasis and migration	Treatment	(146)
Li *et al*, 2020	HCT116 and LoVo	circTADA2A	Down	Glycolysis, cell cycle and apoptosis	Treatment	(147)
Peng *et al*, 2021	LoVo, HCT116 and DLD1	circGALNT16	Down	Proliferation, migration and invasion	Treatment	(148)
Chen J *et al*, 2021	HCT116, Colo320, SW480 and DLD1	circRHOBTB3	Down	Migration, invasion, EMT and glycolysis	Treatment	(149)
Liang *et al*, 2021	HCT8 and DLD1	circPLCE1	Down	Proliferation and migration	Treatment and prognosis	(150)
Zheng R *et al*, 2022	HCT116 and DLD1	circLPAR1	Down	Proliferation, invasion and migration	Diagnosis	(151)
Zhang F *et al*, 2022	Caco2 and HCT15	circMETTL3	Down	Proliferation, invasion and migration	Treatment	(152)
Ding *et al*, 2023	HCT116 and RKO	circRERE	Down	Antitumor immunity	Treatment	(153)

circRNA, circular RNA; Down, downregulated; EMT, epithelial-mesenchymal transition; Up, upregulated.

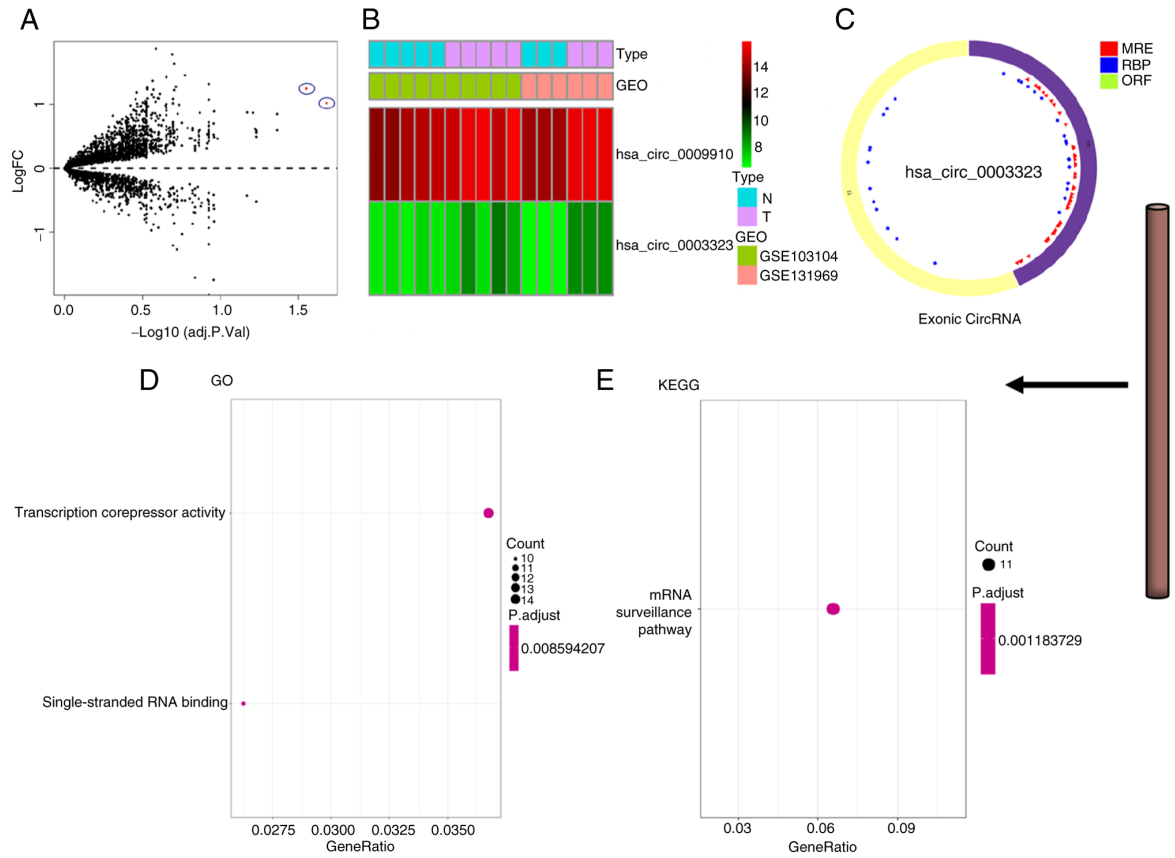

Figure 1. Bioinformatics analysis of circRNA in esophageal cancer. (A) Volcano plot of the circRNA expression differences in the GSE103104 and GSE131969 datasets. (B) Heatmap of differentially expressed circRNAs in the GSE103104 and GSE131969 datasets. (C) Schematic diagram of the basic structural model of hsa_circ_0003323, including MREs, RBPs and ORFs. (D) Bubble chart of GO analysis for hsa_circ_0003323. (E) Bubble chart of KEGG analysis for hsa_circ_0003323. circ, circular; FC, fold change; GEO, Gene Expression Omnibus; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; MRE, microRNA response element; N, normal (tissue); ORF, open reading frame; RBP, RNA binding protein; T, tumor (tissue).

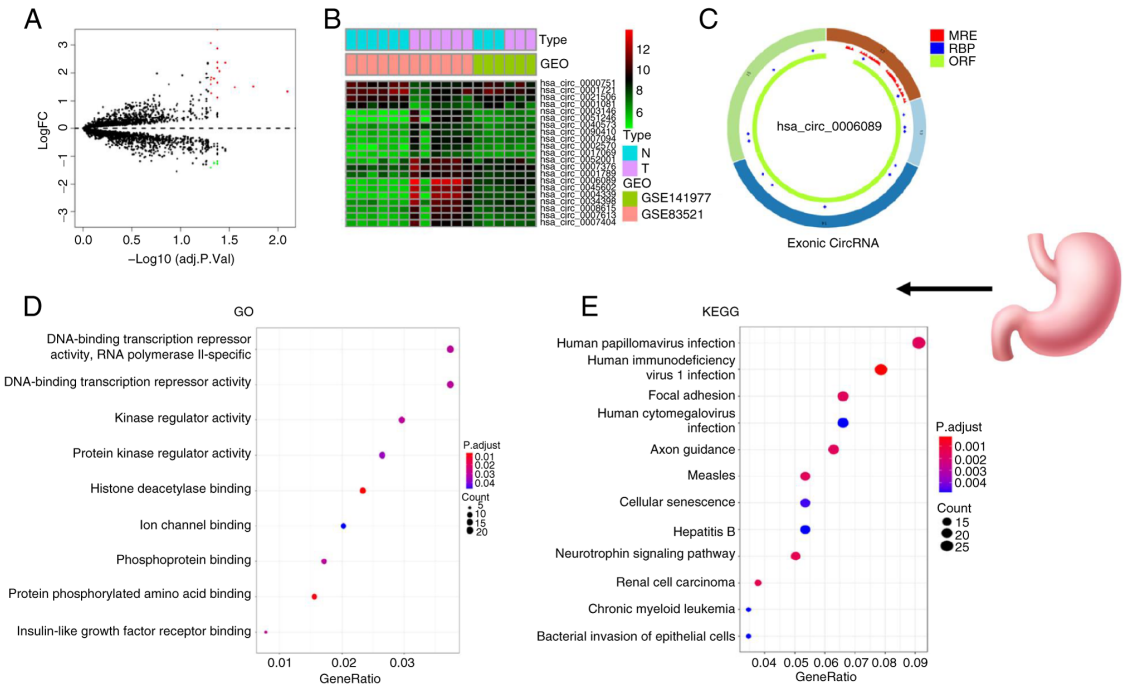

Figure 2. Bioinformatics analysis of circRNA in gastric cancer. (A) Volcano plot of the circRNA expression differences in the GSE141977 and GSE83521 datasets. (B) Heatmap of differentially expressed circRNAs in the GSE141977 and GSE83521 datasets. (C) Schematic diagram of the basic structural model of hsa_circ_0006089, including MREs, RBPs and ORFs. (D) Bubble chart of GO analysis for hsa_circ_0006089. (E) Bubble chart of KEGG analysis for hsa_circ_0006089. circ, circular; FC, fold change; GEO, Gene Expression Omnibus; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; MRE, microRNA response element; N, normal (tissue); ORF, open reading frame; RBP, RNA binding protein; T, tumor (tissue).

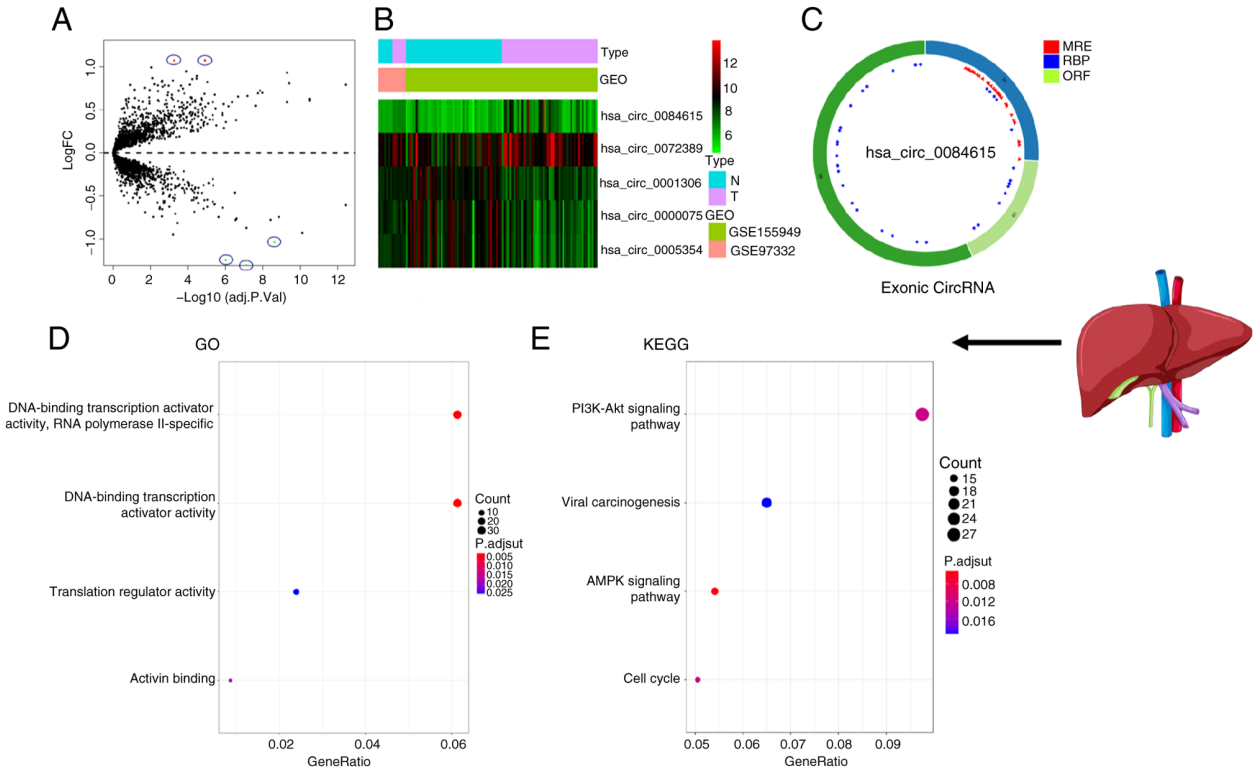

Figure 3. Bioinformatics analysis of circRNA in hepatocellular carcinoma. (A) Volcano plot of the circRNA expression differences in the GSE155949 and GSE97332 datasets. (B) Heatmap of differentially expressed circRNAs in the GSE155949 and GSE97332 datasets. (C) Schematic diagram of the basic structural model of hsa_circ_0084615, including MREs, RBPs and ORFs. (D) Bubble chart of GO analysis for hsa_circ_0084615. (E) Bubble chart of KEGG analysis for hsa_circ_0084615. AMPK, AMP-activated protein kinase; circ, circular; FC, fold change; GEO, Gene Expression Omnibus; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; MRE, microRNA response element; N, normal (tissue); ORF, open reading frame; RBP, RNA binding protein; T, tumor (tissue).

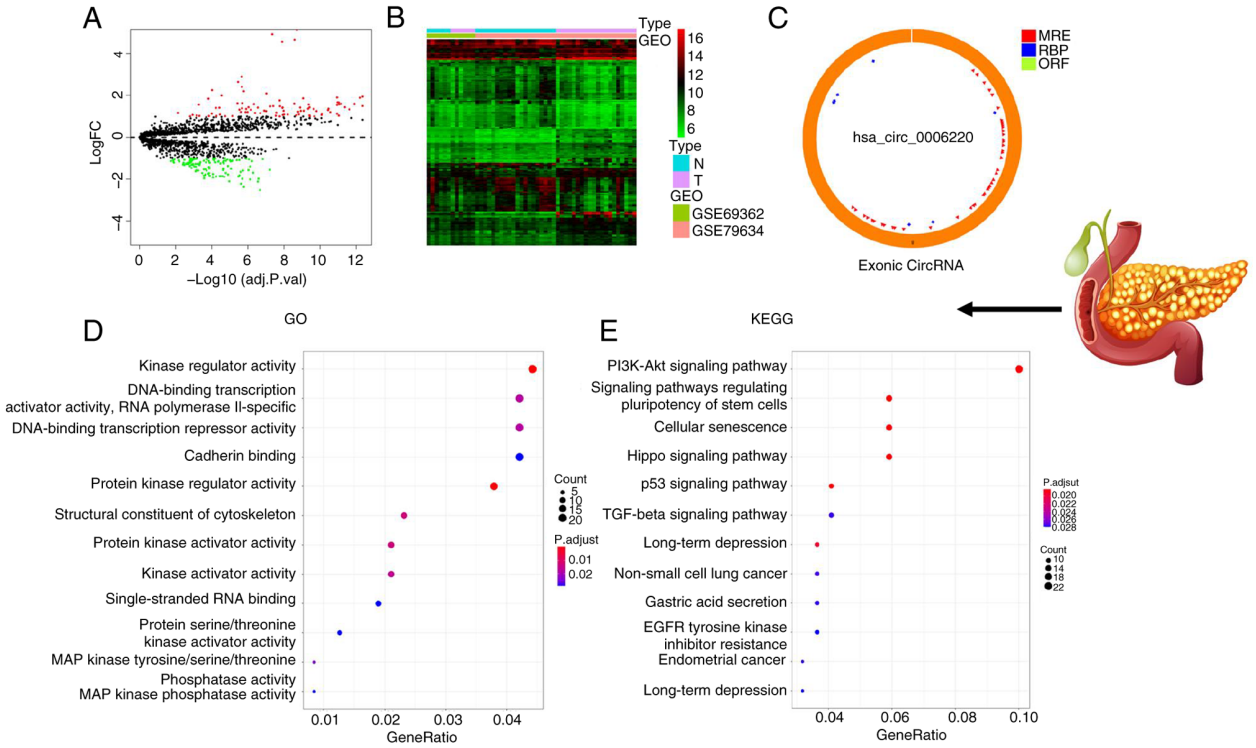

Figure 4. Bioinformatics analysis of circRNA in pancreatic cancer. (A) Volcano plot of the circRNA expression differences in the GSE69362 and GSE79634 datasets. (B) Heatmap of differentially expressed circRNAs in the GSE69362 and GSE79634 datasets. (C) Schematic diagram of the basic structural model of hsa_circ_0006220, including MREs, RBPs and ORFs. (D) Bubble chart of GO analysis for hsa_circ_0006220. (E) Bubble chart of KEGG analysis for hsa_circ_0006220. circ, circular; FC, fold change; GEO, Gene Expression Omnibus; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; MRE, microRNA response element; N, normal (tissue); ORF, open reading frame; RBP, RNA binding protein; T, tumor (tissue).

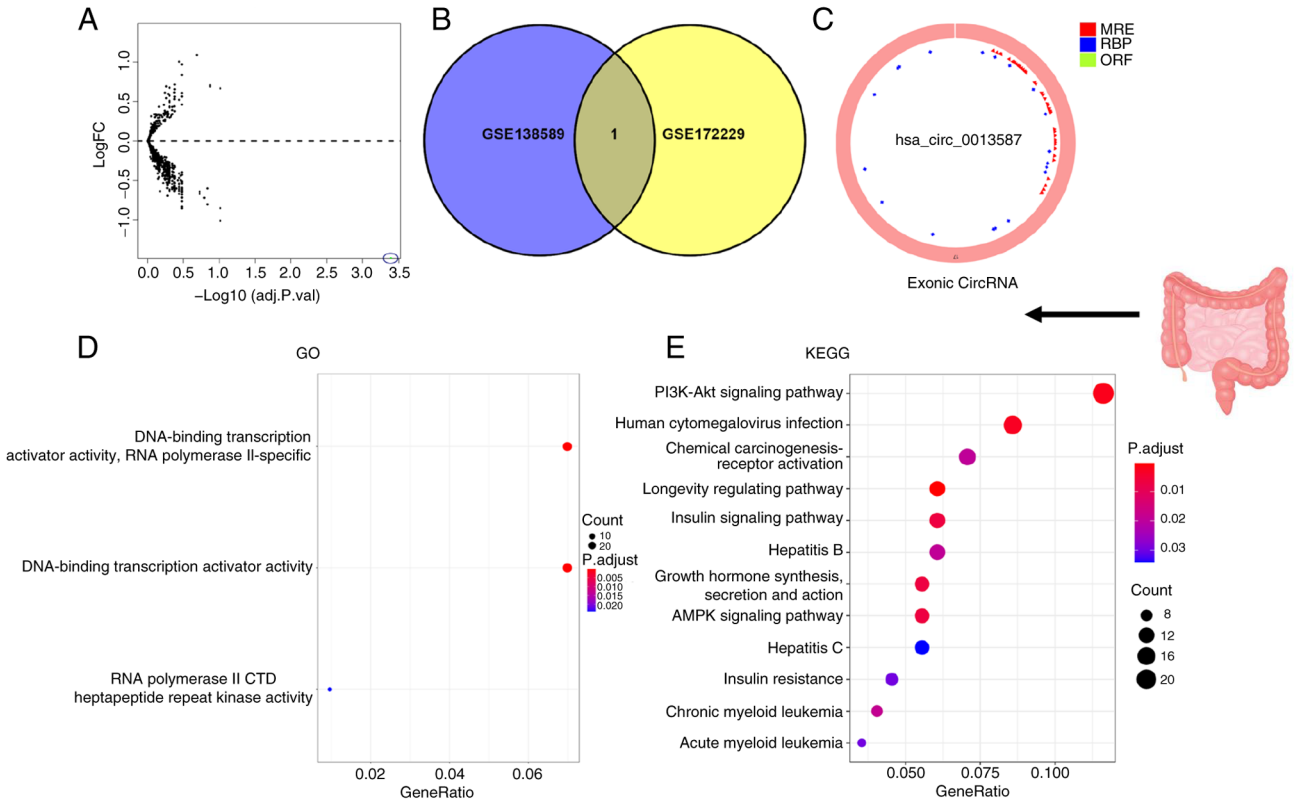

Figure 5. Bioinformatics analysis of circRNA in colorectal cancer. (A) Volcano plot of the circRNA expression differences in the GSE138589 and GSE172229 datasets. (B) Venn diagram of differentially expressed circRNA in the GSE138589 and GSE172229 datasets. (C) Schematic diagram of the basic structural model of hsa_circ_0013587, including MREs, RBPs and ORFs. (D) Bubble chart of GO analysis for hsa_circ_0013587. (E) Bubble chart of KEGG analysis for hsa_circ_0013587. AMPK, AMP-activated protein kinase; circ, circular; CTD, C-terminal domain; FC, fold change; GEO, Gene Expression Omnibus; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; MRE, microRNA response element; N, normal (tissue); ORF, open reading frame; RBP, RNA binding protein; T, tumor (tissue).

binds to HuR and promotes β-transducin repeat-containing protein 1-mediated ubiquitination of HuR, thereby reducing the expression level of the downstream target, PTBP1, and inhibiting the invasion and migration of CRC cells (149). The low expression of circPLCE1 in CRC tissue can encode a new protein termed circPLCE1-411. circPLCE1-411 promotes the ubiquitin-dependent degradation of ribosomal protein S3 (RPS3) by directly binding to the HSP90α/RPS3 complex to reduce NF-κB nuclear translocation in CRC cells, which inhibits NF-κB signaling and CRC cell proliferation and migration (150). Exosomal circLPAR1 shows cancer specificity in a CRC diagnosis, with an area under the ROC curve of 0.875 when combined with carcinoembryonic antigen and carbohydrate antigen 19-9. Exosomal circLPAR1 suppresses CRC tumorigenesis by regulating bromodomain containing 4 levels upon interaction with eukaryotic translation initiation factor 3 (151). circMETTL3 is downregulated in CRC tissues and cells, and circMETTL3 expression is negatively correlated with advanced TNM stages, increased lymph node and distant metastasis of CRC tumors. circMETTL3 serves as a tumor suppressor in CRC *in vivo*. Mechanistically, RUNX family transcription factor 3 directly binds to METTL3 promoter region and activates its transcription, and circMETTL3 directly binds with miR-107 and positively regulates its downstream gene, period circadian regulator 3, expression (152). circRERE, regulated by EP300, exerts antitumor immunity and restrains CRC development by acting as a miR-6837-3p sponge to regulate mitochondrial antiviral signaling protein expression and activate the type I IFN pathway (153).

The relationship between circRNA and the malignant hallmarks of CRC is summarized in Table VI. Several circRNAs such as circNSUN2, circPACRGL, circERBIN, circ-0000392, circ1662, circSPARC, circQSOX1, circREEP3, circCAPRIN1 and exosomal circTUBGCP4, are significantly upregulated in CRC and contribute to tumor progression, metastasis, angiogenesis and immune regulation. Conversely, circTADA2A, circGALNT16, circRHOBTB3, circPLCE1, exosomal circLPAR1, circMETTL3 and circRERE are downregulated in CRC and exhibit tumor-suppressive effects by inhibiting glycolysis, cell cycle progression, invasion, migration and NF-κB signaling, and enhancing apoptosis and antitumor immunity. These findings provide insights into the dysregulation of circRNAs in CRC and their potential as diagnostic markers and therapeutic targets.

5. Bioinformatics screening and functional analysis of circRNAs in digestive tumors

In total, two independent circRNA expression profiles were downloaded for each type of digestive tumor from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/). Bioinformatics data mining was conducted utilizing R (version 4.0.3; https://www.r-project.org/) for the comprehensive analysis of differentially expressed circRNAs

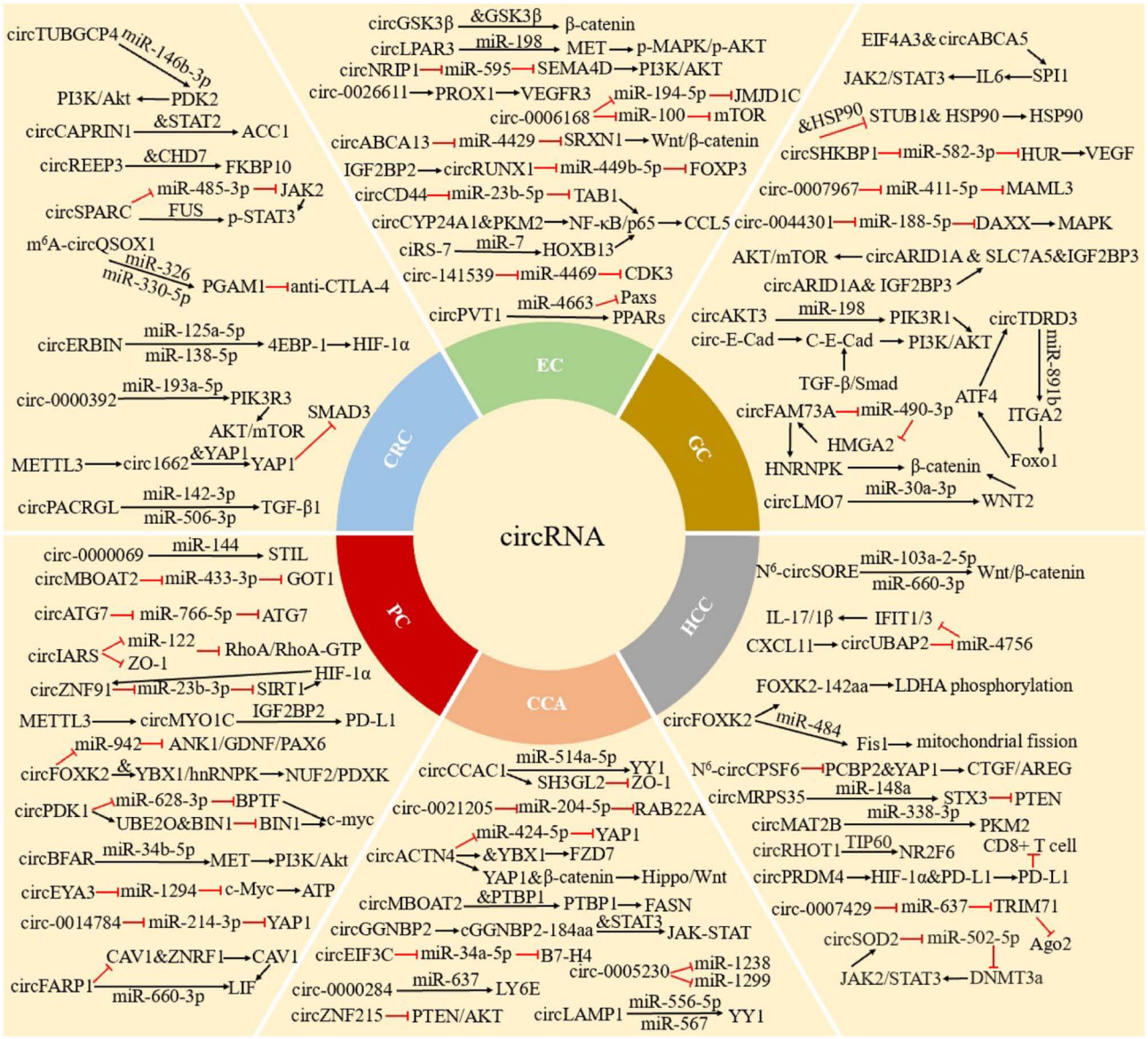

Figure 6. Pathways of upregulated circRNAs in digestive system tumors. CCA, cholangiocarcinoma; circ, circular; CRC, colorectal cancer; EC, esophageal cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; PC, pancreatic cancer.

(DEcircRNAs) from a combined standardized dataset derived from two distinct data matrices in the GEO database. The process encompassed data preprocessing, normalization and differential expression analysis, adhering to the criteria of an absolute value of log2 fold change >2 and P<0.05. The circle diagram of the most significantly upregulated circRNA for each tumor type and its targeted miRNAs were performed using the Cancer-Specific CircRNA website (154). TargetScan (155), miRTarBase (156) and miRDB (157) databases were used to predict miRNA-targeted mRNA. Gene Ontology functional enrichment analysis (http://geneontology.org) and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis (https://www.genome.jp/kegg/) of these targeted mRNAs were conducted to identify the potential functions of the identified circRNA using R.

In EC, two upregulated DEcircRNAs from two datasets [GSE103104 (158) and GSE131969 (44)] were identified. A diagram was constructed to illustrate the structure of hsa_circ_0003323, including the microRNA response element, RBP and ORF (Fig. 1). A bubble diagram was used to visualize the results of the enrichment analysis for potential mRNA targets, which demonstrated that hsa_circ_0003323 may be involved in the biological processes of 'single-stranded RNA binding' and 'transcription corepressor activity', as well as the activation of the 'mRNA surveillance pathway'.

In GC, 21 overlapping DEcircRNAs from two datasets [GSE141977 and GSE83521 (159)] were identified, of which 17 were upregulated and 4 were downregulated. The structural pattern diagram of hsa_circ_0006089 is presented in Fig. 2. The bubble diagram of the potentially targeted mRNA enrichment analysis revealed that hsa_circ_0006089 may be involved in biological processes such as 'kinase regulator activity', 'protein phosphorylated amino acid binding' and 'DNA-binding transcription repressor activity, RNA polymerase II-specific', and pathways related to 'Renal cell

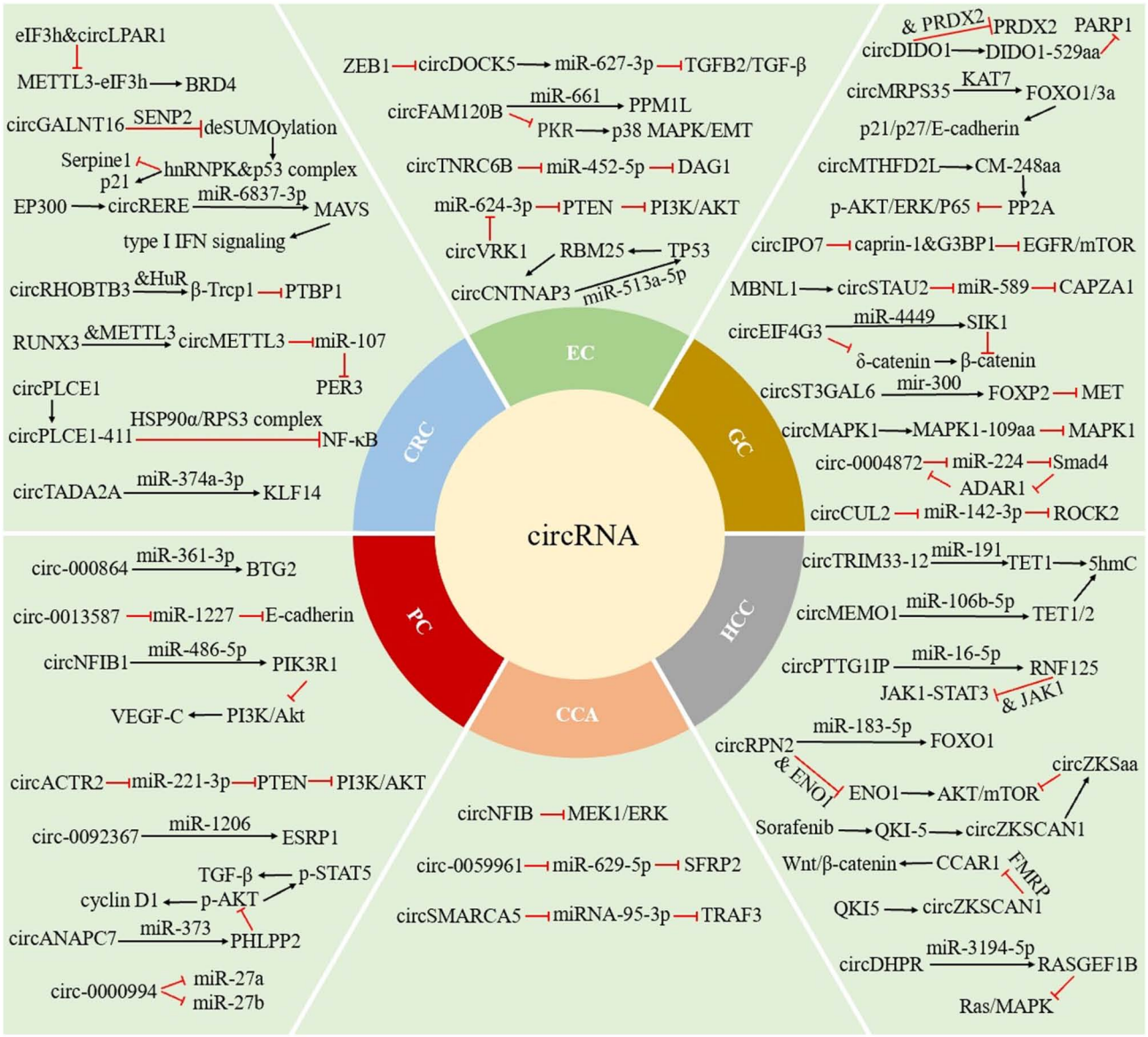

Figure 7. Pathways of downregulated circRNAs in digestive system tumors. CCA, cholangiocarcinoma; circ, circular; CRC, colorectal cancer; EC, esophageal cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; PC, pancreatic cancer.

carcinoma', 'Bacterial invasion of epithelial cells' and 'Human cytomegalovirus infection'.

In HCC, 5 overlapping DEcircRNAs from the GSE155949 (160) and GSE97332 (161) datasets were found. The upregulated DEcircRNAs were hsa_circ_0084615 and hsa_circ_0072389, while the downregulated DEcircRNAs were hsa_circ_0001306, hsa_circ_0000075 and hsa_circ_0005354. The structural pattern diagram of hsa_circ_0084615 is presented in Fig. 3. The bubble diagram of potential targeted mRNA enrichment analysis revealed that hsa_circ_0084615 may be involved in biological processes such as 'DNA-binding transcription activator activity', 'activin binding', 'translation regulator activity' 'PI3K-Akt signaling pathway', 'AMPK signaling pathway' and 'Cell cycle'.

In PC, 207 overlapping DEcircRNAs from the GSE69362 (162,163) and GSE79634 (164) datasets were obtained, of which 90 were upregulated and 117 were downregulated. The structural pattern diagram of hsa_circ_0006220 is presented in Fig. 4. The bubble diagram of potential targeted mRNA enrichment analysis revealed that hsa_circ_0006220 may be involved in biological processes such as 'protein kinase regulator activity', 'single-stranded RNA binding', 'DNA-binding transcription repressor activity', 'PI3K-Akt signaling pathway', 'p53 signaling pathway' and 'Hippo signaling pathway'.

In CRC, only one downregulated DEcircRNA was found in GSE138589 (165) and GSE172229 (148). The structural pattern diagram of hsa_circ_0013587 is presented in Fig. 5. The bubble diagram of potential targeted mRNA enrichment analysis revealed that hsa_circ_0013587 may be involved in biological processes such as 'DNA-binding transcription activator activity', 'RNA polymerase II CTD heptapeptide repeat kinase activity', 'PI3K-Akt signaling pathway', 'AMPK signaling pathway', 'Acute myeloid leukemia', 'Chronic myeloid leukemia' and 'Insulin signaling pathway'.

6. Conclusion

In the present review, a summary of the role and potential mechanisms of different circRNAs in various malignant tumors of the digestive tract was provided (Figs. 6 and 7). Research into the diverse biological functions of circRNAs has elucidated the significance of previously unknown circRNAs in gastrointestinal tumors, as well as their possible molecular mechanisms. Despite being studied for over a decade, the understanding of circRNA remains incomplete. At present, research on circRNA primarily focuses on its ceRNA mechanism. The characterization of other mechanisms, such as the regulatory effect of ciRNA on parental genes and the encoding of functional proteins, has been less extensive. Despite numerous studies confirming the clinical potential of circRNAs as a biomarker, their integration into clinical testing has not been realized. The balance between these mechanisms, where some circRNAs function as miRNA sponges or interact with proteins at multiple sites involving different or even opposing pathways, is maintained through complex regulatory processes. In conclusion, circRNAs have a crucial regulatory role in the formation and development of digestive tumors. They not only influence coding and non-coding RNAs but also have measurable implications on multiple signaling pathways and the biological characteristics of tumors. An increasing number of circRNAs are being identified as ideal serum biomarkers, offering new targets for the clinical diagnosis and treatment of digestive tumors. In the future, there are undoubtedly more circRNAs to be discovered and characterized.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

CZ conceived and designed the manuscript. MQ summarized the data and wrote the manuscript. YC conducted the bioinformatics analysis and drew the figures. All authors have read and approved the final version of the manuscript. MQ and YC confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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