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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc.*

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Circular RNAs in hepatocellular carcinoma: Recent advances

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Abstract

Circular RNAs (circRNAs) have covalently closed loop structures at both ends, exhibiting characteristics dissimilar to those of linear RNAs. Emerging evidence suggests that aberrantly expressed circRNAs play crucial roles in hepatocellular carcinoma (HCC) by affecting the proliferation, apoptosis and invasive capacity of HCC cells. Certain circRNAs may be used as biomarkers to diagnose and predict the prognosis of HCC. Therefore, circRNAs are expected to become novel biomarkers and therapeutic targets for HCC. Herein, we briefly review the characteristics and biological functions of circRNAs, focusing on their roles in HCC to provide new insights for the early diagnosis and targeted therapy of HCC.

Key Words: Hepatocellular carcinoma; Circular RNAs; Function; Diagnosis; Biomarkers; Targeted therapy

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Core Tip: Current studies have shown that aberrantly expressed circular RNAs (circRNAs) play crucial roles in hepatocellular carcinoma (HCC) by affecting the proliferation, apoptosis and invasive capacity of HCC cells. Certain circRNAs may be used as potential biomarkers to diagnose and predict the prognosis of HCC. Therefore, circRNAs are expected to become novel biomarkers and therapeutic targets for HCC. Herein, we briefly review the characteristics and biological functions of circRNAs, focusing on their roles in HCC to provide new insights for the early diagnosis and targeted therapy of HCC.

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INTRODUCTION

Early hepatocellular carcinoma (HCC) usually lacks specific symptoms, and most patients have missed the opportunity for effective treatment because they are diagnosed at middle-to-advanced stages. The emergence of novel therapeutic strategies for HCC, such as immunotherapy and molecularly targeted therapies[1], can prolong the survival of HCC patients. Unfortunately, patients with advanced HCC are prone to metastasis and recurrence, and long-term prognosis remains poor[2]. Therefore, identifying new biomarkers for early diagnosis and effective therapeutic targets of HCC is critical.

Circular RNAs (circRNAs) are covalently closed loops generated by the back splicing of precursor mRNA (pre-mRNA) molecules, which exist widely in mammalian cells and are characterized by stability, conservative evolution, and cell or tissue specificity. These characteristics endow circRNAs with many biological functions, such as acting as microRNA (miRNA) sponges, regulating the transcription of parental genes, binding RNA binding proteins (RBPs), and encoding proteins and peptides[3]. CircRNAs exert their biological functions mainly at the epigenetic, transcriptional and posttranscriptional levels[4,5]. Dysregulated circRNAs play crucial roles in various diseases, particularly with respect to the occurrence and development of tumors and tumor proliferation, apoptosis and metastasis[6-8]. Currently, aberrantly expressed circRNAs are closely associated with the proliferation, cell cycle, apoptosis, migration, epithelial-mesenchymal transition (EMT), invasion, metastasis, cancer stem cells (CSCs), glycolysis, microvascular invasion (MVI), angiogenesis, immune surveillance, immune escape, chemoresistance, and immunotherapy resistance of HCC. Thus, circRNAs may be promising biomarkers for the diagnosis and prognosis of HCC as well as effective therapeutic targets. Herein, we briefly review the characteristics and biological functions of circRNAs, focusing on their roles in HCC to provide new insights into the early diagnosis and targeted therapy of HCC.

CHARACTERISTICS, CATEGORIES AND GENERATION OF CIRC RNAs

Characteristics of circRNAs

Most circRNAs have the following characteristics: (1) High abundance: The abundance of circRNA expression varies greatly; in some cases, the abundance of circRNAs exceeds 10 times that of their linear RNA counterparts[9]; (2) Stability: The stability of circRNAs is 2.5-5 times higher than that of linear transcripts because the unique covalently closed loop of circRNAs lacks 3' and 5' ends, resulting in the absence of ribonuclease binding targets; therefore, circRNAs are not easily degraded[10]; (3) Conservation: CircRNAs are widely present in different species and are evolutionarily conserved. Some studies suggest that most circRNAs in different species are evolutionarily conserved, while a few are not conserved[11]; and (4) Specificity: CircRNAs have tissue and cell specificity, with differential expression in different stages of ontogeny and disease progression[12].

Categories and generation of circRNAs

CircRNAs are categorized into four classes based on their origins: Exon circRNAs (ecircRNAs), intron circRNAs (ciRNAs), exon-ciRNAs (EciRNAs), and intergenic circRNAs[13] (Figure 1). EcircRNAs are predominant and are mainly located in the cytoplasm. CiRNAs and EciRNAs are located in the nucleus. The generation mechanism of circRNAs is very complex and has not yet been understood. Current studies have shown that the cyclization of circRNAs is principally driven by intron pairing, RBPs or transcription factors and lariat[14].

Intron pairing-driven cyclization or "direct back splicing" is the most common cyclization mode of ecircRNA and EciRNA, where the special pre-mRNA containing ALU repeats is sheared to form ecircRNA after reverse base complementary pairing[11]. Lariat-driven cyclization or "exon skipping" connects exons at both ends through donor and acceptor sites provided by spliceosomes to form lariat selective splicing to generate ecircRNA[11]. In RBP-driven circulation, RBPs bound to the complementary sequences on both sides of the intron of pre-mRNA interact with each other to form a circular structure and promote the terminal connection at both ends of the head and tail to form ecircRNA[15]. EciRNAs can be formed if introns are retained between exons during the above three mechanisms[16]. Self-cyclization of introns: When pre-RNA has a 7 nt guanine (G)- and uracil (U)-rich sequence near an exon and an 11 nt cytosine (C)-rich sequence near another exon, the introns escape branching and degradation during the splicing reaction to produce an intron lariat structure and cyclize to form a stable ciRNA[17].

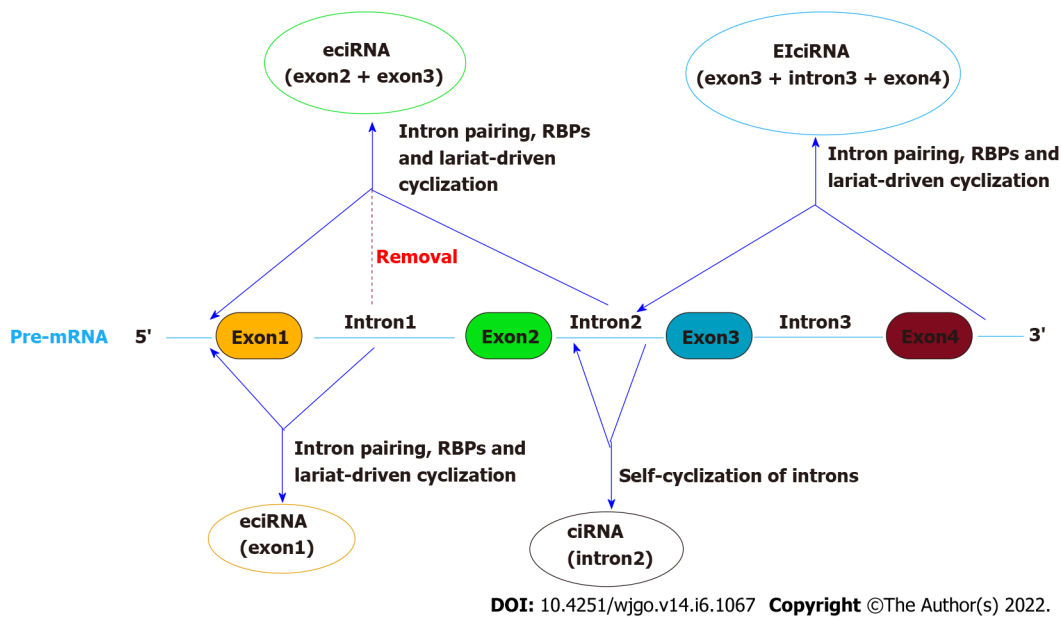


Figure 1 Schematic diagram of biogenesis of circular RNAs. circRNAs: Circular RNAs; pre-mRNA: Pre-messenger RNA; ecircRNAs: Exon circRNAs; ciRNAs: Intron circRNAs; EiciRNAs: Exon-intron circRNAs; RBPs: RNA binding proteins.

BIOLOGICAL FUNCTIONS OF CIRCRNAs

CircRNAs serve in regulatory roles in different biological behaviors through different mechanisms, including acting as sponges of miRNAs, interacting with RBPs, and regulating gene transcription and translation (Figure 2). A recent review analyzed the functions of circRNAs in HCC, of which acting as miRNA sponges accounted for 79.6% [18].

Acting as miRNA sponges

As molecular sponges of miRNAs, circRNAs harbor many miRNA binding sites, which can competitively bind to and restrain the activity of miRNAs [19], thereby regulating the expression of downstream target genes posttranscriptionally. Currently, clinical studies have mainly focused on circRNAs as miRNA molecular sponges [20]. Compared with other types of competing endogenous RNAs, circRNAs have the following advantages. First, circRNAs are not easily degraded by RNA enzymes (RNase or RNA exonucleases) [21,22], which makes the circRNA structure stable and enables the possibility to stably inhibit the performance of miRNA function, with a stronger adsorption capacity for miRNAs than linear mRNAs and long noncoding RNAs. Second, existing studies have shown that the majority of circRNAs are highly expressed and that they can contain substantial miRNA response elements in a single molecule [23-25]; therefore, circRNAs are able to instantly bind or release large amounts of miRNAs to efficiently exert their regulatory roles. For example, circ-7, also known as CDR1as, is a circRNA containing more than 70 miR-7 binding sites [26], which can bind to miR-7 and act downstream of its mRNA. This molecular axis is widely expressed in various malignancies, including oral squamous cell carcinoma and lung cancer [27,28]. In addition, circRNAs may store and transport miRNAs [29]. For example, CDR1as has both miR-7 and miR-671 binding sites [30], and CDR1as first binds to miR-7 and is transported to subcellular locations, where CDR1as is then degraded by miR-671 to eventually release miR-7 [26].

It is worth noting that only circRNAs meeting specific stoichiometric requirements can act as endogenous miRNA sponges, where the abundance of circRNAs as miRNA sponges must match that of miRNAs [31]. Thus, circRNAs as miRNA sponges may not be a universal phenomenon, but one unique to some circRNAs. Only ecircRNAs can act as miRNA sponges, while EiciRNAs and ciRNAs contain few miRNA binding sites that are relatively scattered; thus, EiciRNA and ciRNA may lack the miRNA sponge action ability possessed by ecircRNA [17]. The dysregulation of the circRNA-miRNA-mRNA axis, whether manifesting a promoting or inhibitory role, has been confirmed in many cancers. However, the specific biological mechanism of the circRNA-miRNA-mRNA axis in the occurrence and development of tumors and whether molecular targeted therapy can be improved by intervention in this approach remain to be further studied.

Regulating parental gene transcription

Although most circRNAs are located in the cytoplasm, a fraction exists in the nucleus and participate in regulating RNA transcription. CiRNAs are abundantly expressed in the nucleus and interact with

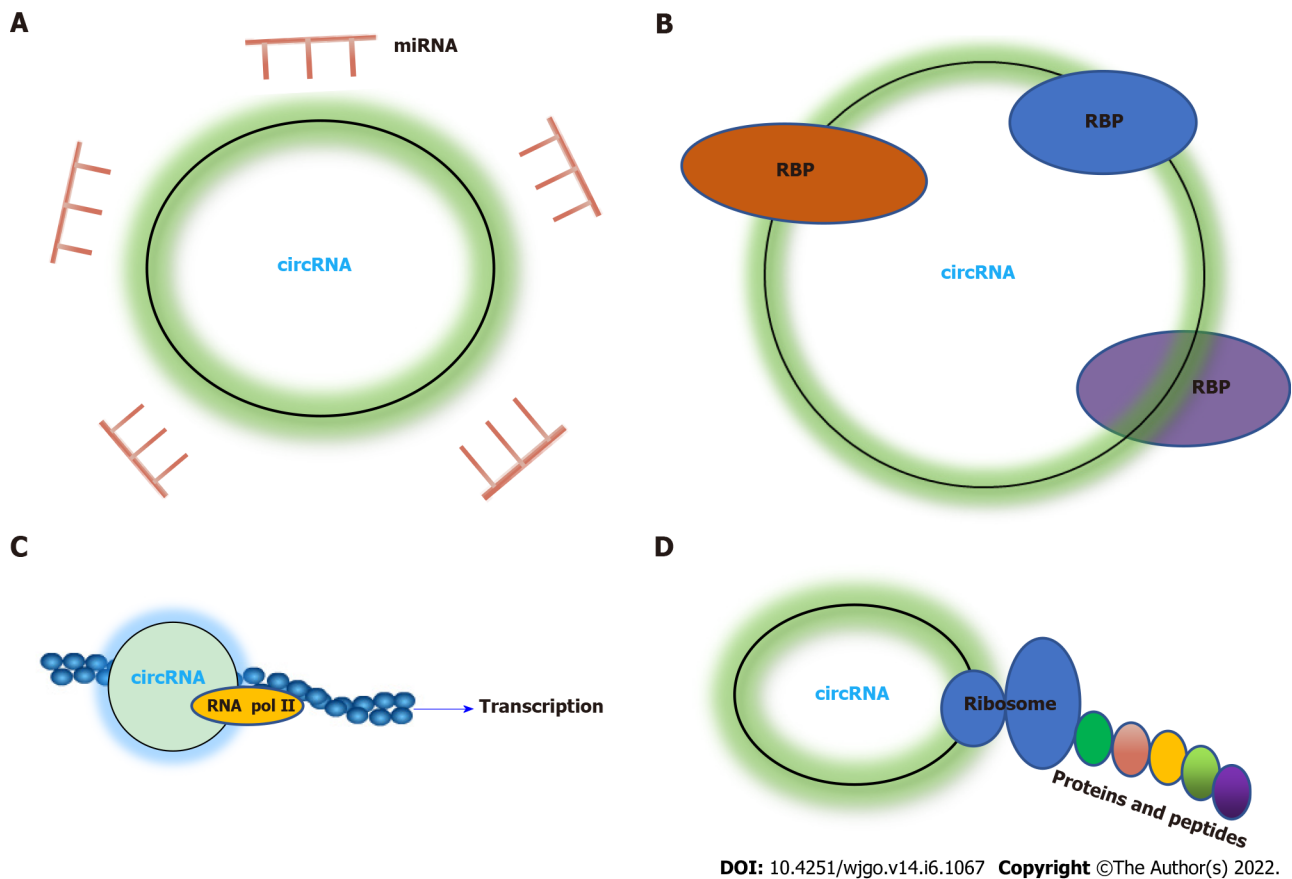


Figure 2 Schematic diagram of biological functions of circular RNAs. A: Acting as microRNA sponges; B: Interacting with RNA binding proteins; C: Regulating gene transcription; D: Encoding proteins and peptides. circRNAs: Circular RNAs; miRNA: MicroRNAs; RBPs: RNA binding proteins.

phosphorylated RNA polymerase II to change its transcriptional activity, thereby playing a role in transcriptional regulation[32]. For example, a circRNA (ci-ankrd52), derived from the intron of the ankyrin repeat domain 52 gene, can enhance the expression of its parent gene ankrin52 by interacting with the RNA polymerase II elongation complex[17]. ElicRNAs are intron-preserving circRNAs located near the promoter of their parent genes and bind to RNA polymerase II to improve transcription efficiency by interacting with the 5' splicing site preserved in introns, thereby promoting the expression of their parent genes[33]. Interestingly, ElicRNAs can act as RBP sponges, like ecircRNAs, and regulate parental gene expression[34]. Additionally, circRNAs can also regulate the expression of parent genes through epigenetic modification. Recently, it has been found that certain circRNAs have N6-methyladenosine (m⁶A) modifications, and these circRNAs will affect the stability of the parent gene[35].

Interacting with RBPs

RBPs are an important class of proteins that participate in posttranscriptional regulation. RBPs interact with circRNAs and play a role in circRNA splicing, replication, folding, stabilization, and localization. The combination of RBPs and circRNAs fulfills roles mainly in the following two ways: (1) RBPs are involved in the action of ceRNA: CircRNAs serve as miRNA “sponges” to modulate mRNA translation, and the potential of these “sponges” is higher than that of their linear counterparts because RBPs participate in the miRNA competition process[36]; and (2) CircRNAs competitively bind to RBPs: CircRNAs play biological roles by binding to RBPs through their specific sequence binding sites[37]. Here we present the most extensively studied RBP, human antigen R (HuR), as an example. HuR, as an RBP, can bind guanylate-rich elements in the 3' untranslated region (UTR) to prevent mRNA from being degraded and accomplishes the function of stabilizing RNA structure[38,39]. HuR is widely expressed in eukaryotic tissues[40], and circE2F2 binds to HuR and enhances the stability of the mRNA of the HuR target gene E2F2[41]. In contrast, circRHOBTB3 binds to HuR and reduces the stability of the mRNA of HuR target gene PTBP1[42]. In addition, circBACH1 can bind to HuR, facilitate HuR translocation to the cytoplasm and inhibit p27 translation[43].

Encoding proteins and peptides

CircRNAs were previously considered to be noncoding RNAs that cannot be translated into proteins. However, emerging evidence suggests that circRNAs can also be translated into proteins and peptides [44-46]. Some circRNAs initiate protein translation by binding to ribosomes *via* the internal ribosome

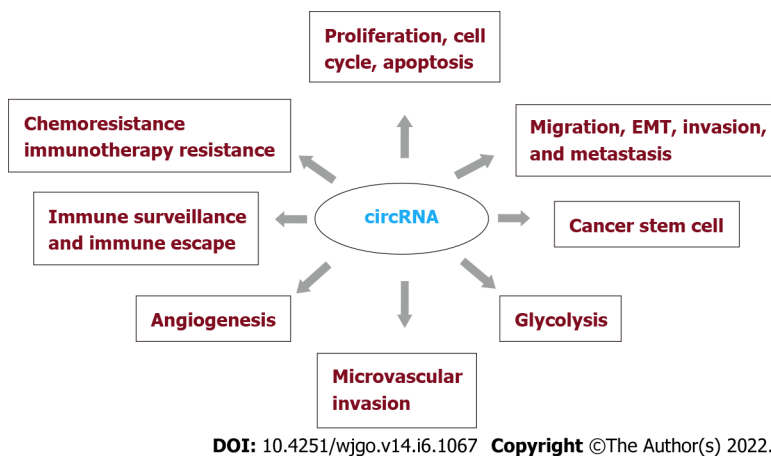


Figure 3 Schematic diagram of the role of circular RNAs in hepatocellular carcinoma. circRNAs: Circular RNAs EMT: Epithelial-mesenchymal transition.

entry site (IRES) sequence or after modifying m⁶A in the 5'UTR[45,47]. In addition, some circRNAs with an open reading frame (ORF) can initiate small proteins or micropeptides[48]. The 40S subunit of eukaryotic ribosomes binds to circRNA and directly initiates *in vitro* translation[49]. Furthermore, unlike other noncoding RNAs, a few circRNAs in the cytoplasm can be translated into functional proteins [11]. Thus, the elements required for circRNA translation are IRES and an m⁶A sequence or ORF. Although circRNAs have translation ability, the translation efficiency is not high because of the influence of their special ring structure, and the functions of circRNA translation products (proteins and peptides) must be further explored.

ROLE OF CIRCRNAS IN HCC

Recent studies have confirmed the different critical roles of aberrantly expressed circRNAs in HCC (Figure 3). Here, we summarize the roles of certain circRNAs in HCC (Table 1).

Proliferation, cell cycle and apoptosis

Aberrant cell cycle regulation, uncontrolled cell proliferation and blocked apoptosis are considered the main causes of malignant tumors. Accumulating studies have highlighted the important regulatory roles of circRNAs in HCC proliferation, the cell cycle and apoptosis, among which oncogenic circRNAs accelerate HCC proliferation and suppress cell cycle arrest and apoptosis. For example, circRNA ZFR serves as an oncogene to facilitate the proliferative ability of HCC by upregulating mitogen-activated protein kinase kinase1 (MAP2K1), a promoter of tumor cell proliferation[50,51]. Similarly, c-Myc, a promoter of cell proliferation[52], and hsa_circ_0091581, as an oncogene, facilitates the proliferation of HCC cells by promoting c-Myc expression through sponging miR-526b[53]. Furthermore, TXNDC5, a promoter of tumor cell proliferation and survival[54], and circ_0000517, an oncogene in HCC, promotes tumor growth and inhibits cell cycle arrest and apoptosis by upregulating TXNDC5 through sponging miR-1296-5p[55]. Conversely, the roles of tumor suppressive circRNAs are opposite those of oncogenic circRNAs. For example, MAPK14, a suppressor of cell proliferation in HCC cells[56], and circSETD3, a tumor suppressor of HCC, enhances MAPK14 expression by sponging miR-421 in HCC, thereby inhibiting proliferation and inducing G1/S arrest[57]. Similarly, exosomal circ-0051443, another tumor suppressor of HCC, upregulates the expression of BRI1-associated kinase 1, a regulator of cell death, by sponging miR-331-3p, stimulating apoptosis and impeding the cell cycle[58,59]. The above findings reveal the importance of circRNAs in regulating HCC cell proliferation, the cell cycle and apoptosis.

Migration, EMT, invasion, and metastasis

EMT is an important phenomenon in the occurrence and development of tumors and can promote the migration, infiltration and metastasis of tumor cells. Invasion and metastasis of tumor cells are the main characteristics of malignant tumors and together constitute the primary cause of death in patients with malignant tumors. Elucidating their molecular mechanisms will help to develop effective interventions for cancer. Recently, many circRNAs have been reported to regulate the progression of HCC cells by affecting migration, EMT, invasion and metastasis. For example, circ-101368 promotes high-mobility group (HMG) box 1 protein/advanced glycation end products signaling by sponging miR-200a, facilitating HCC cell migration[60]. Additionally, circ-CCND1 enhances HMGA2 expression by sponging miR-497-5p, thus promoting HCC proliferation, migration and invasion[61]. Similarly,

Table 1 Roles of circular RNAs in hepatocellular carcinoma

circRNAs	Dysregulation	Mechanism by competitively binding miRNAs/RBP or m ⁶ A modification/mRNA braking	Targets/signaling pathways	Biological functions	Ref.
circRNA ZFR	Up-regulated	N/A	MAP2K1	Promotes HCC proliferation	Cedric <i>et al</i> [50]
		miR-3619-5p	CTNNB1 Wnt/ β -catenin pathway	Promotes HCC proliferation and EMT	Tan <i>et al</i> [99]
hsa_circ_0091581	Up-regulated	miR-526b	c-Myc	Promotes HCC proliferation	Wei <i>et al</i> [53]
circ_0000517	Up-regulated	miR-1296-5p	TXNDC5	Promotes HCC growth and inhibits cell cycle arrest and apoptosis	Zang <i>et al</i> [55]
		miR-326	SMAD6	Promotes HCC invasion and metastasis	He <i>et al</i> [67]
circSETD3	Down-regulated	miR-421	MAPK14	Inhibits HCC proliferation and induces G1/S arrest	Xu <i>et al</i> [57]
		N/A	N/A	Predicts MVI of HCC	Wang <i>et al</i> [85]
Exosomal circ-0051443	Down-regulated	miR-331-3p	BAK1	Promotes HCC cell apoptosis and arrests the cell cycle	Chen <i>et al</i> [58]
circRNA_101368	Up-regulated	miR-200a	HMGB1/RAGE pathway	Promotes HCC cell migration	Li <i>et al</i> [60]
circ-CCND1	Up-regulated	miR-497-5p	HMGA2	Promotes HCC proliferation, migration and invasion	Zheng <i>et al</i> [61]
hsa_circ_0061395	Up-regulated	miR-877-5p	PIK3R3	Promotes HCC proliferation, migration and invasion	Yu <i>et al</i> [62]
		miR-656-3p	SERBP1		Li <i>et al</i> [63]
circRNA-103809	Up-regulated	miR-377-3p	FGFR1/ERK	Facilitates HCC migration, invasion and EMT	Zhan <i>et al</i> [64]
		miR-1270	PLAGL2		Cao <i>et al</i> [65]
circ_MMP2	Up-regulated	miR-136-5p	MMP2	Promotes HCC metastasis	Liu <i>et al</i> [68]
circ-MALAT1	Up-regulated	mRNA braking	PAX5	Promotes self-renewal of HCC stem cells	Chen <i>et al</i> [69]
		miR-6887-3p	JAK2		
circZKSCAN1	Down-regulated	RBP: FMRP	CCAR1, Wnt/ β -catenin pathway	Inhibits HCC stem cell activity	Zhu <i>et al</i> [70]
circMEG3	Down-regulated	m ⁶ A-METTL3	HULC and Cbf5	Inhibits malignant differentiation of human liver CSCs	Jiang <i>et al</i> [71]
circ-PRKCI	Up-regulated	miR-1294 and miR-186-5p	FOXK1	Promotes HCC glycolysis	Chen <i>et al</i> [73]
circZFR	Up-regulated	miR-375	HMGA2	Promotes HCC glycolysis	Xu <i>et al</i> [75]
circMAT2B	Up-regulated	miR-338-3p	PKM2	Promotes HCC glycolysis	Li <i>et al</i> [77]
circ-PRMT5	Up-regulated	miR-188-5p	HK2	Enhances HCC glycolysis	Ding <i>et al</i> [79]
circ_0001445	Down-regulated	miR-942-5p	ALX4	Inhibits HCC metastasis and EMT	Xu <i>et al</i> [81]
ciRS-7	Up-regulated	miR-7	PIK3CD/p70S6K/mTOR	Predicts hepatic MVI	Xu <i>et al</i> [83]

			pathway		
hsa_circ_0068669	Down-regulated	N/A	N/A	Predicts hepatic MVI	Yao <i>et al</i> [84]
circCRIM1	Up-regulated	miR-378a-3p	SKP2	Promotes HCC angiogenesis	Ji <i>et al</i> [86]
hsa_circ-0046600	Up-regulated	miR-640	HIF-1 α	Promotes HCC angiogenesis	Zhai <i>et al</i> [87]
hsa_circ_0000092	Up-regulated	miR-338-3p	HN1	Promotes HCC angiogenesis	Pu <i>et al</i> [89]
circGFRA1	Up-regulated	miR-149	N/A	Promotes HCC angiogenesis	Yu <i>et al</i> [91]
circARSP91	Down-regulated	N/A	ULBP1	Enhances HCC innate immune surveillance	Ma <i>et al</i> [93]
circTRIM33-12	Down-regulated	miR-191	TET1	Inhibits HCC immune escape	Zhang <i>et al</i> [96]
hsa_circ0007456	Down-regulated	miR-6852-3p	ICAM-1	Inhibits HCC immune escape	Shi <i>et al</i> [97]
hsa_circ_104348	Up-regulated	miR-187-3p	RTKN2 Wnt/ β -catenin pathway	Promotes HCC resistance to sorafenib	Huang <i>et al</i> [100]
circ β -catenin	Up-regulated	Translation	Wnt/ β -catenin pathway	Facilitates HCC cell growth	Liang <i>et al</i> [101]
hsa_circ_0004018	Down-regulated	miR-626	DKK3 Wnt/ β -catenin pathway	Restrains HCC proliferation and migration	Zhu <i>et al</i> [102]
circRNA-ITCH	Down-regulated	miR-7 or miR-214	c-myc and cyclinD1Wnt/ β -catenin	Inhibits HCC proliferation and apoptosis	Yang <i>et al</i> [103]
circ-0003418	Down-regulated	miR-7 and miR-383	Wnt/ β -catenin pathway	Increases HCC sensitivity to cisplatin	Chen <i>et al</i> [104]
circ-IGF1R	Up-regulated	N/A	PI3K/AKT pathway	Promotes HCC cell proliferation	Fu <i>et al</i> [106]
hsa_circ_0079299	Down-regulated	N/A	CCNB1PI3K/Akt/mTOR pathway	Inhibits HCC growth	Zheng <i>et al</i> [107]
circSOD2	Up-regulated	miR-502-5p	DNMT3A JAK2/STAT3 pathway	Promotes HCC growth, cell migration and cell cycle progression	Zhao <i>et al</i> [108]
circ_0004913	Down-regulated	miR-184	HAMP JAK2/STAT3/Akt pathway	Inhibits HCC proliferation, migration, invasion, EMT and glycolysis	Wu <i>et al</i> [109]
		N/A	N/A	Predicts better prognosis of HCC	Li <i>et al</i> [150]
circ_0031242	Up-regulated	miR-924	POU3F2	Enhances HCC resistance to cisplatin	Fan <i>et al</i> [112]
circARNT2	Up-regulated	miR-155-5p	PDK1	Promotes HCC resistance to cisplatin	Li <i>et al</i> [115]
circ-G004213	Down-regulated	miR-513b-5p	PRPF39	Facilitates HCC sensitivity to cisplatin	Qin <i>et al</i> [117]
circUBE2D2	Up-regulated	miR-889-3p	LDHA	Promotes HCC resistance to sorafenib	Huang <i>et al</i> [121]
circFN1	Up-regulated	miR-1205	E2F1	Facilitates HCC resistance to sorafenib	Yang <i>et al</i> [122]
circRNA-SORE	Up-regulated	RBP: YBX1	AKT, Raf1, ERK, c-Myc, and TGF- β 1	Promotes HCC resistance to sorafenib	Xu <i>et al</i> [124]
circMEMO1	Down-regulated	miR-106b-5p	TCF21	Increases HCC sensitivity to sorafenib	Dong <i>et al</i> [126]
circUHRF1	Up-regulated	miR-449C-5p	TIM-3	Promotes HCC resistance to PD1 immunotherapy	Zhang <i>et al</i> [131]

circMET	Up-regulated	miR-30-5p	Snail/DPP4/CXCL10 axis	Promotes HCC resistance to PD1 immunotherapy	Huang <i>et al</i> [133]
Exosomal circ_0070396	Up-regulated	N/A	N/A	Serves as a biomarker of early diagnosis of HCC	Lyu <i>et al</i> [139]
circ_104075	Up-regulated	miR-582-3p	YAP	Serves as a biomarker of early diagnosis of HCC	Zhang <i>et al</i> [140]
has_circ_002224 and hsa_circ_00520	Up-regulated	N/A	N/A	Serves as biomarkers of early diagnosis of HCC with HCV infection	Matboli <i>et al</i> [141]
hsa_circ_0000976 hsa_circ_0007750 hsa_circ_0139897	Up-regulated	N/A	N/A	Serves as biomarkers of early diagnosis of HCC with HBV infection	Yu <i>et al</i> [142]
hsa_circ_0091579	Up-regulated	N/A	GPC3	Predicts poorer prognosis of HCC	Zhang <i>et al</i> [144]
circ_0000798		N/A	N/A		Lei <i>et al</i> [145]
circ_0000267	Up-regulated	miR-646	N/A	Predicts poorer prognosis of HCC	Pan <i>et al</i> [146]
circASAP1		miR-326, miR-532-5p	MAPK1		Hu <i>et al</i> [147]
circ-ZNF652	Up-regulated	miR-203/miR-502-5p	Snail-mediated EMT	Predicts poorer prognosis of HCC	Guo <i>et al</i> [148]
hsa_circ_0001649	Down-regulated	N/A	N/A	Predicts better prognosis of HCC	Zhang <i>et al</i> [149]
circSETD3	Down-regulated	miR-421	MMP1	Predicts better prognosis of HCC	Xu <i>et al</i> [57]
hsa_circ_0036683		N/A	N/A		Sunagawa <i>et al</i> [151]
hsa_circ_0005986	Down-regulated	N/A	N/A	Predicts better prognosis of HCC	Kim <i>et al</i> [152]

HCC: Hepatocellular carcinoma; ceRNA: Competitive endogenous RNA; CircRNAs: Circular RNAs; miRNAs: MicroRNAs; RBPs: RNA binding proteins; m⁶A: N⁶-methyladenosine; EMT: Epithelial-mesenchymal transition; MAP2K1: Mitogen-activated protein kinase 1; CTNNB1: Beta-catenin 1; Wnt/ β -catenin: Wingless/beta-catenin; TXNDC5: Thioredoxin domain-containing 5; SMAD6: SMAD family member 6; MAPK14: Mitogen-activated protein kinase 14; MVI: Microvascular invasion; BAK1: BRI1-associated kinase 1; HMGB1/RAGE: High-mobility group box 1 protein/advanced glycation end products; HMGA2: High mobility group A2; PIK3R3: Phosphoinositide-3-kinase regulatory subunit 3; SERBP1: SERPINE1 mRNA binding protein 1; FGFR1/ERK: Fibroblast growth factor receptor 1/extracellular signal-regulated kinase; PLAGL2: PLAG1 like zinc finger 2; MMP2: Matrix metalloproteinase 2; PAX5: Paired box protein 5; AUF1: AU-rich binding factor 1; FMRP: Fragile X mental retardation protein; CCAR1: Cell division cycle and apoptosis regulator 1; METTL3: Methyltransferase-like 3; HULC: Highly upregulated in liver cancer; Cbf5: Centromere-binding factor 5; CSCs: Cancer stem cells; FOXK1: Forkhead box K1; PKM2: Pyruvate kinase M2; HK2: Hexokinase 2; ALX4: Aristaless-like homeobox 4; PIK3CD/p70S6K/mTOR: PI3Kdelta catalytic p110delta/Ribosomal protein S6 kinase/mammalian target of rapamycin; SKP2: S-phase kinase-associated protein 2; HIF-1 α : Hypoxia inducible factor-1 α ; HN1: Hematological and neurological expressed 1; ULBP1: UL16-binding protein 1; TET1: Ten-eleven translocation 1; ICAM-1: Intercellular adhesion molecule-1; RTKN2: Rhotekin 2; DKK3: Dickkopf-3; PI3K/Akt: Phosphoinositide-3-kinase/protein kinase B; CCNB1: Cyclin B1; DNMT3A: DNA methyltransferase 3A; JAK/STAT: Janus kinases/signal transducer and activator of transcription; JAK2/Stat3: Janus kinase 2/signal transducers and activators of transcription; HAMP: Hepcidin; POU3F2: POU class 3 homeobox 2; PDK1: Pyruvate dehydrogenase kinase 1; PRPF39: Pre-mRNA splicing factor 39; LDHA: Lactate dehydrogenase A; E2F1: E2F transcription factor 1; YBX1: Y-box-binding protein 1; Raf1: Proto-oncogene serine/threonine-protein kinase-1; ERK: Extracellular signal-regulated kinase; TGF- β 1: Transforming growth factor beta1; TCF21: Transcription factor 21; Tim-3: T cell immunoglobulin and mucin domain 3; PD1: Programmed cell death protein 1; DPP4: Dipeptidyl peptidase 4; CXCL10: Chemokine C-X-C ligand 10; Yap: Yes-associated protein; HCV: Hepatitis C virus; HBV: Hepatitis B virus; GPC3: Glypican-3 protein; MAPK1: Mitogen-activated protein kinase 1; MMP1: Matrix metalloproteinase 1; MAPK1: Mitogen-activated protein kinase 1; AFP: Alpha fetoprotein; AFP-L3: Alpha-fetoprotein variants; DCP: Des-carboxy prothrombin; OS: Overall survival; RFS: Recurrence-free survival; PFS: Progression-free survival; N/A: Not applicable.

hsa_circ_0061395 upregulates the expression of PIK3R3 and SERBP1 by sponging miR-877-5p and miR-656-3p, respectively, promoting HCC proliferation, invasion and migration[62,63]. Furthermore, circRNA-103809 up-regulates the expression of FGFR1/extracellular signal-regulated kinase and PLAGL2 by sponging miR-377-3p and miR-1270, respectively, and facilitates HCC migration, EMT and invasion[64,65]. Additionally, circ_0000517, another oncogenic circRNA, is related to poor HCC prognosis[66]. Another subsequent study has investigated the possible mechanism of action of circ_0000517 by enhancing the expression of SMAD6 by sponging miR-326 to promote HCC cell invasion and metastasis[67]. Circ_matrix metalloproteinase (MMP) 2 can also promote HCC metastasis, which is the result of enhancing MMP2 expression by sponging miR-136-5p[68]. Thus, circRNAs are

critical for regulating HCC migration, EMT, invasion and metastasis.

CSCs

CSCs are considered the root cause of tumor occurrence, invasion, metastasis, recurrence, and resistance to radiotherapy and chemotherapy because of their self-renewal ability, sustained proliferation potential and therapeutic resistance. CircRNAs and tumor stem cells are closely related to cancer. For example, the high expression of circ-MALAT1 in HCC CSC samples mediated by RBP AU-rich binding factor 1 is closely associated with the regeneration of HCC CSCs. Mechanistically, circ-MALAT1 blocks paired box protein 5 mRNA translation on the ribosome and forms a trimer with the ribosome and mRNA to facilitate self-renewal of CSCs. This blocking mechanism is known as “circRNA braking” and has become another posttranscriptional regulatory mechanism in addition to the function of circRNA subsponges[69]. Additionally, circZKSCAN1 inhibits HCC stem cell activity by mediating the function of fragile X mental retardation protein (FMRP). Regarding the mechanism, circZKSCAN1 competes with FMRP, which serves as RBP, for the target gene cell division cycle and apoptosis regulator 1 (CCAR1), thereby inactivating the Wntless (Wnt) pathway[70]. Similarly, circMEG3 inhibits malignant differentiation of CSCs by restraining highly upregulated in liver cancer and centromere-binding factor 5 in HCC CSCs[71]. The above findings indicate that circRNAs may provide novel treatment strategies for HCC by targeting CSCs.

Glycolysis

Aberrant glucose metabolism is the most prominent feature of tumor metabolism. In recent years, numerous studies have shown that circRNAs regulate glucose metabolism, among which oncogenic circRNAs promote glycolysis in HCC cells. For example, Forkhead box K1 (FOXK1) is an inducer of aerobic glycolysis[72], and circ-PRKCI promotes HCC glycolysis by enhancing FOXK1 expression by sponging miR-1294 and miR-186-5p[73]. Similarly, HMGA2 promotes HCC tumor growth and metastasis[74], and circZFR promotes glycolysis in HCC cells by inhibiting miR-375 and increasing HMGA2 expression[75]. Furthermore, PKM2 serves as a mediator of aerobic glycolysis of cancer cells [76], and circMAT2B facilitates HCC glycolysis by strengthening PKM2 expression by acting as a sponge of miR-338-3p[77]. Hexokinase 2 (HK2) is also a regulator of aerobic glycolysis in HCC[78], and circ-PRMT5 promotes HCC glycolysis by sponging miR-188-5p to increase HK2 expression[79]. In contrast, tumor suppressive circRNAs impede HCC glycolysis. For example, aristaless-like homeobox 4 (ALX4) inhibits HCC proliferation and invasion[80], and circ_0001445, a tumor suppressor, enhances ALX4 expression by sponging miR-942-5p, thus inhibiting HCC glycolysis[81]. Collectively, circRNAs have become important regulatory factors in glycolysis in HCC cells, but the specific mechanism of their regulation of metabolism remains to be elucidated. Considering the characteristics of circRNAs in regulating glycolysis in HCC cells, it is possible to interfere with the abnormal expression of downstream genes and some key action sites of specific circRNAs, thereby altering the metabolic pathways of HCC cells and opening up novel therapeutic approaches for HCC.

MVI

MVI is a characteristic of HCC and an independent risk factor affecting the prognosis of HCC patients. The exact mechanism by which MVI occurs in HCC has not been fully elucidated. Emerging evidence suggests that circRNAs play important roles in the MVI process of HCC. For example, ciRS-7 (Cdr1as), an oncogene in HCC[82], facilitates HCC MVI by competitively inhibiting miR-7 and interfering with the PI3Kdelta catalytic p110delta/ribosomal protein S6 kinase/mammalian target of rapamycin (mTOR) pathway[83]. Conversely, the downregulation of hsa_circ_0068669, a tumor suppressor, is correlated with HCC MVI[84]. Similarly, low expression of circSETD3, another tumor suppressor, in HCC is associated with the existence of MVI[85]. In summary, circRNAs are associated with the occurrence of MVI in HCC and can be used as indicators for the early detection of MVI and clinical intervention to reduce recurrence and improve the survival rate of patients with HCC.

Angiogenesis

HCC is a solid tumor rich in blood vessels with obvious vascular hyperplasia and vascular abnormalities in HCC. Tumor angiogenesis refers to tumor-induced capillary angiogenesis and the formation of microcirculation networks within the tumor. Tumor angiogenesis is responsible for HCC proliferation, invasion and metastasis. Nevertheless, the regulatory mechanism underlying HCC angiogenesis is unclear, although multiple studies have found that circRNAs can regulate angiogenesis. For example, circCRIM1 can promote HCC angiogenesis by upregulating SKP2 expression *via* sponging miR-378a-3p [86]. Additionally, hsa-circ-0046600 affects malignant angiogenesis in HCC cells by sponging miR-640 to facilitate the expression of hypoxia inducible factor-1 α , a promoter of angiogenesis[87,88]. Similarly, hsa_circ_0000092 facilitates HCC angiogenesis by competitively binding to miR-338-3p to elevate the expression of hematological and neurological expressed 1, a promoter of tumor growth and invasion[89, 90]. Furthermore, circGFRA1 promotes the angiogenic activity of HCC by binding to miR-149[91]. Taken together, the above findings confirm that circRNAs play an essential role in HCC angiogenesis, thus contributing to clarification of the regulatory mechanism of HCC angiogenesis and highlighting the

usefulness of circRNAs in targeted therapy for HCC angiogenesis.

Immune surveillance and immune escape

Abnormal circRNAs may act as tumor antigens in immunocytes to activate antitumor immunity[92]. Natural killer (NK) cells play a pivotal role in tumor immune surveillance. CircARSP91 increases the cytotoxicity of NK cells by elevating UL16-binding protein 1 in HCC, thereby enhancing innate immune surveillance[93].

The immune system monitors and kills tumor cells through specific and nonspecific pathways. When malignant cells appear in the body, the immune system recognizes and eliminates these cells specifically through the immune mechanism to resist the occurrence and development of tumors. However, in some cases, malignant cells can escape the recognition and attack of the immune system through various mechanisms to achieve immune escape in order to survive and proliferate in the body[94]. Current studies have shown that circRNAs play a critical role in tumor immune escape, which is closely associated with drug resistance and tumor recurrence[95]. For example, the low expression of tumor suppressive circTRIM33-12 promotes the immune escape ability of HCC cells by upregulating ten-eleven translocation 1 expression through sponging miR-191[96]. Similarly, hsa_circ0007456, another tumor suppressor, shows low expression in HCC and can promote tumor immune escape by regulating the expression of intercellular adhesion molecule-1 by sponging miR-6852-3p[97]. These findings indicate that circRNAs that regulate immune escape are promising immunotherapeutic targets for HCC.

Modulating the malignant progression of HCC by mediating signaling pathways

Various circRNAs mediate the Wnt/ β -catenin (Wnt/ β -catenin), phosphoinositide-3-kinase/protein kinase B (PI3K/Akt) or Janus kinase 2/signal transducers and activators of transcription (JAK2/Stat3) pathways by sponging miRNAs to modulate the malignant progression of HCC. In addition to circRNA-miRNA regulation, no study has investigated circRNAs modulating these signaling pathways through direct regulation of processes such as gene transcription and protein translation.

Wnt/ β -catenin pathway: Aberrant activation of this pathway is prevalent in HCC occurrence and progression, and this is considered the most frequently activated carcinogenic pathway in HCC[98]. Emerging evidence suggests that circRNAs affect the malignant progression of HCC by mediating the Wnt/ β -catenin pathway, among which oncogenic circRNAs can promote HCC progression by triggering the Wnt/ β -catenin pathway. For example, circZFR upregulates β -catenin 1 and activates the Wnt/ β -catenin pathway by sponging miR-3619-5p to promote the proliferation and EMT of HCC cells[99]. Similarly, hsa_circ_104348 facilitates HCC proliferation, migration, and invasion by sponging miR-187-3p to elevate rhodkin 2 expression and activate the Wnt/ β -catenin pathway[100]. In particular, circ β -catenin, an oncogenic circRNA in HCC, facilitates HCC cell growth by activating the Wnt/ β -catenin pathway[101]. Instead, tumor suppressive circRNAs can restrain HCC progression by inhibiting the Wnt/ β -catenin pathway. For example, hsa_circ_0004018 enhances Dickkopf-3 expression and inhibits the Wnt/ β -catenin pathway by sponging miR-626, thereby restraining HCC proliferation and migration[102]. Similarly, circRNA-ITCH restrains the Wnt/ β -catenin pathway and decreases c-myc and cyclin D1 expression by sponging miR-7 or miR-214, thereby inhibiting HCC proliferation and apoptosis[103]. Intriguingly, circ-0003418 plays a tumor suppressor role in HCC and enhances cisplatin sensitivity of HCC cells by restraining the Wnt/ β -catenin pathway[104].

PI3K/Akt/mTOR pathway: Aberrant activation of this pathway frequently occurs in HCC and is closely related to HCC growth[105], invasion and metastasis. Current studies support that circRNAs mediate the PI3K/AKT or PI3K/AKT/mTOR pathway to modulate HCC progression. For example, circ-insulin-like growth factor 1 receptor promotes HCC cell proliferation by activating the PI3K/AKT pathway[106]. Additionally, the overexpression of tumor-suppressive hsa_circ_0079299 inhibits HCC growth and retards cell cycle progression partly by mediating the PI3K/Akt/mTOR pathway[107].

JAK2/STAT3 pathway: As a signal transduction pathway stimulated by cytokines, activation of the JAK/STAT pathway is closely related to tumor cell proliferation, apoptosis and differentiation. The JAK2/STAT3 pathway, an important component of the JAK/STAT pathway, is activated in diverse malignant tumors, including HCC. For example, circSOD2 enhances DNA methyltransferase 3A expression and activates the JAK2/STAT3 pathway by sponging miR-502-5p, thereby promoting the growth, migration and cell cycle progression of HCC cells[108]. Additionally, CIRC_0004913 upregulates hepcidin expression and inhibits the JAK2/STAT3/Akt pathway by sponging miR-184 and suppressing HCC proliferation, migration, invasion, EMT and glycolysis[109]. Taken together, the above findings demonstrate that circRNAs modulate the malignant progression of HCC by mediating signaling pathways, such as the Wnt/ β -catenin, PI3K/Akt/mTOR and JAK2/Stat3 pathways. These pathway-associated circRNAs may serve as novel therapeutic targets in HCC.

Chemoresistance

Chemotherapy is a comprehensive treatment for advanced HCC, although the drug resistance of HCC cells considerably limits its efficacy. Multidrug resistance is the principal factor leading to the failure of

chemotherapy for HCC, and its mechanism is extremely complex. Therefore, clarifying the mechanisms of drug resistance to improve the drug resistance of patients with HCC is critical. Recent evidence has prioritized the importance of abnormally expressed circRNAs in the chemotherapy resistance of HCC.

Cisplatin resistance: Cisplatin is one of the few most common chemotherapy drugs used to treat HCC. However, thus far, the drug resistance of HCC cells during chemotherapy has been revealed to be the main factor affecting chemotherapy failure[110,111]. Therefore, how to control the occurrence of cisplatin resistance in HCC cells and improve drug sensitivity and therapeutic effects are critical to prolonging the survival of patients with advanced HCC. Current studies have confirmed that circRNAs impact HCC cisplatin resistance. For example, circ_0031242 enhances cisplatin resistance in HCC by sponging miR-924 to enhance the expression of POU class 3 homeobox 2, a promoter of tumor progression and metastasis[112,113]. Additionally, pyruvate dehydrogenase kinase 1 (PDK1), a glycolytic enzyme, is closely associated with chemotherapy resistance[114]. As an oncogene, circARNT2 promotes cisplatin resistance in HCC cells, an activity mechanistically achieved by upregulating PDK1 through sponging miR-155-5p[115]. Analogously, PRPF39 is closely associated with cisplatin sensitivity [116], circ-G004213 promotes HCC cisplatin sensitivity by sponging miR-513b-5p to increase PRPF39 expression[117].

Sorafenib resistance: Sorafenib is an oral multikinase multitarget inhibitor and an important targeted therapy for advanced HCC[118]. However, sorafenib resistance is a common problem in clinical applications, substantially limiting its application[119]. The mechanism leading to sorafenib resistance remains incompletely understood. Therefore, further research on the possible mechanisms of sorafenib resistance and reducing its resistance are crucial for the treatment of HCC. CircRNAs also affect sorafenib resistance in HCC. For example, overexpression of lactate dehydrogenase A (LDHA), an oncogene, facilitates cancer cell invasion and metastasis[120]. CircUBE2D2 promotes sorafenib resistance to HCC, possibly because of the upregulation of LDHA by sponging miR-889-3p[121]. Additionally, circFN1 contributes to sorafenib resistance in HCC cells by elevating the expression of E2F1, a transcription factor associated with cancer chemotherapy resistance, by acting as a miR-1205 sponge[122,123]. Analogously, circRNA-SORE induces sorafenib resistance in HCC by binding to Y-box-binding protein 1, a regulator of EMT in cancer cells[124,125]. In particular, circMEMO1 promotes the sensitivity of HCC to sorafenib by upregulating transcription factor 21 (TCF21) expression by sponging miR-106b-5p[126].

Although the existing evidence partially reveals the critical role of circRNAs in HCC chemotherapy resistance, it suggests that circRNAs associated with chemotherapy resistance offer potential value in predicting and monitoring the efficacy of HCC and even reversing chemotherapy resistance. However, further clinical samples and *in vivo* experiments are needed to validate the relevant molecular mechanisms involved.

Immunotherapy resistance

Immunotherapy is currently an effective therapeutic modality for advanced HCC. Immunotherapy enhances antigen presentation, activates the immune response and improves the immunosuppressive status of the tumor microenvironment in different ways, thus improving survival benefits. However, increasing clinical evidence indicates that only 20%-30% of patients treated with programmed death 1 (PD1) and programmed death-ligand 1 are sensitive to immunotherapy, and 70%-80% of patients show an ineffective response because of drug resistance[127]. Therefore, further exploration and understanding of the mechanism of immunotherapy resistance may provide important insight to guide clinical practice. T cell immunoglobulin and mucin domain 3 (TIM-3) is an immunoregulatory receptor that binds to NK cell-dominated ligands in tumor cells and the microenvironment to inhibit NK cell-mediated antitumor immunity in various cancers, including HCC[128-130]. CircUHRF1, an exosome derived from HCC, upregulates TIM-3 expression in NK cells by sponging miR-449C-5p in patients' resistant to PD1 immunotherapy, leading to NK cell dysfunction and driving HCC resistance to PD1 [131]. Additionally, circMET is an oncogene in the chromosome 7q21-7q31 region, and the amplification of this region is considered to be related to HCC prognosis[132]. CircMET overexpression induces the development and immune tolerance of HCC through the miR-30-5p/Snail/dipeptidyl peptidase (DPP) 4/chemokine C-X-C ligand (CXCL) 10 axis, while DPP4 inhibitors such as sitagliptin block the progression of the pathway, which can enhance the efficacy of PD1 inhibitors in the treatment of HCC [133]. Taken together, the above findings demonstrate that circRNAs participate in regulating HCC immunotherapy resistance, and that intervention by circRNAs may be an effective means to improve the immunotherapy tolerance of HCC cells.

BIOMARKERS FOR HCC DIAGNOSIS AND PROGNOSIS

CircRNAs are characterized by high abundance, stability and conservatism. CircRNAs are not easily degraded by RNA enzymes and stably exist in human tissues, serum, saliva and urine. Additionally, the expression profiles of circRNAs in HCC patients are significantly different from those of normal

controls. Thus, abnormally expressed circRNAs may be utilized as biomarkers to diagnose and predict the prognosis of HCC patients[134-136].

Biomarkers of the early diagnosis of HCC

There are certain limitations of commonly used clinical diagnostic markers for HCC, such as alpha-fetoprotein (AFP), AFP variants (AFP-L3) and Des-carboxy prothrombin (DCP), and only approximately 1/3 of patients can be diagnosed early[137,138]. The high mortality rate of HCC indicates that exploring new biomarkers for the early diagnosis of HCC is the most reliable strategy to improve the survival rate of HCC patients.

Emerging evidence thus far supports the possibility of utilizing circRNAs as ideal biomarkers to diagnose HCC. For example, exosome CIRC_0070396 has better diagnostic accuracy than AFP with respect to HCC patients[139]. Analogously, the sensitivity (96.0%) and specificity (98.3%) of serum circ_104075 to predict HCC are higher than those of AFP, DCP and AFP-L3, indicating the possibility of employing circ_104075 as an effective serum biomarker for HCC diagnosis[140]. Additionally, compared with AFP, hsa_circ_00224 and hsa_circ_00520 show higher sensitivity and specificity in diagnosing HCC patients with hepatitis C virus infection[141]. Furthermore, the accuracy of plasma hsa_circ_0000976, hsa_circ_0007750, and hsa_circ_0139897 is superior to AFP in diagnosing HCC patients with hepatitis B virus infection[142].

Although the existing evidence supports the feasibility of using specific circRNAs as noninvasive circulating diagnostic biomarkers for the early detection and screening of HCC, further analysis of their sensitivity and specificity and suitable patient populations is warranted. The pathogenesis of HCC is extremely complex and varies among ethnic and regional populations, and circRNAs that can be used as biomarkers in single-center studies may not be applicable to other ethnic and regional populations. Therefore, multicenter trials and large-scale studies are required to verify the performance of serum or plasma circRNAs as biomarkers. Additionally, it is necessary to establish accepted standards, unified detection and analysis methods and to use a rigorous experimental design with the best clinical samples to determine universally representative and practical diagnostic circRNA molecules.

Prognostic biomarkers of HCC

Because of the delay in diagnosis and the high rates of postoperative recurrence and metastasis, the prognosis of HCC patients remains poor[143]. Therefore, exploring more effective HCC markers for prognosis assessment is crucial. Existing evidence has shown the feasibility of circRNAs as biomarkers to predict HCC prognosis. Among these circRNAs, oncogenic circRNAs are associated with worse overall survival (OS) or worse OS and recurrence-free survival (RFS). For example, high expression of hsa_circ_0091579 or circ_0000798 is correlated with shorter OS of HCC patients[144,145]. Similarly, high expression of circ_0000267 or circASAP1 is closely related to poorer OS in HCC patients[146,147]. Additionally, high circ-ZNF652 (hsa_circ_0003258) expression indicates shorter OS and RFS of HCC patients[148]. Conversely, tumor suppressive circRNAs are associated with better OS and RFS or better OS and progression-free survival (PFS). For example, high expression of hsa_circ_0001649 or circ_0004913 signifies longer OS in HCC patients[149,150]. Furthermore, high circSETD3 or hsa_circ_0036683 expression indicates better OS and RFS in HCC patients[57,151]. Moreover, high hsa_circ_0005986 expression implies better OS and PFS in HCC patients[152]. The above findings support the feasibility of the use of circRNAs as biomarkers for predicting HCC prognosis.

CONCLUSION

In conclusion, circRNAs play important roles in HCC and are expected to be ideal diagnostic biomarkers and therapeutic targets for HCC. However, problems persist that must be solved. First, determining the exact mechanism underlying certain circRNAs in pathogenesis is challenging because of the different nomenclatures of circRNAs, mechanisms of action and tumorigenicities. Second, current studies on circRNAs mainly focus on the function of circRNAs as molecular sponges. We should further explore the biological functions of circRNAs, such as regulating the transcription of parental genes, binding RBPs, and encoding proteins and peptides, in the context of the malignant behavior of HCC. Third, some studies have only investigated circRNA expression in HCC cell lines without detection in clinical samples, and the clinical value of such circRNAs is uncertain. Fourth, most of the studies only knocked down the expression level of circRNAs but did not perform reverse verification by overexpression of circRNAs. Fifth, presently, studies on the pathogenesis of circRNAs in HCC remain in the preliminary stage. The pathogenesis of HCC is complex and heterogeneous, and the disease states of different HCC patients may involve different primary pathogenetic pathways and pathogenic molecules. Exploring the pathogenesis of a certain class of HCC patients with stronger homogeneity at the beginning of the experimental design is crucial to obtain more reproducible conclusions. In summary, we must improve these issues to better clarify the roles and mechanisms of circRNAs in HCC so that circRNAs can become useful diagnostic indicators and therapeutic targets for HCC.

FOOTNOTES

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