Life Sciences 231 (2019) 116660

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Circular RNAs in hepatocellular carcinoma: Biomarkers, functions and mechanisms

Lipeng Qiu[a], Han Xu[b], Mengchen Ji[a], Dongsheng Shang[b], Ziwen Lu[b], Yihang Wu[c], Zhigang Tu[a], Hanqing Liu[b,*]

[a] Institute of Life Sciences, Jiangsu University, Zhenjiang, Jiangsu 212013, China
[b] School of Pharmacy, Jiangsu University, Zhenjiang, Jiangsu 212013, China
[c] Department of Pharmacy, College of Life Sciences, China Jiliang University, Hangzhou, Zhejiang 310018, China

ARTICLE INFO

Keywords:
Circular RNA
Hepatocellular carcinoma
Diagnostic biomarker
Prognostic biomarker
Therapeutic target
miRNA sponge

ABSTRACT

Hepatocellular carcinoma (HCC), a leading cause of cancer-related death with high invasive and metastatic potential, has a low survival rate. To improve the survival and quality of life in HCC patients, it is urgently needed to explore novel biomarkers for early diagnosis and prognosis of HCC, as well as therapeutic strategies. Circular RNAs (circRNAs) are a class of highly conserved, stable and abundant non-coding RNAs (ncRNAs) that can regulate gene expression at transcriptional or post-transcriptional levels. Recently, some circRNAs are identified to be potential biomarkers for HCC diagnosis and prognosis. Furthermore, some circRNAs are found to play oncogenic or suppressive roles in HCC progression by regulating various biological processes, including cell proliferation, migration, invasion and metastasis, epithelial-mesenchymal transition (EMT), as well as apoptosis. In this review, we summarize recent findings of deregulated circRNAs, their functions and molecular mechanisms in HCC, and discuss their potential roles as diagnostic biomarkers, prognostic biomarkers, as well as therapeutic targets for HCC.

1. Introduction

Primary liver cancer is one of the most commonly diagnosed cancer and leading cause of cancer-related death in the world. Hepatocellular carcinoma (HCC), a major histological subtype of primary liver cancer with high invasive and metastatic potential, accounting for 75–85% of all primary liver cancers, and has a low survival rate [1]. Due to limited symptoms of HCC patients at early stages and lack of effective biomarkers for early diagnosis, most patients are diagnosed only at advanced stages of HCC when curative therapies are not eligible; while for those patients who could receive resection and liver transplantation, their survival after surgery are frequently reduced by relapse and metastasis. To improve the survival and quality of life in HCC patients, it is urgently needed to explore novel biomarkers for early diagnosis and prognosis of HCC, as well as therapeutic strategies.

Circular RNAs (circRNAs) are a class of highly conserved, stable and abundant non-coding RNAs (ncRNAs) that can regulate gene expression at transcriptional or post-transcriptional levels [2–5]. Recent studies showed that some circRNAs are deregulated in HCC, and may participate in various biological processes involved in HCC progression. Some circRNAs, for example, cSMARCA5 and circ-ZEB1.33, are deregulated in the circulation and tumor tissues of HCC patients, and are identified to be potential biomarkers for HCC diagnosis or prognosis [6–9]. Other circRNAs, such as circFBLIM1, circHIPK3, circMTO1, circSETD3, and circSMAD2, are found to play oncogenic or suppressive roles in HCC progression by regulating the proliferation, migration, invasion and metastasis, epithelial-mesenchymal transition (EMT), and apoptosis of HCC cells [10–14]. Understanding the molecular mechanisms and associated signaling pathways of these functional circRNAs may facilitate the identification of potential biomarkers and therapeutic targets for HCC. In this review, we summarize recent findings of deregulated circRNAs (Table 1), their functions and underlying mechanisms in HCC, and discuss their potential roles as diagnostic biomarkers, prognostic biomarkers, as well as therapeutic targets for HCC.

2. Identification of deregulated circRNAs in HCC

Deregulated circRNAs in HCC are primarily screened by circRNA microarray and RNA sequencing, and then validated by quantitative real-time PCR (qRT-PCR) using divergent primers and *in situ* hybridization (ISH). Due to the unique characteristics of circRNAs, their circularization can be confirmed by Sanger sequencing of head-to-tail

* Corresponding author at: School of Pharmacy, Jiangsu University, 301 Xuefu Road, Jingkou District, Zhenjiang, Jiangsu 212013, China.
E-mail address: hanqing@ujs.edu.cn (H. Liu).

https://doi.org/10.1016/j.lfs.2019.116660
Received 20 May 2019; Received in revised form 3 July 2019; Accepted 14 July 2019
Available online 15 July 2019

Table 1
Circular RNAs (circRNAs) in hepatocellular carcinoma (HCC).

No.	CircRNA	Current circBase ID	Genomic position	Spliced length (bp)	Gene symbol	Clinical samples	Ref.
Up-regulated circRNAs							
1	circ-BIRC6	hsa_circ_0003288	chr2:32703702–32718734	1400	BIRC6	Tissues	[15]
2	circ-CDYL	hsa_circ_0008285	chr6:4891946–4892613	667	CDYL	Tissues	[16]
3	circ-DB	hsa_circ_0025129	chr12:6450941–6451283	342	TNFRSF1A	Plasma exosome	[17]
4	circ-ZEB1.33	hsa_circ_0002140	chr10:31749965–31750166	201	ZEB1	Tissues, serum	[9]
5	circ-ZNF652	hsa_circ_0003258	chr17:47388673–47389404	261	ZNF652	Tissues	[18]
6	Circβ-catenin	hsa_circ-0004194	chr3:41265511–41268843	1129	CTNNB1	Tissues	[19]
7	circDYNC1H1	hsa_circ_0033351	chr14:102499401–102507010	1862	DYNC1H1	Tissues	[20]
8	circFBLIM1	hsa_circ_0010090	chr1:16084668–16113084	3935	FBLIM1	Tissues	[10]
9	circHIPK3	hsa_circ_0000284	chr11:33307958–33309057	1099	HIPK3	Tissues	[11,21]
10	circMAT2B	hsa_circ_0074854	chr5:162940560–162944680	576	MAT2B	Tissues	[22]
11	circPTGR1 isoform	hsa_circ_0003731	chr9:114341075–114348445	442	PTGR1	Serum exosome	[23]
12	circPTGR1 isoform	hsa_circ_0008043	chr9:114332370–114348445	670	PTGR1	Serum exosome	[23]
13	circPTGR1 isoform	hsa_circ_0088030	chr9:114337013–114348445	551	PTGR1	Serum exosome	[23]
14	circRBM23	hsa_circ_0000524	chr14:23378691–23380612	189	RBM23	Tissues	[24]
15	circSLC3A2	hsa_circ_0022587	chr11:62650379–62653080	669	SLC3A2	Tissues	[25]
16	hsa_circ-10720	hsa_circ_0018189	chr10:35321362–35338693	747	CUL2	Tissues	[26]
17	hsa_circ_000224	hsa_circ_0000737	chr17:4803230–4803902	581	c17orf107	Serum	[27]
18	hsa_circ_000839	hsa_circ_0000497	chr13:78293666–78327493	788	SLAIN1	Tissues	[28]
19	hsa_circ_001569	hsa_circ_0000677	chr16:16101672–16162159	1776	ABCC1	Tissues	[29]
20	hsa_circ_100338	hsa_circ_0000130	chr1:151611363–151611595	232	SNX27	Tissues	[30]
21	hsa_circ_101368	hsa_circ_0003028	chr14:66028054–66028484	430	FUT8	Tissues	[31]
22	hsa_circ_104075	hsa_circ_0075736	chr6:17669523–17669777	162	NUP153	Tissue, serum	[32]
23	hsa_circ_101280	hsa_circ_0100929	chr13:78293666–78335245	1071	SLAIN1	Tissues	[33]
24	hsa_circ_0000267	hsa_circ_0000267	chr10:126370175–126370948	773	FAM53B	Tissues	[34]
25	hsa_circ_0000798	hsa_circ_0000798	Chr17: 65941524–65944422	1226	BPTF	PBMC	[35]
26	hsa_circ_0005075	hsa_circ_0005075	chr1:21377358–21415706	205	EIF4G3	Tissues	[36,37]
27	hsa_circ_0008450	hsa_circ_0008450	chr16:66642211–66643906	497	CMTM3	Tissues	[38]
28	hsa_circ_0016788	hsa_circ_0016788	chr1:228581376–228594517	2691	TRIM11	Tissues	[39]
29	hsa_circ_0067934, circ-PRKCI	hsa_circ_0067934	chr3:170013698–170015181	170	PRKCI	Tissues	[40,41]
30	hsa_circ_0078710	hsa_circ_0078710	chr6:169625239–169654137	3021	THBS2	Tissues	[42]
31	hsa_circ_0091579	hsa_circ_0091579	chrX:132795757–132888203	1145	GPC3	Tissues	[43]
32	hsa_circ_0103809	hsa_circ_0103809	chr15:51242247–51250991	422	AP4E1	Tissues	[44]
33	hsa_circ_0128298	hsa_circ_0128298	chr5:147210311–147211162	851	SPINK1	Tissues	[45]
Down-regulated circRNAs							
1	circ-ITCH	hsa_circ_0001141	chr20:33001547–33037285	873	ITCH	Tissues	[46]
2	circADAMTS13	hsa_circ_0089372	chr9:136302868–136303486	270	ADAMTS13	Tissues	[47]
3	circADAMTS14	hsa_circ_0018665	chr10:72468343–72496549	929	ADAMTS14	Tissues	[48]
4	circC3P1	–	–	–	C3P1	Tissues	[49]
5	circCDK13	has_circ_0001699	chr7:40027197–40041630	1142	CDK13	Tissues	[50]
6	circHIAT1	–	–	–	HIAT1	Tissues	[51]
7	circLARP4	hsa_circ_0003322	chr20:34446223–34459751	942	LARP4	Tissues	[52]
8	circMTO1	hsa_circ_0007874	chr6:74175931–74176329	318	MTO1	Tissues	[12]
9	circSETD3	hsa_circ_0000567	chr14:99924615–99932150	683	SETD3	Tissues	[13]
10	circSMAD2	hsa_circ_0000847	chr18:45391429–45423180	783	SMAD2	Tissues	[14]
11	circTRIM33–12	–	–	–	TRIM33	Tissues	[53]
12	circZKSCAN1	hsa_circ_0001727	chr7:99621041–99621930	668	ZKSCAN1	Tissues	[54]
13	cSMARCA5, circSMARCA5	hsa_circ_0001445	chr4:144464661–144465125	269	SMARCA5	Tissue, plasma	[6–8]
14	hsa_circ_000520	hsa_circ_0011245	chr1:31447497–31454252	348	PUM1	Serum	[27]
15	hsa_circ_001565	hsa_circ_0000064	chr1:44446997–44447136	139	B4GALT2	Serum	[27]
16	has_circ_103809	hsa_circ_0072088	chr5:32379220–32388780	693	ZFR	Tissues	[55]
17	hsa_circ_0001649	hsa_circ_0001649	chr6:146209155–146216113	440	SHPRH	Tissues	[56–58]
18	hsa_circ_0003570	hsa_circ_0003570	chr10:126370175–126384781	828	FAM53B	Tissues	[59]
19	hsa_circ_0004018	hsa_circ_0004018	chr17:1703150–1704318	1168	SMYD4	Tissues	[60]
20	hsa_circ_0005986	hsa_circ_0005986	chr1:14057494–14068652	375	PRDM2	Tissues	[61]
21	hsa_circ_0064428	hsa_circ_0064428	chr3:14487224–14520076	1221	SLC6A6	Plasma	[62]
22	hsa_circ_0068669	hsa_circ_0068669	chr3:196612021–196613565	1544	SENP5	Tissues	[63]
23	hsa_circ_0067531	hsa_circ_0067531	chr3:138413627–138417937	311	PIK3CB	Tissues	[64]
24	hsa_circ_0078602	hsa_circ_0078602	chr6:160553263–160560899	761	SLC22A1	Tissues	[65]
25	hsa_circ_0079929	hsa_circ_0079929	chr7:40027197–40027857	660	CDK13	Tissues	[66]
Others							
1	ciRS-7, CDR1as	hsa_circ_0001946	chrX:139865339–139866824	1485	CDR1	Tissues	[67,68]
2	circ5379–6	–	–	–	PPARα	–	[69]
3	circARSP91	hsa_circ_0085154	chr8:101721360–101721451	91	PABPC1	–	[70]

splicing in the qPCR product, qPCR using oligo(dT)18 primers/random hexamers, resistance to digestion by RNase R, as well as their long half-life than linear transcripts by transcription inhibitor intervention, such as actinomycin D.

CircRNA microarray is widely used for high throughput screening of differentially expressed circRNAs (DECs). Among different samples for microarray, HCC tissues are the most frequently used ones. Other samples include plasma/serum or serum exosomes, peripheral blood mononuclear cells (PBMCs) from HCC patients, as well as HCC cell lines. In most studies, three to seven paired HCC and control samples were used, and hundreds or dozens of DECs were obtained with the threshold of $|\log_2 FC| > 1$ and $p < 0.05$. Subsequently, several most

up- or down-regulated circRNAs were selected for further validation by one or more technologies. For example, by circRNA microarray, Fu et al. revealed 527 DECs (174 up-regulated and 353 down-regulated) between five paired HCC and adjacent non-cancerous liver (ANL) tissues (GSE94508), and validated the down-regulation of hsa_circ_0004018 in HCC tissues and cell lines by qRT-PCR and Sanger sequencing [60]. Similarly, Han et al. also found series of DECs from their circRNA microarray profile containing seven paired HCC and ANL tissues (GSE97332), validated the down-regulation of several circRNAs in HCC tissues by qRT-PCR, including circMTO1, circARID1B, circFAM13B, and circFARP2, and confirmed the expression of circMTO1 by ISH on HCC tissue chip [12]. Microarray results from Lei et al. identified 58 DECs (21 up-regulated and 37 down-regulated) in PBMCs from four HCC patients compared with three healthy controls (GSE120663), and validated the deregulation of six circRNAs by qRT-PCR [35]. In several other studies, microarray was performed to identify DECs between different subsets of HCC samples, such as hepatitis B virus-associated HCC and paired ANL tissues, plasma of HCC patients with high tumor-infiltrating lymphocytes (TILs) and low TILs, plasma exosomes in HCC patients with higher and lower body fat ratios, and $CD90^{+}$ cancer stem cells and $CD90^{-}$ cells isolated from HCC cells [17,62,63,71,72].

RNA-sequencing, a newly developed technology to measure the expression of both known and novel genes, was also used for identification of DECs in several studies. For example, Yu et al. found 236 DECs (108 up-regulated and 128 down-regulated) from 5 paired HCC and ANL tissues by RNA sequencing, and confirmed the deregulation of ten DECs in HCC tissues by qRT-PCR and Sanger sequencing; Cai et al. identified 41 DECs (19 up-regulated and 21 down-regulated) by RNA sequencing, and validated the up-regulation of five circRNAs by qRT-PCR; while Qiu et al. revealed 42 DECs (38 down-regulated and 4 up-regulated) from 10 paired HCC and ANL tissues from RNA sequencing data, and validated the deregulation of three circRNAs by qRT-PCR [7,44,47].

Based on data from microarray and RNA sequencing, several other studies were carried out to validate the deregulation of some circRNAs and predict the possible targets and associated signaling pathways of these deregulated circRNAs. For example, with the HCC circRNA microarray datasets GSE94508 and GSE97332, and HCC microRNA (miRNA)/mRNA microarray datasets GSE22058, Lin et al. obtained the DECs, differentially expressed miRNAs and mRNAs in HCC tissues, predicted their interactions and associated signaling pathways, and then generated circRNA-miRNA-mRNA network [73]. In two other studies, Li et al. and Xiong et al. identified several DECs using GSE94508, GSE97332, as well as another liver cancer circRNA microarray datasets GSE78520, validated the deregulation of these circRNAs by qRT-PCR, and then constructed a circRNA-miRNA-mRNA network based on specific circRNAs, their potential target miRNAs and mRNAs [55,74].

3. CircRNA diagnostic biomarkers in HCC

A major reason for poor overall survival (OS) rate of HCC patients is lack of effective biomarkers for early and accurate diagnosis of HCC. Classically biomarkers, such as α-fetoprotein (AFP), AFP-L3, and des-gamma-carboxyprothrombin (DCP), only achieve modest diagnosis for HCC [75]. Recently, ncRNAs, such as miRNAs and long non-coding RNAs (lncRNAs), have been reported to be potential biomarkers for HCC diagnosis [76,77]. Regarding to their higher stability and abundance in HCC tissues and body fluids, circRNAs are a perfect source for developing novel biomarkers for early diagnosis of HCC as listed in Table 2.

Recently, some circRNAs have been reported to be potential diagnostic biomarkers in HCC, and their deregulation is associated with clinicopathological features in HCC patients. In HCC tissues, the up-regulation of six circRNAs, including circ_0005075, circ_0016788, ciRS-7, circ_0128298, circ_0091579, and circ-CDYL, constitutes potential diagnostic biomarkers in HCC [16,36,39,43,45,68]. Among them, circ_005075 and circ_0016788 reached higher area under the receiver operating characteristic curve (AUC) values of 0.94 and 0.851, respectively; and the expression of circ_005075 was correlated with tumor size [36,39]. In contrast, the up-regulation of ciRS-7, circ_0128298, circ_0091579, and circ-CDYL demonstrated relatively poorer diagnosis of HCC with AUC curves of 0.68, 0.668, 0.656, and 0.64, respectively [16,43,45,68]. Clinically, ciRS-7 expression was correlated with serum AFP level and microvascular invasion (MVI); and circ_0128298 expression was associated with vascular cancer embolus, lymphatic invasion, and organ metastasis [45,68]. Except for these up-regulated circRNAs, several circRNAs were down-regulated in HCC tissues with promising diagnostic values for HCC. Among these, three circRNAs, including circ_0004018, circZKSCAN1, and circ_0003570 achieved better diagnostic potential with AUC values of 0.848, 0.834, and 0.70, respectively [54,59,60]. The lower expression of circ_0004018 and circ_0003570 was associated higher serum AFP level, larger tumor size, poor differentiation, Barcelona Clinic Liver Cancer (BCLC) stage and tumor-node-metastasis (TNM) stage; while the lower expression of circZKSCAN1 was correlated with tumor numbers, cirrhosis, vascular invasion, MVI, and tumor grade [54,59,60]. Other two down-regulated circRNAs, including circ_0068669 and circ_0001649, were relatively poorer for diagnosis of HCC with AUC values of 0.64 and 0.63, respectively [56,64]. Correlation analysis indicated that the expression of circ_0068669 in HCC tissues was associated with MVI and TNM stages, while lower expression of this circ_0001649 was correlated with larger tumor size and higher occurrence of tumor embolus in HCC [56,64].

Except HCC tissues, circRNAs are also found to be deregulated in plasma, serum, and PBMC, which make them as potential non-invasive circulating biomarkers for HCC diagnosis. Two circRNAs, including circ_000244 and circ_104075, were greatly up-regulated in HCC tissues and serums; while three other circRNAs, including circ_000520, cSMARCA5, and circ_001565, were reported to be down-regulated in HCC tissues and serum/plasma of HCC patients [6–8,27,32]. Among them, circ_104075 showed a potent diagnostic value (AUC value: 0.973, sensitivity: 0.960; specificity: 0.983), which was better than some classical protein biomarkers, including AFP (AUC value: 0.726; sensitivity: 0.779; specificity: 0.823), DCP (AUC value: 0.771; sensitivity: 0.703; specificity: 0.750), and AFP-L3 (AUC value: 0.766; sensitivity: 0.772; specificity: 0.633), as well as some lncRNA and miRNA biomarkers, including DANCR, HULC, miR-223, miR-21, and UCA1, suggesting that serum circ_104075 may serve as a promising diagnostic biomarker in HCC [32]. In another study, circ_000244, circ_000520, circ_001565 exhibited AUC values of 0.974, 0.943, and 0.839, respectively, which were higher than AFP (0.726), indicating the potential diagnostic value of these three circRNAs [27]. Two additional studies revealed that cSMARCA5 reached favorable AUC values of 0.938 and 0.862, respectively, and lower expression of cSMARCA5 was associated with poor tumor differentiation, more advanced tumor stage, tumor size and MVI [6,8]. Except for serum circRNA diagnostic markers, deregulated circRNAs in PBMCs of HCC patients were also studied [35]. Results showed that the expression of circ_0000798 was significantly up-regulated with an AUC value of 0.703, and the expression of this circRNA was positively correlated with tumor size and cirrhosis of HCC patients, indicating the potential role of circ_0000798 as diagnostic biomarker in HCC [35].

4. CircRNA prognostic biomarkers in HCC

Accurate prognostication for HCC patient outcome can help guide HCC treatment decisions, and hence may largely improve the OS and recurrence/relapse free survival (RFS) of HCC patients. Although no validated prognostic biomarkers are applied in HCC, some candidates have been identified. Owing to their high stability and robust

Table 2
CircRNA diagnostic biomarkers in HCC.

circRNA	Samples	Deregulation in HCC	HCC case no.	Diagnostic value						Ref.
				AUC	SEN	SPE	Cut-off	YI	95% CI	
hsa_circ_0005075	Tissues	↑	30	0.94	0.833	0.900	0.000586	–	–	[36]
hsa_circ_0016788	Tissues	↑	40	0.851	–	–	–	–	–	[39]
ciRS-7	Tissues	↑	108	0.68	–	–	0.135	–	0.58–0.79	[68]
hsa_circ_0128298	Tissues	↑	78	0.668	0.674	0.805	–	–	0.503–0.794	[45]
hsa_circ_0091579	Tissues	↑	105	0.656	0.97	0.4	–	0.37	–	[43]
circ-CDYL	Tissues	↑	80	0.64	0.333	0.928			0.55–0.72	[16]
hsa_circ_0004018	Tissues	↓	102	0.848	0.716	0.815	–	0.531	0.803–0.894	[60]
circZKSCAN1	Tissues	↓	102	0.834	0.822	0.724	–	–	–	[54]
hsa_circ_0003570	Tissues	↓	107	0.70	0.449	0.868	12.24	–	–	[59]
hsa_circ_0068669	Tissues	↓	100	0.64	0.59	0.71	–	–	–	[64]
hsa_circ_0001649	Tissues	↓	89	0.63	0.81	0.69	0.0007855	–	–	[56]
hsa_circ_000244	Serum	↑	68	0.974	0.956	0.927	1.27	–	0.948–0999	[27]
hsa_circ_104075	Serum	↑	101	0.973	0.960	0.983	–	0.943	–	[32]
hsa_circ_000520	Serum	↓	68	0.943	0.971	0.896	1.4	–	0.902–0.984	[27]
cSMARCA5	Plasma	↓	135	0.938	0.867	0.893	–	–	0.91–0.966	[6]
	Plasma	↓	104	0.862	0.712	0.942	–	–	0.710–0.845	[8]
hsa_circ_001565	Serum	↓	68	0.839	0.735	0.823	0.9	–	0.771–0.907	[27]
hsa_circ_0000798	PBMC	↑	72	0.703	–	–	–	–	0.604–0.803	[35]

AUC: area under the receiver operating characteristic curve; SEN: sensitivity; SPE: specificity; YI: Youden index; CI: concordance index; PBMC: peripheral blood mononuclear cells; ↑: up-regulated; ↓: down-regulated.

Table 3
CircRNA prognostic biomarkers in HCC.

CircRNA	Samples	Deregulation	HCC case no.	prognosis	Univariate analysis			Multivariate analysis			Ref.
					HR	95% CI	*p*	HR	95% CI	*p*	
hsa_circ_0000267	Tissues	↑	59	Poor OS	2.641	1.433–4.869	0.002	2.107	1.093–4.064	0.026	[34]
hsa_circ_001569	Tissues	↑	70	Poor OS	2.423	1.383–4.243	0.002	2.291	1.059–4.954	0.035	[29]
hsa_circ_0008450	Tissues	↑	70	Poor OS	2.182	1.265–3.762	0.005	2.028	1.162–3.538	0.013	[38]
hsa_circ_101368	Tissues	↑	51	Poor OS	4.908	1.930–12.480	0.001	3.246	1.098–9.594	0.033	[31]
hsa_circ_0128298	Tissues	↑	78	Poor OS	1.978	1.341–3.024	0.009	6.661	2.661–8.418	0.014	[45]
circ-BIRC6	Tissues	↑	55	Poor OS	2.820	1.225–5.026	0.005	2.343	1.088–5.044	0.030	[15]
circMAT2B	Tissues	↑	100	Poor OS	3.044	1.513–6.215	0.002	2.170	1.070–4.399	0.032	[22]
hsa_circ_100338	Tissues	↑	80	Poor OS	–	–	–	–	–	–	[30]
hsa_circ-10720	Tissues	↑	381	Poor OS	–	–	–	–	–	–	[26]
hsa_circ_0067934	Tissues	↑	49	Poor OS	–	–	–	–	–	–	[40]
hsa_circ_0091579	Tissues	↑	75	Poor OS	–	–	–	–	–	–	[43]
crcSLC3A2	Tissues	↑	90	Poor OS	–	–	–	–	–	–	[25]
circ-ZNF652	Tissues	↑	96	Poor OS	–	–	–	–	–	–	[18]
		↑	96	Poor RFS	–	–	–	–	–	–	[18]
ciRS-7	Tissues	↑	108	MVI	2.65	1.06–6.63	0.037	4.08	1.06–15.74	0.041	[68]
hsa_circ_0001649	Tissues	↓	77	Poor OS	0.283	0.097–0.826	0.015	0.191	0.053–0.682	0.011	[57]
circTRIM33-12	Tissues	↓	200	Poor OS	–	–	0.002	0.504	0.932–1.942	0.007	[53]
		↓	200	Poor RFS	–	–	0.001	0.534	0.344–0.830	0.005	[53]
circLARP4	Tissues	↓	70	Poor OS	–	–	–	3.997	1.747–9.142	0.001	[52]
		↓	70	Poor RFS	–	–	–	2.347	1.119–4.923	0.024	[52]
cSMARCA5	Tissues	↓	163	Poor OS	–	–	–	2.470	1.459–4.182	0.001	[7]
		↓	163	Poor RFS	–	–	–	1.673	1.080–2.591	0.021	[7]
circSETD3	Tissues	↓	132	Poor OS	–	–	–	–	–	–	[13]
		↓	132	Poor RFS	–	–	–	–	–	–	[13]
circC3P1	Tissues	↓	47	Poor OS	–	–	–	–	–	–	[49]
hsa_circ_0078602	Tissues	↓	79	Poor OS	–	–	–	–	–	–	[65]
circADAMTS13	Tissues	↓	102	Poor RFS	–	–	–	–	–	–	[47]
circHIAT1	Tissues	↓	80	Poor OS	–	–	–	–	–	–	[51]
circMTO1	Tissues	↓	116	Poor OS	–	–	–	–	–	–	[12]
circ-ITCH	Tissues	↓	288	Poor OS	–	–	–	–	–	–	[46]
circ-ZEB1.33	Tissues	↑	64	Poor OS	–	–	–	–	–	–	[9]
	Serum	↑	64	Poor OS	–	–	–	–	–	–	[9]
hsa_circ_000520	Serum	↑	66	Poor RFS	–	–	–	0.035	0.003–0.360	0.005	[27]
hsa_circ_0003731	Serum exosome	↑	82	Poor OS	–	–	–	–	–	–	[23]
hsa_circ_0008043	Serum exosome	↑	82	Poor OS	–	–	–	–	–	–	[23]
hsa_circ_0088030	Serum exosome	↑	82	Poor OS	–	–	–	–	–	–	[23]
hsa_circ_0064428	Plasma	↑	120	Poor OS	–	–	–	–	–	–	[62]
hsa_circ_0000798	PBMC	↑	72	Poor OS	–	–	–	–	–	–	[35]

OS: overall survival; RFS: recurrence/relapse free survival; HR: hazard ratio; CI: confidence interval; MVI: microvascular invasion; PBMC: peripheral blood mononuclear cells; ↑: up-regulated; ↓: down-regulated.

expression patterns in clinical samples, circRNAs also show great potential as prognostic biomarkers in HCC as listed in Table 3.

In HCC tissues, higher expression of fourteen circRNAs has been identified to be potential prognostic biomarkers for poor outcome in HCC by Kaplan-Meier (KM) analysis. Among them, seven were confirmed to be independent prognostic indicators for HCC patients by multivariable analyses, including circ_0000267, circ_001569, and circ_0008450, circ_101368, circ_0128298, circ-BIRC6, and circMAT2B [15,22,29,31,34,38,45]. Clinically, the expression of circ_0000267, circ_001569, and circ_0008450 in HCC tissues was associated with tumor size and TNM stages; circ_101368 expression was correlated with tumor size, TNM stage and distant metastasis; while circ_0128298 expression was associated with vascular cancer embolus, lymphatic metastasis, and organ metastasis [29,31,34,38,45]. The expression of circ-BIRC6 was correlated with TNM stage and vascular invasion; while circMAT2B expression was mainly associated with tumor size, vascular invasion, tumor encapsulation, TNM stage and Edmonson stage [15,22]. Except these, six other circRNAs were also confirmed to be potential prognostic biomarkers for poor OS, including circ_100338, circ-10720, circ_0067934, circ_0091579, circSLC3A2, circ-ZNF652; in addition, higher expression of circ-ZNF652 also predicts poor RFS [18,25,26,30,40,41,43]. Clinically, circ_100338 was related with TNM stage, vascular invasion, and lung metastasis; circ-10720 expression was associated with clinical stages and pathological Grades, as well as serum AFP levels; circ_0067934 expression was related with advanced TNM stages, lymph node metastasis and distant metastasis; while circ-ZNF652 expression was correlated with vascular invasion, intrahepatic and distant metastasis [18,26,30,40,41]. Interestingly, higher expression of another circRNA, ciRS-7, however, predicted MVI in HCC [68]. Clinically, ciRS-7 expression was found to be associated with serum AFP level and MVI; univariate and multivariate analyses demonstrated that higher expression of this circRNA was an independent risk factor of MVI [68].

In contrast to these up-regulated circRNAs, lower expression of other circRNAs could predict poor outcome of HCC patients. Six circRNAs, including circ_0001649, circTRIM33-12, circLARP4, cSMARCA5, circSETD3, and circC3P1, was greatly down-regulated in HCC tissues and cell lines [7,13,49,52,53,57]. Clinically, lower expression of circ_0001649 was associated to larger tumor size and the occurrence of tumor embolus in HCC patients; lower expression of circTRIM33-12 was correlated with larger tumor size, multiple tumors, encapsulation invasion and MVI, as well as elevated AFP levels; while reduced expression of circLARP4 was associated with larger tumor size, advanced Edmondson stage and TNM stage [52,53,57]. Decreased expression of cSMARCA5 was related to larger tumor size, poor tumor differentiation, advanced tumor stage and MVI; while lower expression of circSETD3 was correlated with larger tumor size and poor tumor differentiation [7,13]. KM analyses indicated that lower expression of all these six circRNAs was correlated with poor OS of HCC patients [7,13,49,52,53,57]. In addition, reduced expression of circTRIM33-12, circLARP4, circSETD3, and cSMARCA5 was also associated with shorter RFS of HCC patients [7,13,52,53]. Multivariate analyses revealed that the expression of circTRIM33-12, circLARP4 and cSMARCA5 in HCC patients may serve as an independent prognostic factor for OS and RFS; while the expression of circ_0001649 was an independent risk factor for poor OS of HCC patients [7,52,53,57]. Five other circRNAs, including, circ_0078602, circADAMTS13, circHIAT1, circMTO1, and circ-ITCH, were also found to be significantly down-regulated in HCC tissues, and lower expression of circADAMTS13 was related to larger tumor size, advanced BCLC stages, and absence of liver cirrhosis [12,46,47,51,65]. KM analysis indicated that HCC patients with lower expression of circ_0078602, circHIAT1, circMTO1, or circ-ITCH tend to have poorer OS, while HCC patients with lower expression of circADAMTS13 tend to have shorter RFS time [12,46,47,51,65]. Additionally, two single nucleotide polymorphisms (SNPs) of circ-ITCH, including rs10485505 and rs4911154, were associated with HCC risk [46].

Except for HCC tissues, several circRNAs deregulated in serum or serum-derived exosomes, plasma, or PBMCs, were identified as potential non-invasive prognostic biomarkers. For example, the expression of Circ-ZEB1.33 and circ_000520, were enhanced in HCC-associated serum [9,27]. Higher expression of circ-ZEB1.33 in HCC tissues and associated serum was related to TNM stages and lower OS in HCC patients; while circ_000520 in serum was associated with RFS of HCC patients, and may serve as an independent prognostic indicator for RFS of HCC patients [9,27]. Interestingly, the expression of three serum exosome circRNAs transcribed from *prostaglandin reductase 1* (*PTGR1*), including circ_0003731, circ_0008043, and circ_0088030, was also increased in HCC patients, and HCC patients with higher expression of these three circRNAs tend to have poor OS [23]. In another study, lower plasma expression circ_0064428 was associated with higher level of TILs in HCC tissues, lower differentiation grade and TNM stage, as well as smaller tumor size; KM analysis demonstrated that lower expression of circ_0064428 was related to better OS, suggesting that circ_0064428 may serve as a prognostic biomarker for HCC patients [62]. Besides, in the PBMCs of HCC patients, circ_0000798 expression was identified to be up-regulated, and higher expression of this circRNA in PBMCs was correlated with larger tumor size, liver cirrhosis and poor OS of HCC patients [35].

5. Functions of circRNAs in HCC progression

Studies showed that the deregulation of some circRNAs can impact on different biological processes, including cell proliferation, invasion and metastasis, and apoptosis, thus contribute to HCC progression. The function of specific circRNAs in HCC progression can be assessed both *in vitro* and *in vivo*. In *in vitro* studies, altered expression of circRNA by over-expression mediated *via* expressing vectors or lentiviruses, or knock-down mediated *via* targeted small interfering RNAs (siRNAs), short hairpin RNA (shRNA) vectors or lentiviruses, may resulted in alteration of HCC progression. In general, CCK-8/MTT, colony formation, EdU incorporation, as well as cell cycle progression assays can be used to detect the proliferative abilities of HCC cells; wound-healing and transwell assays can be carried out to evaluate the migratory and invasive abilities of HCC cells; while flow cytometry and JC-1 assay can be applied to observe the apoptosis of HCC cells. Further *in vivo* experiments are often carried out to validate those results obtained from *in vitro* studies. In these experiments, HCC cells are injected subcutaneously to establish xenograft mouse model; or injected from the tail vein of nude mice to establish metastatic mouse model. The alteration of circRNA expression could be achieved by directly injecting circRNA over-expressing or knocking-down HCC cells into nude mice, or directly injecting targeted siRNAs into tumor tissues formed by HCC cells. After mice are sacrificed, tumor volumes, sizes, weights, and locations of these mice are recorded and analyzed, pathology and the expression of specific genes can be evaluated by different technologies, such as hematoxylin-eosin (HE) staining, qRT-PCR, Western blot, immunohistochemistry (IHC), immunofluorescence (IF), *etc*. Functions of circRNAs in different biological processes involved in HCC progression is depicted in Fig. 1.

Among deregulated circRNAs in HCC, fourteen were identified to be up-regulated and play promotional effects on HCC progression in both *in vitro* and *in vivo* studies. Among these, six circRNAs, including circRBM23, circ-10720, circ_001569, circ_0078710, circβ-catenin, and circMAT2B, demonstrated promotional effects on HCC progression by enhancing the proliferation, migration and invasion of HCC cells [19,22,24,26,29,42]. Four circRNAs, including circ_0067934, circ_101280, circFBLIM1, and circ-BIRC6, promoted the proliferation and invasion, while inhibited the apoptosis, of HCC cells [10,15,33,40,41]. circ-CDYL promoted the proliferation, chemoresistance, and stem-like characteristics of HCC cells; circDYNC1H1 modulated HCC cell proliferation and migration; circ_0016788 function on HCC cell proliferation, invasion and apoptosis; while circ-ZNF652

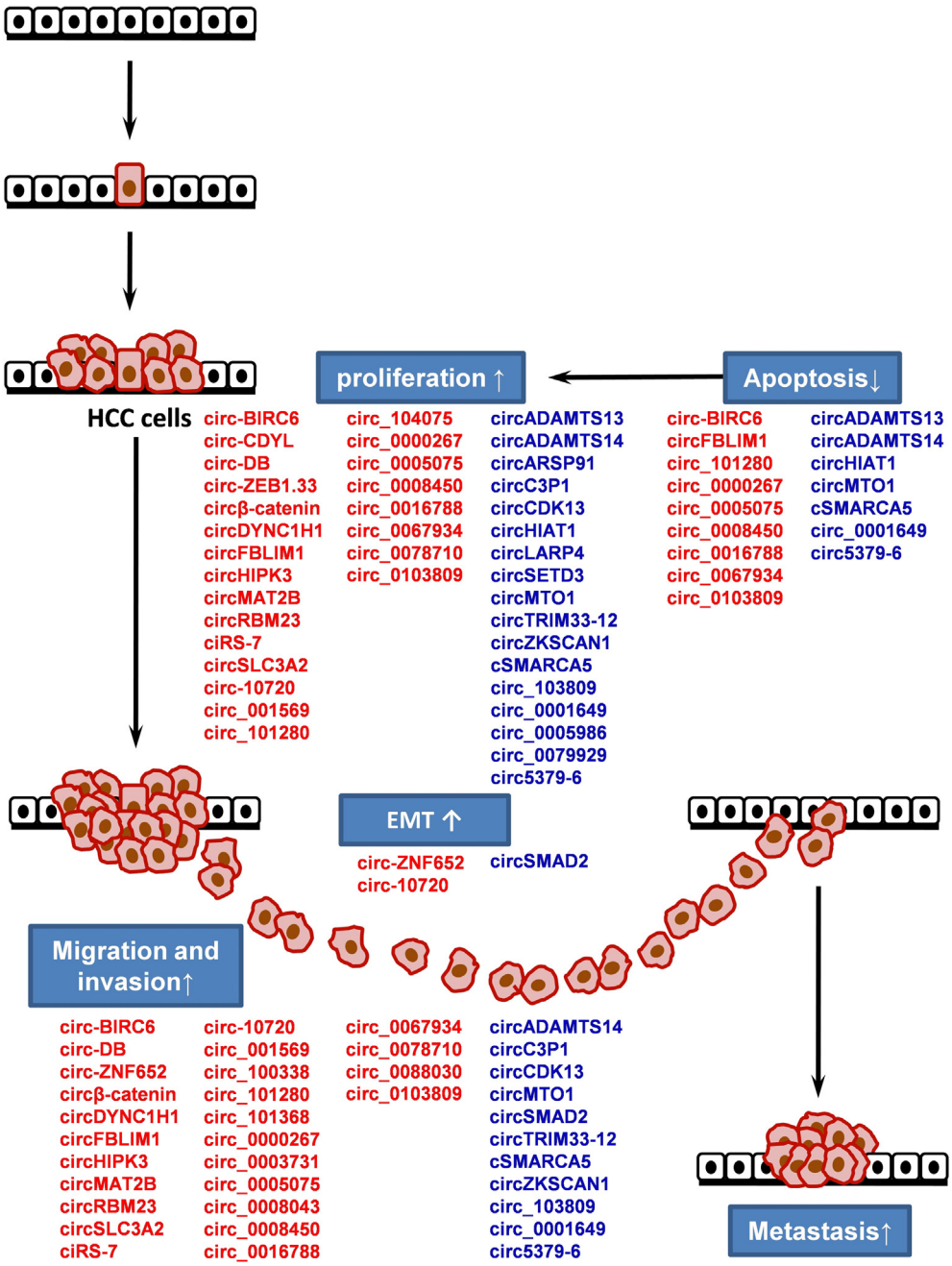

Fig. 1. Functions of circular RNAs (circRNAs) in hepatocellular carcinoma (HCC) pathogenesis. Schematic diagram of circRNAs involved in HCC progression. Oncogenic and suppressive circRNAs function in different biological processes involved in HCC progression are presented in red and blue color, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

enhanced HCC cell migration and invasion [16,18,20,39]. *In vivo* experiments demonstrated that five circRNAs, including circ_001569, circ_0067934, circβ-catenin, circFBLIM1, circMAT2B, exhibited promotional effects on HCC tumor growth and metastasis [10,19,22,29,40]; circ-ZNF652 showed acceleration effects on HCC tumor metastasis [18]; while other circRNAs could facilitate HCC tumor growth [15,16,20,24,26,33,39,42]. Except these, other ten circRNAs were also found to be increased in HCC, while they were demonstrated to promote HCC progression in only *in vitro* experiments. Among them, circ_104075 and circ-ZEB1.33 could promote the HCC cell proliferation; circHIPK3 could accelerate HCC cell proliferation and migration; whereas circ_101368 and circ_100338 could enhance the HCC cell migration and invasion [9,11,30–32]. CircSLC3A2 could facilitate HCC cell proliferation and invasion; whereas other four circRNAs, including circ_0000267, circ_0005075, circ_0008450, and circ_0103809, could elevate the proliferation, migration and invasion, while inhibit the apoptosis, of HCC cells [25,34,37,38,44]. Interestingly, several circRNAs, including circ-DB and three circRNAs derived from *PTGR1* gene, which were named as circPTGR1 (circ_0008043, circ_0003731, and circ_0088030), were found to be up-regulated in serum-derived exosomes, and could promote HCC progression in both *in vitro* and *in vivo* experiments [17,23]. Specially, exosome circ-DB was significantly up-regulated in HCC patients with higher body fat ratios compared with those with lower body fat ratios, and could enhance HCC tumor growth and metastasis; whereas circPTGR1 was up-regulated in serum exosomes of HCC patients and HCC cells with enhanced invasive abilities, and could facilitate HCC tumor metastasis [17,23].

In contrast to those up-regulated circRNAs, some circRNAs were

found to be down-regulated in HCC tissues and cell lines. Among them, ten have been confirmed to play inhibitory roles in HCC progression in both *in vitro* and *in vivo* experiments. In *in vitro* experiments, two circRNAs, including circ_0079929, circSETD3, showed inhibitory effects on the proliferation of HCC cells; circLARP4 exhibited suppression of proliferation, and induction of senescence on HCC cells; while circHIAT1 reduced the proliferation, and enhanced the apoptosis of HCC cells [13,51,52,66]. Other six circRNAs, including circ_0001649, circADAMTS14, circC3P1, circTRIM33-12, cSMARCA5, and circZKSCAN1, could inhibit the proliferation, migration and invasion of HCC cells; In addition, circ_0001649, circADAMTS14 and cSMARCA5 could also induce apoptosis of HCC cells [7,48,49,53,54,58]. *In vivo* experiments demonstrated that circC3P1 and cSMARCA5 could inhibit both HCC tumor growth and metastasis, while other eight circRNAs could suppress HCC tumor growth [7,13,48,49,51–54,58,66]. Except these, six circRNAs were reported to be decreased in HCC, and also showed suppression on HCC progression in *in vitro* experiments. Among them, circ_0005986 inhibited the proliferation of HCC cells, circSMAD2 suppressed the migration and invasion, as well as EMT of HCC cells; whereas circADAMTS13 reduced the proliferation, while promoted the apoptosis of HCC cells [14,47,61]. Three circRNAs, including circ_103809, circCDK13, and circMTO1, were capable of inhibiting the proliferation, migration and invasion of HCC cells; among them, circMTO1 also promote the apoptosis of HCC cells [12,50,55].

Although the deregulation of ciRS-7 in HCC remains controversial, ciRS-7 has been showed to promote the proliferation and invasion of HCC cells [67,68,78]. Other two circRNAs, including circ5379-6 and circARSP91, also demonstrated to participate in HCC progression, while their deregulation in HCC were not studied [69,70]. Circ5379-6, a circRNA derived from tumor suppressive gene *PPARα*, exhibited inhibitory effects on HCC progression by suppressing the proliferation, migration and invasion, and promoting apoptosis of HCC cells, while it did not impact on cell cycle progression [69]. CircARSP91, a circRNA down-regulated by androgen receptor, also suppressed the proliferation of HCC cells [70]. *In vivo* experiments confirmed that both circ5379-6 and circARSP91 reduced tumor growth of HCC [69,70].

6. Mechanisms of circRNAs in HCC progression

For the mechanism study of circRNAs, their subcellular localization is essential. Current studies showed that majority of circRNAs are mainly distributed in cytoplasm, and could regulate gene expression at post-transcriptional levels by sponging miRNAs to promoting the expression of miRNA targeted genes; while some circRNAs are abundant in nucleus, and are capable of modulating gene expression at transcriptional and post-transcriptional levels [2–5]. The subcellular localization of a specific circRNA could be detected by fluorescence *in situ* hybridization (FISH), or qRT-PCR of nuclear and cytoplasmic RNAs [7,10,52]. Currently, most functional circRNAs in HCC were reported to be predominantly distributed in cytoplasm and function as miRNA sponges. The interaction between circRNAs and miRNAs, as well as miRNAs and their possible target mRNAs, could be first predicted using different online tools, such as miRanda (http://www.microrna.org), TargetScan (http://www.targetscan.org/), Circinteractome (https://circinteractome.nia.nih.gov/), starBase (http://starbase.sysu.edu.cn), and PicTar (http://pictar.mdc-berlin.de/), then validated by luciferase reporter assay, RNA immunoprecipitation (RIP), RNA pull-down, *etc.* [79–83]. Furthermore, the expression and correlation among circRNAs, miRNAs, and mRNA/proteins could be verified in HCC tissues, cell lines and mouse model. Finally, the role of circRNA-miRNA axis in HCC progression could be studied by rescue assay. Aberrant expressed circRNAs and their targets involved in HCC progression is depicted in Fig. 2.

Among all the techniques to validate the predicted circRNA-miRNA interaction, luciferase reporter assay is one of the most popular techniques, followed by RIP, RNA pull-down, or FISH assays. In few studies, circRNA-miRNA interaction was confirmed by two or more techniques listed above. For example, circMAT2B-miR-338-3p interaction was validated by all four techniques; cSMARCA5-miR-17-3p/miR-181-5p, circLARP5-miR-761, and circ-BIRC6-miR-3918 interactions were identified by luciferase reporter, RIP, and FISH co-localization assays [7,15,22,52]. Circ_104075-miR-582-3p, circDYNC1H1-miR-140-5p, circFBLIM1-miR-346, circSETD3-miR-421, and circ-ZNF652-miR-203/miR-502-5p interactions were confirmed by either RIP or RNA pull-down, together with luciferase reporter assay; while circMTO1-miR-9 interaction was validated by FISH and RNA pull-down assays [10,12,13,18,20,32]. Except these studies, most interactions, such as circ_101280-miR-375, circ-ZEB1.33-miR-200a-3p, and circADAMTS14-miR-572, were verified by single technique [9,33,48]. Similarly, few studies revealed the miRNA-mRNA interaction by two or more techniques. For instance, miR-582-3p and miR-34a, which were demonstrated to interact with circ_104075 and circ-DB, respectively, were confirmed to bind to the 3′-UTR of YAP and USP7 mRNAs, separately, by either RIP or RNA pull-down, together with luciferase reporter assay [17,32]; while most other studies verified miRNA-mRNA interaction by luciferase assay alone [33,42,48,49].

In HCC, most up-regulated circRNAs play oncogenic roles in HCC progression, while their interacting miRNAs often function as tumor suppressors by modulating the expression of their targeted oncogenic genes. In contrast, down-regulated circRNAs usually exert inhibitory effects on HCC progression, while their interacting miRNAs may act as oncogenes to reducing the expression of their targeted tumor-suppressive genes. Hence, in HCC tissues and cell lines, the expression of circRNAs often inversely correlate with that of their interacting miRNAs, while positively correlated with that of miRNA-targeted genes. Likely, over-expression or knocking down of circRNAs may impact on the expression levels of their associated miRNAs and mRNAs/proteins in both *in vitro* and *in vivo* experiments. For example, in HCC tissues, circHIPK3 expression was up-regulated; the expression of its interacting miRNA, miR-124, was down-regulated; while the expression of miR-124 targeted gene AQP3 was also up-regulated [11]. Correlation analysis indicated that the expression of circHIPK3 and AQP3 was positively correlated, while their expression was inversely correlated with miR-124 [11]. *In vitro* and *in vivo* experiments showed that circHIPK3 inhibition also reduced the expression of miR-124 target gene AQP3 in HCC cells and tissues, suggesting that circHIPK3 may promote the expression of AQP3 by repressing miR-124 [11]. Some circRNAs, such as circ-BIRC6, circ-DB, circADAMTS14, circLARP4, as well as their interacting miRNAs and miRNA-targeted mRNAs, showed similar correlation pattern as circHIPK3-miR-124-AQP3 in both *in vitro* and *in vivo* experiments [15,17,48,52]; while for most other cirRNAs, the circRNA-miRNA-mRNA expression trend and correlation were validated in *in vitro* studies [9,24,44,49].

To study the role of circRNA-miRNA axis in HCC progression, rescue assay are often carried out. In this experiment, alteration of circRNA expression impacts on HCC progression, and inversely regulates the expression of miRNAs which could interact with this circRNA. If the circRNA-miRNA interaction is pivotal to HCC progression, then co-silencing or co-overexpression of miRNA could rescue miRNA expression, and then at least partially reverse the influence of circRNA on HCC progression. For example, circ_0000267 promotes HCC progression. In HCC cells, co-silencing of miR-646, a miRNA interacting with circ_0000267, could rescue the inhibitory effect of circ_0000267 depletion; while co-transfection of miR-646 mimic could partially restore the oncogenic behaviors induced by circ_0000267, suggesting that the oncogenic role of circ_0000267 on HCC progression was mediated by miR-626 [34]. Similarly, miR-548p inhibitor rescued the suppressive effect of circ_0008450 inhibition; while miR-548p mimics reversed the promotional effect induced by circ_0008450, indicating the important role of circ_0008450-miR-548p interaction in HCC progression [38]. Except them, many other interactions, such as circHIPK3-miR-124, cSMARCA5-miR-17-3p/miR-181-5p, circLARP4-miR-761, and

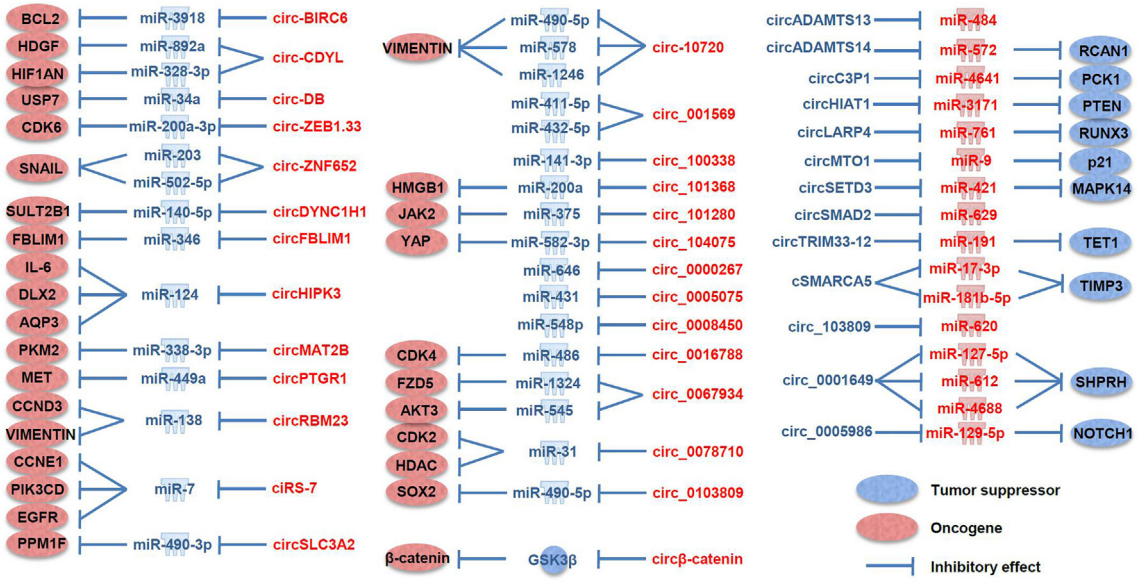

Fig. 2. CircRNAs and their targets involved in HCC progression. USP7: ubiquitin specific peptidase 7; HDGF: hepatoma-derived growth factor; HIF1AN: hypoxia inducible factor asparagine hydroxylase; BCL2: B-cell lymphoma 2; CDK6: cyclin dependent kinase 6; SNAIL: snail family transcriptional repressor 1; SULT2B1: sulfotransferase family 2B member 1; FBLIM1: filamin binding LIM protein 1; IL-6: interleukin 6; DLX2: distal-less homeobox 2; AQP3: aquaporin 3; PKM2: pyruvate kinase M1/2; MET: MET proto-oncogene, receptor tyrosine kinase; CCND3: cyclin D3; CCNE1: cyclin E1; PIK3CD: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta; EGFR: epithelial growth factor receptor; PPM1F: protein phosphatase, Mg^{2+}/Mn^{2+} dependent 1F; HMGB1: High Mobility Group Box 1; JAK2: Janus Kinase 2; YAP: Yes Associated Protein 1; CDK4: cyclin dependent kinase 4; FZD5: Frizzled Class Receptor 5; CDK2: cyclin dependent kinase 2; HDAC: histone deacetylase; SOX2: SRY-Box 2; RCAN: regulator of calcineurin 1; PCK1: phosphoenolpyruvate carboxykinase 1; PTEN: phosphatase and tensin homolog; RUNX3: runt related transcription factor 3; p21: cyclin-dependent kinase inhibitor 1A; MAPK14: mitogen-activated protein kinase 14; TET1: tet methylcytosine dioxygenase 1; TIMP3: tissue inhibitor of metalloproteinases 3; SHPRH: SNF2 histone linker PHD RING helicase; NOTCH1: notch receptor 1.

circMTO1-miR-9, are demonstrated to be crucial for the function of these circRNAs in HCC progression [7,11,12,21,52].

Interestingly, a latest study revealed a non-canonical mechanism of a novel circRNA in HCC [19]. Unlike most other circRNAs which function by sponging miRNAs, circβ-catenin, a circRNA generated from the exon 2 to exon 7of β-catenin, was found to promote HCC progression by producing a new protein isoform of β-catenin, β-catenin-370aa [19]. Sharing extensive sequence homology with β-catenin, β-catenin-370aa may function as a decoy to prevent the binding of β-catenin and GSK3β, and thus improve the stability of full-length β-catenin to activate the Wnt signaling pathway [19].

7. Future perspectives

Compared with their linear counterparts, circRNAs are highly stable and abundance in plasma, serum and serum-derived exosomes, as well as PBMCs, making them a promising non-invasive biomarker source for HCC diagnosis and prognosis. For instance, circ_104075, circ_000244, and circ_000520 exhibited promising diagnostic values superior to classical protein biomarkers such as AFP; circMAT2B, cSMARCA5, circMTO1, and circADAMTS13 demonstrated favorable prognostic values for OS and/or RFS of HCC patients; while ciRS-7 may serve as an independent risk factor of MVI in HCC [7,12,22,27,32,47,68]. Furthermore, circRNA based biomarker panels, or the combination of circRNA with classical biomarkers may provide better accuracy for HCC diagnosis. For example, a three circRNA panel, including circ_001565, circ_000244, and circ_000520, achieved significantly high sensitivity and better specificity than AFP; while the combination of cSMARCA5 and AFP reached high AUC values of 0.970 and 0.992 in two independent studies [6,8,27]. Interestingly, recent studies demonstrated that specific fusion-circRNA may generate from fusion gene of cancer patients, and these fusion-circRNAs may also serve as biomarkers for cancer diagnosis and prognosis, as well as therapeutic targets for cancer treatment [84–86]. F-circEA-4a, a circRNA derived from oncogenic *EML4-ALK* fusion gene of non-small cell lung cancer (NSCLC) patients, was demonstrated to be a potential plasma diagnostic biomarker for *EML4-ALK*-positive NSCLC [86]. F-circEA-4a and another fusion-circRNA, F-circEA-2a, which derived from the same fusion gene as F-circEA-4a, were reported to promote the migration and invasion of NSCLC cells [86]. Another fusion-circRNA f-circM9, which derived from *MLL/AF9* translocation in leukemia patients, exhibited promotional effects on tumor cells, as well as resistance to chemotherapies of cytarabine and arsenic trioxide [84]. It is possible that fusion-circRNAs may exist and play pivotal roles in the diagnosis, prognosis, progression and chemoresistance of HCC.

Since circRNAs are highly stable than linear RNAs, and the majority of circRNAs reported are function as miRNA sponges, artificial circRNAs can be constructed to achieve better inhibitory effects on oncogenic or pathogenic miRNAs. In an HCV cell culture system, artificial circRNAs containing eight repeated miR-122 bulged or perfectly complementary binding sites successfully inhibited HCV translation by sponging miR-122, the efficiency of which were similar to locked nucleic acid-modified antisense oligonucleotide [87]. Moreover, these artificial circRNAs were still detectable five days post transfection [87]. In another study, artificial circRNA containing five repeated miR-21 bulged binding sites exhibited better inhibitory effect on the proliferation, as well as promotional effect on the apoptosis, of gastric cancer cells than miR-21 inhibitor [88]. These results indicated that artificial circRNAs sponging specific miRNAs are a promising strategy to regulate cancer progression and viral replication.

Given that sex hormone and their receptors contribute to gender discrepancy in HCC, circRNAs that could be regulated by these hormones or their receptors may serve as potential HCC biomarkers, or play roles in HCC initiation and progression [89–91]. In prostate cancer, cSMARCA5 could be induced by androgen dihydrotestosterone, and increased expression of this circRNA promoted cancer cell proliferation by accelerating cell cycle and suppressing cell apoptosis [92]. In clear cell renal cell carcinoma, circHIAT1 could be transcriptionally

inhibited by androgen receptor, and high expression of this circRNA suppressed cell migration and invasion *in vitro* and *in vivo* [93]. In HCC, circARSP91 was also reported to be reduced by androgen receptor, and high expression of this circRNA inhibited HCC cell growth *in vitro* and *in vivo* [70].

Although great progress has been made in understanding the function of circRNAs in HCC, it will be a long time before they could be used in clinic. In most studies, circRNA biomarkers are identified by comparing HCC and healthy controls with limited cohort sizes. Given the heterogeneity in HCC, more extensive studies could be carried out with larger sample sizes to clarify specific circRNA signatures in HCC patients at different stages or with different etiologies. Furthermore, the biogenesis and regulators of most circRNAs, as well as their functions and mechanisms in HCC progression, are still far to be fully elucidated.

8. Conclusion

During the past few years, our understanding of the roles of circRNAs in onset, progression and treatment of cancer is starting to be fully appreciated. High stability and abundance of circRNAs in tissues and the circulation enable them to be promising diagnostic and/or prognostic biomarkers for HCC patients. Furthermore, circRNAs contribute to HCC progression by modulating the proliferation, apoptosis, invasion, and metastasis of HCC cells *via* interacting with miRNAs/proteins or translating into functional proteins. Identification of functional circRNAs, elucidation of their targeted molecules and signaling pathways will facilitate the potential clinical application of circRNAs as therapeutic targets in HCC.

Declaration of Competing Interest

The authors have declared no conflict of interest.

Acknowledgements

This work was supported by the National Natural Science Foundation of China [grant number 81402840, 31471294, 31771521, 81672582]; the Natural Science Foundation of Jiangsu Province, China [grant number BK20130495, BE2016718]; the Natural Science Foundation of Jiangsu Province for Distinguished Young Scholars [grant number BK20160013]; the National Key Research and Development Program of China [grant number 2018YFA0108400]; Six Talent Peaks Project in Jiangsu Province [grant number 2015-SWYY-019, 2016-SWYY-011]; Senior Talent Foundation of Jiangsu University [grant number 14JDG050, 14JDG011]; the Training Project of Young Backbone Teachers of Jiangsu University; Top Talent of Innovative Research Team of Jiangsu Province; Start-up Scientific Research Fund for the Returned Oversea Scholars from Ministry of Education of China.

References

[1] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (2018) 394–424.

[2] W.R. Jeck, J.A. Sorrentino, K. Wang, M.K. Slevin, C.E. Burd, J. Liu, W.F. Marzluff, N.E. Sharpless, Circular RNAs are abundant, conserved, and associated with ALU repeats, RNA 19 (2013) 141–157.

[3] J. Salzman, R.E. Chen, M.N. Olsen, P.L. Wang, P.O. Brown, Cell-type specific features of circular RNA expression, PLoS Genet. 9 (2013) e1003777.

[4] S. Memczak, M. Jens, A. Elefsinioti, F. Torti, J. Krueger, A. Rybak, L. Maier, S.D. Mackowiak, L.H. Gregersen, M. Munschauer, A. Loewer, U. Ziebold, M. Landthaler, C. Kocks, F. le Noble, N. Rajewsky, Circular RNAs are a large class of animal RNAs with regulatory potency, Nature 495 (2013) 333–338.

[5] B. Yu, G. Shan, Functions of long noncoding RNAs in the nucleus, Nucleus 7 (2016) 155–166.

[6] Z. Li, Y. Zhou, G. Yang, S. He, X. Qiu, L. Zhang, Q. Deng, F. Zheng, Using circular RNA SMARCA5 as a potential novel biomarker for hepatocellular carcinoma, Clin. Chim. Acta 492 (2019) 37–44.

[7] J. Yu, Q.G. Xu, Z.G. Wang, Y. Yang, L. Zhang, J.Z. Ma, S.H. Sun, F. Yang, W.P. Zhou, Circular RNA cSMARCA5 inhibits growth and metastasis in hepatocellular carcinoma, J. Hepatol. 68 (2018) 1214–1227.

[8] X. Zhang, H. Zhou, W. Jing, P. Luo, S. Qiu, X. Liu, M. Zhu, C. Liang, M. Yu, J. Tu, The circular RNA hsa_circ_0001445 regulates the proliferation and migration of hepatocellular carcinoma and may serve as a diagnostic biomarker, Dis. Markers 2018 (2018) 3073467.

[9] Y. Gong, J. Mao, D. Wu, X. Wang, L. Li, L. Zhu, R. Song, Circ-ZEB1.33 promotes the proliferation of human HCC by sponging miR-200a-3p and upregulating CDK6, Cancer Cell Int. 18 (2018) 116.

[10] N. Bai, E. Peng, X. Qiu, N. Lyu, Z. Zhang, Y. Tao, X. Li, Z. Wang, circFBLIM1 act as a ceRNA to promote hepatocellular cancer progression by sponging miR-346, J. Exp. Clin. Cancer Res. 37 (2018) 172.

[11] G. Chen, Y. Shi, M. Liu, J. Sun, circHIPK3 regulates cell proliferation and migration by sponging miR-124 and regulating AQP3 expression in hepatocellular carcinoma, Cell Death Dis. 9 (2018) 175.

[12] D. Han, J. Li, H. Wang, X. Su, J. Hou, Y. Gu, C. Qian, Y. Lin, X. Liu, M. Huang, N. Li, W. Zhou, Y. Yu, X. Cao, Circular RNA circMTO1 acts as the sponge of microRNA-9 to suppress hepatocellular carcinoma progression, Hepatology 66 (2017) 1151–1164.

[13] L. Xu, X. Feng, X. Hao, P. Wang, Y. Zhang, X. Zheng, L. Li, S. Ren, M. Zhang, M. Xu, CircSETD3 (Hsa_circ_0000567) acts as a sponge for microRNA-421 inhibiting hepatocellular carcinoma growth, J. Exp. Clin. Cancer Res. 38 (2019) 98.

[14] X. Zhang, P. Luo, W. Jing, H. Zhou, C. Liang, J. Tu, circSMAD2 inhibits the epithelial-mesenchymal transition by targeting miR-629 in hepatocellular carcinoma, Onco. Targets Ther. 11 (2018) 2853–2863.

[15] G. Yang, X. Wang, B. Liu, Z. Lu, Z. Xu, P. Xiu, Z. Liu, J. Li, circ-BIRC6, a circular RNA, promotes hepatocellular carcinoma progression by targeting the miR-3918/Bcl2 axis, Cell Cycle 18 (2019) 976–989.

[16] Y. Wei, X. Chen, C. Liang, Y. Ling, X. Yang, X. Ye, H. Zhang, P. Yang, X. Cui, Y. Ren, X. Xin, H. Li, R. Wang, W. Wang, F. Jiang, S. Liu, J. Ding, B. Zhang, L. Li, H. Wang, A noncoding regulatory RNAs network driven by circ-CDYL acts specifically in the early stages hepatocellular carcinoma, Hepatology (2019) (In press).

[17] H. Zhang, T. Deng, S. Ge, Y. Liu, M. Bai, K. Zhu, Q. Fan, J. Li, T. Ning, F. Tian, H. Li, W. Sun, G. Ying, Y. Ba, Exosome circRNA secreted from adipocytes promotes the growth of hepatocellular carcinoma by targeting deubiquitination-related USP7, Oncogene 38 (2019) 2844–2859.

[18] J. Guo, H. Duan, Y. Li, L. Yang, L. Yuan, A novel circular RNA circ-ZNF652 promotes hepatocellular carcinoma metastasis through inducing snail-mediated epithelial-mesenchymal transition by sponging miR-203/miR-502-5p, Biochem. Biophys. Res. Commun. 513 (2019) 812–819.

[19] W. Liang, C. Wong, P. Liang, M. Shi, Y. Cao, S. Rao, S. Tsui, M. Waye, Q. Zhang, W. Fu, J. Zhang, Translation of the circular RNA circβ-catenin promotes liver cancer cell growth through activation of the Wnt pathway, Genome Biol. 20 (2019) 84.

[20] Z.Y. Wang, Z. Zhu, H.F. Wang, B. Qin, J. Liu, X.H. Yao, W.C. Li, K.S. Chen, Downregulation of circDYNC1H1 exhibits inhibitor effect on cell proliferation and migration in hepatocellular carcinoma through miR-140-5p, J. Cell. Physiol. 234 (2019) 17775–17785.

[21] Q. Zheng, C. Bao, W. Guo, S. Li, J. Chen, B. Chen, Y. Luo, D. Lyu, Y. Li, G. Shi, L. Liang, J. Gu, X. He, S. Huang, Circular RNA profiling reveals an abundant circHIPK3 that regulates cell growth by sponging multiple miRNAs, Nat. Commun. 7 (2016) 11215.

[22] Q. Li, X. Pan, D. Zhu, Z. Deng, R. Jiang, X. Wang, Circular RNA MAT2B promotes glycolysis and malignancy of hepatocellular carcinoma via the miR-338-3p/PKM2 axis under hypoxic stress, Hepatology (2019) (In press).

[23] G. Wang, W. Liu, Y. Zou, G. Wang, Y. Deng, J. Luo, Y. Zhang, H. Li, Q. Zhang, Y. Yang, G. Chen, Three isoforms of exosomal circPTGR1 promote hepatocellular carcinoma metastasis via the miR449a-MET pathway, EBioMedicine 40 (2019) 432–445.

[24] B. Wang, H. Chen, C. Zhang, T. Yang, Q. Zhao, Y. Yan, Y. Zhang, F. Xu, Effects of hsa_circRBM23 on hepatocellular carcinoma cell viability and migration as produced by regulating miR-138 expression, Cancer Biother. Radiopharm. 33 (2018) 194–202.

[25] H. Wang, W. Chen, M. Jin, L. Hou, X. Chen, R. Zhang, J. Zhang, J. Zhu, CircSLC3A2 functions as an oncogenic factor in hepatocellular carcinoma by sponging miR-490-3p and regulating PPM1F expression, Mol. Cancer 17 (2018) 165.

[26] J. Meng, S. Chen, J.X. Han, B. Qian, X.R. Wang, W.L. Zhong, Y. Qin, H. Zhang, W.F. Gao, Y.Y. Lei, W. Yang, L. Yang, C. Zhang, H.J. Liu, Y.R. Liu, H.G. Zhou, T. Sun, C. Yang, Twist1 regulates vimentin through Cul2 circular RNA to promote EMT in hepatocellular carcinoma, Cancer Res. 78 (2018) 4150–4162.

[27] M. Matboli, A.E. Shafei, M.A. Ali, A.M. Ashry, K.M. Kamal, M.A. Agag, I. Reda, E.F. Tash, M. Ali, circRNAs (hsa_circ_00156, hsa_circ_000224, and hsa_circ _000520) are novel potential biomarkers in hepatocellular carcinoma, J. Cell. Biochem. (2019) (In press).

[28] B.G. Wang, J.S. Li, Y.F. Liu, Q. Xu, MicroRNA-200b suppresses the invasion and migration of hepatocellular carcinoma by downregulating RhoA and circRNA_000839, Tumour Biol. 39 (2017) 1010428317719577.

[29] H. Liu, L. Xue, C. Song, F. Liu, T. Jiang, X. Yang, Overexpression of circular RNA circ_001569 indicates poor prognosis in hepatocellular carcinoma and promotes cell growth and metastasis by sponging miR-411-5p and miR-432-5p, Biochem. Biophys. Res. Commun. 503 (2018) 2659–2665.

[30] X.Y. Huang, Z.L. Huang, Y.H. Xu, Q. Zheng, Z. Chen, W. Song, J. Zhou, Z.Y. Tang, X.Y. Huang, Comprehensive circular RNA profiling reveals the regulatory role of the circRNA-100338/miR-141-3p pathway in hepatitis B-related hepatocellular carcinoma, Sci. Rep. 7 (2017) 5428.

[31] S. Li, H. Gu, Y. Huang, R. Zhou, P. Yi, R. Chen, Z. Huang, X. Hu, Y. Huang, D. Tang, Circular RNA 101368/miR-200a axis modulates the migration of hepatocellular carcinoma through HMGB1/RAGE signaling, Cell Cycle 17 (2018) 2349–2359.

[32] X. Zhang, Y. Xu, Z. Qian, W. Zheng, Q. Wu, Y. Chen, G. Zhu, Y. Liu, Z. Bian, W. Xu, Y. Zhang, F. Sun, Q. Pan, J. Wang, L. Du, Y. Yu, circRNA_104075 stimulates YAP-dependent tumorigenesis through the regulation of HNF4a and may serve as a diagnostic marker in hepatocellular carcinoma, Cell Death Dis. 9 (2018) 1091.
[33] S. Cao, G. Wang, J. Wang, C. Li, L. Zhang, Hsa_circ_101280 promotes hepatocellular carcinoma by regulating miR-375/JAK2, Immunol. Cell Biol. 97 (2019) 218–228.
[34] H. Pan, L. Tang, H. Jiang, X. Li, R. Wang, J. Gao, Q. Li, Enhanced expression of circ_0000267 in hepatocellular carcinoma indicates poor prognosis and facilitates cell progression by sponging miR-646, J. Cell. Biochem. (2019) (In press).
[35] B. Lei, J. Zhou, X. Xuan, Z. Tian, M. Zhang, W. Gao, Y. Lin, B. Ni, H. Pang, W. Fan, Circular RNA expression profiles of peripheral blood mononuclear cells in hepatocellular carcinoma patients by sequence analysis, Cancer Med. 8 (2019) 1423–1433.
[36] X. Shang, G. Li, H. Liu, T. Li, J. Liu, Q. Zhao, C. Wang, Comprehensive circular RNA profiling reveals that hsa_circ_0005075, a new circular RNA biomarker, is involved in hepatocellular carcinoma development, Medicine (Baltimore) 95 (2016) e3811.
[37] M.F. Li, Y.H. Li, Y.H. He, Q. Wang, Y. Zhang, X.F. Li, X.M. Meng, C. Huang, J. Li, Emerging roles of hsa_circ_0005075 targeting miR-431 in the progress of HCC, Biomed. Pharmacother. 99 (2018) 848–858.
[38] J. Zhang, Y. Chang, L. Xu, L. Qin, Elevated expression of circular RNA circ_0008450 predicts dismal prognosis in hepatocellular carcinoma and regulates cell proliferation, apoptosis, and invasion via sponging miR-548p, J. Cell. Biochem. 120 (2019) 9487–9494.
[39] Z. Guan, J. Tan, W. Gao, X. Li, Y. Yang, X. Li, Y. Li, Q. Wang, Circular RNA hsa_circ_0016788 regulates hepatocellular carcinoma tumorigenesis through miR-486/CDK4 pathway, J. Cell. Physiol. 234 (2018) 500–508.
[40] Q. Zhu, G. Lu, Z. Luo, F. Gui, J. Wu, D. Zhang, Y. Ni, CircRNA circ_0067934 promotes tumor growth and metastasis in hepatocellular carcinoma through regulation of miR-1324/FZD5/Wnt/beta-catenin axis, Biochem. Biophys. Res. Commun. 497 (2018) 626–632.
[41] S. Qi, H. Sun, H. Liu, J. Yu, Z. Jiang, P. Yan, Role and mechanism of circ-PRKCI in hepatocellular carcinoma, World J. Gastroenterol. 25 (2019) 1964–1974.
[42] B. Xie, Z. Zhao, Q. Liu, X. Wang, Z. Ma, H. Li, CircRNA has_circ_0078710 acts as the sponge of microRNA-31 involved in hepatocellular carcinoma progression, Gene 683 (2019) 253–261.
[43] C. Zhang, J. Lin, H. Wang, Circular RNA Hsa_Circ_0091579 serves as a diagnostic and prognostic marker for hepatocellular carcinoma, Cell. Physiol. Biochem. 51 (2018) 290–300.
[44] H. Cai, B. Hu, L. Ji, X. Ruan, Z. Zheng, Hsa_circ_0103809 promotes cell proliferation and inhibits apoptosis in hepatocellular carcinoma by targeting miR-490-5p/SOX2 signaling pathway, Am. J. Transl. Res. 10 (2018) 1690–1702.
[45] D. Chen, C. Zhang, J. Lin, X. Song, H. Wang, Screening differential circular RNA expression profiles reveal that hsa_circ_0128298 is a biomarker in the diagnosis and prognosis of hepatocellular carcinoma, Cancer Manag. Res. 10 (2018) 1275–1283.
[46] W. Guo, J. Zhang, D. Zhang, S. Cao, G. Li, S. Zhang, Z. Wang, P. Wen, H. Yang, X. Shi, J. Pan, H. Ye, Polymorphisms and expression pattern of circular RNA circITCH contributes to the carcinogenesis of hepatocellular carcinoma, Oncotarget 8 (2017) 48169–48177.
[47] L. Qiu, Y. Huang, Z. Li, X. Dong, G. Chen, H. Xu, Y. Zeng, Z. Cai, X. Liu, J. Liu, Circular RNA profiling identifies circADAMTS13 as a miR-484 sponge which suppresses cell proliferation in hepatocellular carcinoma, Mol. Oncol. 13 (2019) 441–455.
[48] C. Song, D. Li, H. Liu, H. Sun, Z. Liu, L. Zhang, Y. Hu, The competing endogenous circular RNA ADAMTS14 suppressed hepatocellular carcinoma progression through regulating microRNA-572/regulator of calcineurin 1, J. Cell. Physiol. 234 (2019) 2460–2470.
[49] L. Zhong, Y. Wang, Y. Cheng, W. Wang, B. Lu, L. Zhu, Y. Ma, Circular RNA circC3P1 suppresses hepatocellular carcinoma growth and metastasis through miR-4641/PCK1 pathway, Biochem. Biophys. Res. Commun. 499 (2018) 1044–1049.
[50] Q. Lin, Y.B. Ling, J.W. Chen, C.R. Zhou, J. Chen, X. Li, M.S. Huang, Circular RNA circCDK13 suppresses cell proliferation, migration and invasion by modulating the JAK/STAT and PI3K/AKT pathways in liver cancer, Int. J. Oncol. 53 (2018) 246–256.
[51] Z. Wang, Y. Zhao, Y. Wang, C. Jin, Circular RNA circHIAT1 inhibits cell growth in hepatocellular carcinoma by regulating miR-3171/PTEN axis, Biomed. Pharmacother. 116 (2019) 108932.
[52] Z. Chen, X. Zuo, L. Pu, Y. Zhang, G. Han, L. Zhang, J. Wu, X. Wang, circLARP4 induces cellular senescence through regulating miR-761/RUNX3/p53/p21 signaling in hepatocellular carcinoma, Cancer Sci. 110 (2019) 568–581.
[53] P. Zhang, C. Wei, X. Huang, R. Peng, X. Yang, J. Lu, C. Zhang, C. Gao, J. Cai, P. Gao, D. Gao, G. Shi, A. Ke, J. Fan, Circular RNA circTRIM33-12 acts as the sponge of microRNA-191 to suppress hepatocellular carcinoma progression, Mol. Cancer 18 (2019) 105.
[54] Z. Yao, J. Luo, K. Hu, J. Lin, H. Huang, Q. Wang, P. Zhang, Z. Xiong, C. He, Z. Huang, B. Liu, Y. Yang, ZKSCAN1 gene and its related circular RNA (circZKSCAN1) both inhibit hepatocellular carcinoma cell growth, migration, and invasion but through different signaling pathways, Mol. Oncol. 11 (2017) 422–437.
[55] X. Li, M. Shen, Circular RNA hsa_circ_103809 suppresses hepatocellular carcinoma proliferation and invasion by sponging miR-620, Eur. Rev. Med. Pharmacol. Sci. 23 (2019) 555–566.
[56] M. Qin, G. Liu, X. Huo, X. Tao, X. Sun, Z. Ge, J. Yang, J. Fan, L. Liu, W. Qin, Hsa_circ_0001649: a circular RNA and potential novel biomarker for hepatocellular carcinoma, Cancer Biomark. 16 (2016) 161–169.
[57] X. Zhang, S. Qiu, P. Luo, H. Zhou, W. Jing, C. Liang, J. Tu, Down-regulation of hsa_circ_0001649 in hepatocellular carcinoma predicts a poor prognosis, Cancer Biomark. 22 (2018) 135–142.
[58] Y. Su, C. Xu, Y. Liu, Y. Hu, H. Wu, Circular RNA hsa_circ_0001649 inhibits hepatocellular carcinoma progression via multiple miRNAs sponge, Aging 11 (2019) 3362–3375 (In press).
[59] L. Fu, S. Wu, T. Yao, Q. Chen, Y. Xie, S. Ying, Z. Chen, B. Xiao, Y. Hu, Decreased expression of hsa_circ_0003570 in hepatocellular carcinoma and its clinical significance, J. Clin. Lab. Anal. 32 (2018) e22239.
[60] L. Fu, T. Yao, Q. Chen, Y.H. X Mo, J. Guo, Screening differential circular RNA expression profiles reveals hsa_circ_0004018 is associated with hepatocellular carcinoma, Oncotarget 8 (2017) 58405–58416.
[61] L, Fu, Q, Chen, T, Yao, T, Li, S, Ying, Y, Hu, J, Guo, Hsa_circ_0005986 inhibits carcinogenesis by acting as a miR-129-5p sponge and is used as a novel biomarker for hepatocellular carcinoma, Oncotarget 8 (2017) 43878–43888.
[62] Q. Weng, M. Chen, M. Li, Y.F. Zheng, G. Shao, W. Fan, X.M. Xu, J. Ji, Global microarray profiling identified hsa_circ_0064428 as a potential immune-associated prognosis biomarker for hepatocellular carcinoma, J. Med. Genet. 56 (2019) 32–38.
[63] K. Zhang, S. Che, Z. Su, S. Zheng, H. Zhang, S. Yang, W. Li, J. Liu, CD90 promotes cell migration, viability and sphereforming ability of hepatocellular carcinoma cells, Int. J. Mol. Med. 41 (2018) 946–954.
[64] T. Yao, Q. Chen, Z. Shao, Z. Song, L. Fu, B. Xiao, Circular RNA 0068669 as a new biomarker for hepatocellular carcinoma metastasis, J. Clin. Lab. Anal. 32 (2018) e22572.
[65] P. Kou, C. Zhang, J. Lin, H. Wang, Circular RNA hsa_circ_0078602 may have potential as a prognostic biomarker for patients with hepatocellular carcinoma, Oncol. Lett. 17 (2019) 2091–2098.
[66] H. Zheng, T. Chen, C. Li, C. Xu, C. Ding, J. Chen, S. Ju, Z. Zhang, Z. Liang, Z. Cui, J. Zhao, A circular RNA hsa_circ_0079929 inhibits tumor growth in hepatocellular carcinoma, Cancer Manag. Res. 11 (2019) 443–454.
[67] L. Yu, X. Gong, L. Sun, Q. Zhou, B. Lu, L. Zhu, The circular RNA Cdr1as act as an oncogene in hepatocellular carcinoma through targeting miR-7 expression, PLoS One 11 (2016) e0158347.
[68] L. Xu, M. Zhang, X. Zheng, P. Yi, C. Lan, M. Xu, The circular RNA ciRS-7 (Cdr1as) acts as a risk factor of hepatic microvascular invasion in hepatocellular carcinoma, J. Cancer Res. Clin. Oncol. 143 (2017) 17–27.
[69] N. Zhang, G. Li, X. Li, L. Xu, M. Chen, Circ5379-6, a circular form of tumor suppressor PPARalpha, participates in the inhibition of hepatocellular carcinoma tumorigenesis and metastasis, Am. J. Transl. Res. 10 (2018) 3493–3503.
[70] L. Shi, P. Yan, Y. Liang, Y. Sun, J. Shen, S. Zhou, H. Lin, X. Liang, X. Cai, Circular RNA expression is suppressed by androgen receptor (AR)-regulated adenosine deaminase that acts on RNA (ADAR1) in human hepatocellular carcinoma, Cell Death Dis. 8 (2017) e3171.
[71] S. Cui, Z. Qian, Y. Chen, L. Li, P. Li, H. Ding, Screening of up- and downregulation of circRNAs in HBV-related hepatocellular carcinoma by microarray, Oncol. Lett. 15 (2018) 423–432.
[72] S. Wang, S. Cui, W. Zhao, Z. Qian, H. Liu, Y. Chen, F. Lv, H.G. Ding, Screening and bioinformatics analysis of circular RNA expression profiles in hepatitis B-related hepatocellular carcinoma, Cancer Biomark. 22 (2018) 631–640.
[73] X. Lin, Y. Chen, Identification of potentially functional circRNA-miRNA-mRNA regulatory network in hepatocellular carcinoma by integrated microarray analysis, Med. Sci. Monit. Basic Res. 24 (2018) 70–78.
[74] D.D. Xiong, Y.W. Dang, P. Lin, D.Y. Wen, R.Q. He, D.Z. Luo, Z.B. Feng, G. Chen, A circRNA-miRNA-mRNA network identification for exploring underlying pathogenesis and therapy strategy of hepatocellular carcinoma, J. Transl. Med. 16 (2018) 220.
[75] E. Juarez-Hernandez, D. Motola-Kuba, N.C. Chavez-Tapia, M. Uribe, V. Barbero Becerra, Biomarkers in hepatocellular carcinoma: an overview, Expert Rev. Gastroenterol. Hepatol. 11 (2017) 549–558.
[76] S.M. Parizadeh, R. Jafarzadeh-Esfehani, M. Ghandehari, F. Goldani, S.M.R. Parizadeh, S.M. Hassanian, M. Ghayour-Mobarhan, G.A. Ferns, A. Avan, MicroRNAs as potential diagnostic and prognostic biomarkers in hepatocellular carcinoma, Curr. Drug Targets (2019) (In press).
[77] L. Qiu, Q. Tang, G. Li, K. Chen, Long non-coding RNAs as biomarkers and therapeutic targets: recent insights into hepatocellular carcinoma, Life Sci. 191 (2017) 273–282.
[78] X. Yang, Q. Xiong, Y. Wu, S. Li, F. Ge, Quantitative proteomics reveals the regulatory networks of circular RNA CDR1as in hepatocellular carcinoma cells, J. Proteome Res. 16 (2017) 3891–3902.
[79] D. Betel, M. Wilson, A. Gabow, D.S. Marks, C. Sander, The microRNA.org resource: targets and expression, Nucleic Acids Res. 36 (2008) D149–D153 Database issue.
[80] B.P. Lewis, C.B. Burge, D.P. Bartel, Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets, Cell 120 (2005) 15–20.
[81] D.B. Dudekula, A.C. Panda, I. Grammatikakis, S. De, K. Abdelmohsen, M. Gorospe, CircInteractome: a web tool for exploring circular RNAs and their interacting proteins and microRNAs, RNA Biol. 13 (2016) 34–42.
[82] J.H. Li, S. Liu, H. Zhou, L.H. Qu, J.H. Yang, starBase v2.0: decoding miRNA-ceRNA, miRNA-ncRNA and protein-RNA interaction networks from large-scale CLIP-Seq data, Nucleic Acids Res. 42 (2014) D92–D97 Database issue.
[83] A. Krek, D. Grun, M.N. Poy, R. Wolf, L. Rosenberg, E.J. Epstein, P. MacMenamin, I. da Piedade, K.C. Gunsalus, M. Stoffel, N. Rajewsky, Combinatorial microRNA target predictions, Nat. Genet. 37 (2005) 495–500.
[84] J. Guarnerio, M. Bezzi, J.C. Jeong, S.V. Paffenholz, K. Berry, M.M. Naldini, F. Lo-Coco, Y. Tay, A.H. Beck, P.P. Pandolfi, Oncogenic role of fusion-circRNAs derived from cancer-associated chromosomal translocations, Cell 165 (2016) 289–302.
[85] S. Tan, D. Sun, W. Pu, Q. Gou, C. Guo, Y. Gong, J. Li, Y.Q. Wei, L. Liu, Y. Zhao, Y. Peng, Circular RNA F-circEA-2a derived from EML4-ALK fusion gene promotes cell migration and invasion in non-small cell lung cancer, Mol. Cancer 17 (2018) 138.

[86] S. Tan, Q. Gou, W. Pu, C. Guo, Y. Yang, K. Wu, Y. Liu, L. Liu, Y.Q. Wei, Y. Peng, Circular RNA F-circEA produced from EML4-ALK fusion gene as a novel liquid biopsy biomarker for non-small cell lung cancer, Cell Res. 28 (2018) 693–695.
[87] I. Jost, L.A. Shalamova, G.K. Gerresheim, M. Niepmann, A. Bindereif, O. Rossbach, Functional sequestration of microRNA-122 from Hepatitis C Virus by circular RNA sponges, RNA Biol. 15 (2018) 1032–1039.
[88] X. Liu, J.M. Abraham, Y. Cheng, Z. Wang, Z. Wang, G. Zhang, H. Ashktorab, D.T. Smoot, R.N. Cole, T.N. Boronina, L.R. DeVine, C.C. Talbot Jr., Z. Liu, S.J. Meltzer, Synthetic circular RNA functions as a miR-21 sponge to suppress gastric carcinoma cell proliferation, Mol. Ther. Nucleic Acids 13 (2018) 312–321.
[89] H. Zhang, X.X. Li, Y. Yang, Y. Zhang, H.Y. Wang, X.F.S. Zheng, Significance and mechanism of androgen receptor overexpression and androgen receptor/mechanistic target of rapamycin cross-talk in hepatocellular carcinoma, Hepatology 67 (2018) 2271–2286.
[90] N. De Maria, M. Manno, E. Villa, Sex hormones and liver cancer, Mol. Cell. Endocrinol. 193 (2002) 59–63.
[91] W.H. Liu, S.H. Yeh, C.C. Lu, S.L. Yu, H.Y. Chen, C.Y. Lin, D.S. Chen, P.J. Chen, MicroRNA-18a prevents estrogen receptor-alpha expression, promoting proliferation of hepatocellular carcinoma cells, Gastroenterology 136 (2009) 683–693.
[92] Z. Kong, X. Wan, Y. Zhang, P. Zhang, Y. Zhang, X. Zhang, X. Qi, H. Wu, J. Huang, Y. Li, Androgen-responsive circular RNA circSMARCA5 is up-regulated and promotes cell proliferation in prostate cancer, Biochem. Biophys. Res. Commun. 493 (2017) 1217–1223.
[93] K. Wang, Y. Sun, W. Tao, X. Fei, C. Chang, Androgen receptor (AR) promotes clear cell renal cell carcinoma (ccRCC) migration and invasion via altering the circHIAT1/miR-195-5p/29c-3p/CDC42 signals, Cancer Lett. 394 (2017) 1–12.