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REVIEW

Roles of circRNAs in the Tumorigenesis and Metastasis of HCC: A Mini Review

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Abstract: Circular RNAs (circRNAs) are a class of non-coding RNAs with loop structures that are stable and widely distributed in different tumor tissues. The development of high-throughput sequencing and in silico tools has enabled the discovery of numerous functional circRNAs. Hepatocellular carcinoma (HCC) is a malignant tumor, and the mechanism involved in its progression has remained unclear. In recent years, an increasing number of circRNAs have been identified in HCC, contributing to tumorigenesis and metastasis and with the potential role as biomarkers through competitive endogenous RNAs (ceRNAs) as miRNA sponges or by interacting with RNA binding proteins (RBPs). In this review, we summarize the regulatory roles of circRNAs in HCC development as well as the use of bioinformatics tools in the annotation and prioritization of circRNA and highlight the participation of exosomal circRNAs in HCC metastasis and drug resistance.

Keywords: circRNAs, HCC, tumorigenesis, metastasis, exosome, biomarker

Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, with an increasing global incidence, and a leading cause of cancer-related mortality.[1] Although hepatitis B and C virus infections, cirrhosis, alcohol intake, and non-alcoholic fatty liver disease (NAFLD) are the main risk factors contributing to HCC.[1,2] Approximately 25% of HCC patients present with potentially actionable mutations; however, this has not been translated into clinical practice.[2] The mechanisms underlying tumorigenesis and metastasis need to be elucidated towards the identification of potential therapeutic approaches and biomarkers. Alpha-fetoprotein (AFP) is the most widely used biomarker of HCC, which has been used for several decades; however, its effectiveness is still far from satisfactory.[3] Owing to the current difficulty in the early diagnosis of HCC and poor prognosis due to the high frequency of metastasis and recurrence, a novel biomarker with high efficiency and cost-efficiency is still required for HCC. Recently, emerging evidence has suggested the crucial role of non-coding RNAs (ncRNAs) in the tumorigenesis and metastasis of HCC through the regulation of *Wnt, STAT3*, and other signaling pathways.[4,5]

Circular RNAs (circRNAs) are loop-structure ncRNA with neither 5' to 3' polarity nor a polyadenylated tail.[6] Compared with linear RNAs, the covalently closed loop structure can protect circRNAs from exonuclease-mediated degradation.[7] CircRNAs were first recognized as a by-product of aberrant splicing events[8] or described as "scrambled exons".[9] The biogenesis of circRNAs is mainly through a non-canonical splicing mechanism called back-splicing, which is regulated by both *cis*-elements and *trans*-factors.[10,11] For advances in high-throughput sequencing and development in bioinformatics, numerous circRNAs that are evolutionarily conserved and in high abundance have been identified in eukaryotes,[12] which enables us to investigate the biological function of circRNAs and the underlying molecular mechanism. Recent studies have elucidated the wide distribution of circRNAs in multi-species[13] and their tissue-[14] or cell-type-[15] specific expression.

CircRNAs can compete for miRNA binding and remove the inhibitory effect of miRNA-targeted mRNA. It has been clarified that circRNAs can perform regulatory functions in tumor development and act as molecular biomarkers in

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colorectal cancer (CRC),[16,17] HCC,[18] glioblastoma (GBM)[19–21] and lung cancer.[22] Several circRNAs are aberrantly expressed in HCC, and hence, they may be potential biomarkers for the diagnosis and prognosis of this disease.[23–26] The circRNA-miRNA-mRNA regulatory axis has been found in many circRNAs in HCC. Recently, exosomal circRNAs that transfer biological functions have shed light on HCC with regard to tumorigenesis, metastasis, and drug resistance. It is necessary to investigate the role of circRNAs in HCC to uncover the underlying mechanism. In addition, the full-length circRNAs identification computational pipelines, as well as the circRNA-related databases, can provide accurate annotation of candidate circRNAs. Herein, we summarize the findings of current research on the involvement of circRNAs in HCC tumorigenesis, metastasis, and drug resistance, and highlight the insights and limitations of current circRNA research in HCC.

Biogenesis and Biological Functions of circRNAs

CircRNAs are mainly derived from protein-coding genes, consisting mainly of exonic circRNAs (EcircRNAs). Circular intronic RNAs (ciRNAs) and exon-intron circRNAs (EIcircRNAs) also exist as small subtypes of circRNAs. Compared with their linear counterparts, circRNAs were derived from canonical splice sites in the back-splicing manner[7,27] by pairing the inverted repeat element in the flanking intronic regions or the interaction of *trans*-acting RNA binding proteins (RBPs). For example, the RNA-binding protein RBM3[28] can promote cell proliferation in HCC by the regulation of circRNA production. In addition, the intermediate lariat precursors that escape from debranching in exon-skipping[29] or intron cleavage[30] processes can also generate circRNAs. Most circRNAs are exported to the cytoplasm, while ciRNAs and EIcircRNAs are predominantly located in the nucleus and regulate the transcription of their parental genes.[30,31] For EcircRNAs, by harbor of miRNA binding sites, they can act as ceRNAs to participate in the regulation of miRNA target mRNA,[27,32] the most well-studied circRNA is Cdr1as. In addition to functioning as a miRNA sponge, the interaction with proteins is also a general mechanism associated with the regulatory roles of circRNAs in different biological processes. For example, Circ-Foxo3 acts as a protein scaffold to promote MDM2-dependent p53 ubiquitination and induce apoptosis in cancer cells.[33] Although circRNAs are considered to be non-coding for the lack of necessary elements for cap-dependent translation, the finding of the internal ribosome entry site (IRES) enables the coding ability of circRNA,[34,35] and the novel open reading frame (ORF) provides a novel circRNA-derived peptide sequence differing from its linear counterpart and has a potential regulatory role in biological processes. The translation of circRNAs may occur under certain conditions, such as cellular responses to environmental stress.[34]

CircRNAs in HCC

Recent studies have revealed the critical role of circRNAs in HCC with regard to tumorigenesis, metastasis, and drug resistance, which is mediated by their ability to act as miRNA sponges or interact with proteins. Based on their functional role in tumor progression, we categorized circRNAs into suppressors and promoters. Plasma exosomal circRNAs also show potential as diagnostic and prognostic biomarkers of HCC.[36,37] In the tumor microenvironment, exosomal circRNAs also mediate the crosstalk between normal and cancer cells to regulate HCC metastasis.[36,38] These results suggest that circRNAs should not be ignored as competitive regulators in HCC.

Promoter Role of circRNA in HCC

Many differentially expressed circRNAs have been identified in HCC, and some show promoter roles by being upregulated in HCC cells or tissues.[24,39] The most characterized circRNA Cdr1as is also found in HCC[25,40] and regulates cell proliferation and migration to promote tumorigenesis in the ceRNA manner.[1] In addition, high-risk factors for HCC, such as hepatitis B, obesity, and hypoxia, are also associated with some circRNAs.[41–43] Association with organ-specific metastasis has also been found in HCC-related circRNAs. CircASAP1 promotes HCC lung metastasis and progression and mediates tumor-associated macrophage infiltration by regulating miR326/miR-532-5p-CSF-1 signaling.[39]

The main regulatory modes, which include ceRNA as miRNA sponge, interaction with RBPs, and circRNA-derived peptides, are all present in HCC tumorigenesis. The highly expressed circRHOT1 can promote HCC development by interaction with TIP60 to regulate NR2F6 expression, which was found correlated with HCC patients' prognosis as well.[24] Peptides derived from circβ-catenin can stabilize full-length β-catenin by antagonizing

GSK3β-induced phosphorylation and degradation of β-catenin, leading to the activation of the Wnt pathway.[44] Moreover, has_circ_104348 also participates in the activation of the Wnt/β-catenin pathway and is related to HCC lung metastasis.[45] In drug resistance studies, circRNA can also act as promoter role. The upregulated level of circRNA-SORE was found to be modulated by N6-methyladenosine (m6A) in sorafenib-resistant cells and activated the Wnt/β-catenin pathway by acting as miRNA sponges of miR-103a-2-5p and miR-660-3p.[46] Many studies have shown that m6A plays a vital role in the regulation of RNA metabolism,[47] and it can participate in the modulation of circRNA translation efficiency.[34,35,48] Both of these show the complexity of circRNA regulatory mechanism.

Suppressor Role of circRNA in HCC

Some significantly downregulated circRNAs have also been reported in HCC with poor prognosis.[49,50] CircSETD3 (hsa_circ_0000567) was downregulated in HCC, and it inhibited tumor growth through the circSETD3/miR-421/MAPK14 pathway.[51] For the ZKSCAN1 gene and the circular isoform, circZKSCAN1 was downregulated in HCC tissues and cells, but with different downstream regulated genes.[18] The modulation of RBPs for the production of suppressor circRNAs is also important in HCC. The biogenesis of circular RNA cSMARCA5 from pre-mRNA of SMARCA5 (pSMARCA5) was modulated by DHX9 in HCC, but the mRNA and protein levels of SMARCA5 were upregulated due to the high expression of pSMARCA5.[50] This showed that, in comparison to their linear counterparts, circRNAs have independent biogenesis and functions. CircRNA_101505 was decreased in cisplatin-resistant HCC tissues and cells and associated with poor prognosis,[52] which shows suppressor circRNAs could be involved in drug resistance.

CircZKSCAN1 regulates cell stemness in HCC by competing against FMRP and blocking the binding between FMRP and CCAR1, thereby deactivating the Wnt/β-catenin signaling pathway.[53] It also identified that a decrease in QKI5 can cause a reduction in the level of circZKSCAN1, which provides a novel insight into the complexity of the regulatory role of circRNAs in HCC. The downregulation of circ-0051443 in plasma exosomes from HCC patients also shows its suppressor role in tumorigenesis and suggests that it may be a potential biomarker for HCC.[36] Some downregulated circRNAs with the UGUA motif were modulated by NUDT21,[54] and the decreased circRNAs contributed to tumorigenesis in HCC. Another study focused on the modulation of circRNA expression in HCC and showed that high expression of CPSF4 can reduce circRNA expression by recognizing the polyadenylation site and the inhibition of circRNA/miRNA pathway was associated with poor prognosis.[55] These studies on the regulatory mechanism of circRNA biogenesis may elucidate HCC tumorigenesis and make cancer-associated circRNAs promising candidates as potential therapeutic targets.

Exosomal circRNA-Mediated Metastasis and Drug Resistance in HCC

Exosomes are extracellular vesicles (100 nm in diameter) that play critical roles in the TME. Cell proliferation, migration, invasion, angiogenesis, metastasis, and drug resistance are regulated by exosomes. Recent studies have found the expression of functional circRNAs in HCC cells/tissue-derived exosomes[36–38,56,57] (Table 1). Paracrine secretion gives exosomes the ability to transfer compounds to alter the biological functions of recipient cells. In this manner, exosomal circRNAs are involved in the TME, including in the promotion and suppression of tumorigenesis, metastasis, immune response, and drug resistance. Some serum exosomal circRNAs also have potential as biomarkers for prognosis and tumor monitoring.

Several stable and highly expressed exosomal circRNAs, such as circANTXR1,[58] and in vitro assays showed that silencing circANTXR1 inhibited the proliferation, migration, and invasion of HCC cells through the circANTXR1/miR-532-5p/XRCC5 regulatory axis. A higher expression of circANTXR1 was detected in highly metastatic cells, compared with that in low metastasis or normal cells. Recently, exosomal circRNA-DB[42] was identified in adipocytes, which provided insight into the mechanism of obesity as a risk factor for HCC. Adipocyte-derived circRNA-DB bound to miR-41a and activated the USP7/cyclin-A2 pathway both in vivo and in vitro. siRNA can reverse the promotion of tumor growth and inhibition of DNA damage induced by circRNA-DB.

Exosome-mediated drug resistance was observed with sorafenib as the first-line treatment for unresectable HCC. CircRNA-SORE is highly expressed in sorafenib-resistant HCC cells.[57] Silencing of YBX1, the binding partner of

Table 1 Dysregulated Exosomal circRNAs in HCC

Ref	CircRNA Name	Parental Gene	Expression in HCC	Regulatory Axis	Function	Sample Sources	Year
[56]	circPTGR1	PTGR1	Upregulated	miR449a/ MET	Increasing migratory and invasion and metastasis, potential prognosis biomarker	HepG2, 97L, LM3; serum from HCC patients	2019
[42]	circ-DB	TNFRSF1A	Upregulated	miR-34a/ USP7	Promoting tumor growth and reducing DNA damage	HepG2, Hepa 1–6, 3T3L1; HCC tissue	2018
[36]	hsa_circ_0051443	TRAPPC6A	Downregulated	miR-331-3p/ BAK1	Suppressing HCC progression, promoting cell apoptosis and arresting the cell cycle, diagnosis biomarker of HCC	HL-7702, HuH7, Hep3b; plasma samples from HCC patients and health control, tissue and adjacent from HCC patients	2020
[38]	circRNA-100338	SNX27	Upregulated	Not provide	Enhancing invasiveness and angiogenesis, promoting metastasis, as a risk indicator of pulmonary metastasis and poor survival.	L02, Hep3B, HLE, Huh7, BEL7402, SMCC7721, MHCC97L, MHCC97H, HCCLM3 and HCCLM6, HUVECs; HCC tissues, lung metastatic nodules or pulmonary puncture specimens, plasma exosomes	2020
[71]	circFBLIM1	FBLIM1	Upregulated	miR-338/ LRP6	Promoting HCC progression and glycolysis	THLE-2, SNU-387, Huh7; serum from HCC patients and healthy control	2020
[57]	circRNA-SORE	TLE4	Upregulated	YBX1	Mediating sorafenib resistance in HCC	HepG2-SR, LM3-SR, and SKhep1-SR; Tissue samples and blood samples from HCC patients	2020
[37]	circUHRF1	UHRF1	Upregulated	miR-449c-5p/ TIM-3	Contributing to immunosuppression by inducing NK cell dysfunction in HCC, casuing resistance to anti-PD1 immunotherapy	HepG2, HCCLM3, SMMC- 7721, Huh 7, PLC/PRF/5, and Hep3B; serum of HCC patients	2020
[72]	circTMEM45A	TMEM45A	Upregulated	miR-665/ IGF2	Promoting cell mobility in vitro, as well as in vivo tumorigenesis, acting as a diagnosis biomarker	L02, Hep3B, HLE, Huh7, BEL7402, SMCC7721, MHCC97L, MHCC97H, HCCLM3, HCCLM6; HCC tissues and adjacent normal tissues	2020
[58]	circANTXR1	ANTXR1	Upregulated	miR-532-5p/ XRCC5	Promoting the proliferation, migration and invasion of HCC cells	HuH-7, HCCLM3, THLE-2; Peripheral blood, tumor tissues and normal tissues from HCC patients	2021
[25]	Cdr1as	CDR1-AS	Upregulated	miR-1270/ AFP	Promoting proliferative and migratory	SMMC-7721, Bel-7402, HepG2, Hep3B, Huh-7, HB611; HCC tissues and the matched para-carcinoma tissues from HCC patients	2019
[61]	circAKT3	AKT3	Upregulated	Not provide	Associating with a higher risk of HCC recurrence and mortality	Serum samples from HCC patients and healthy control	2020

circRNA-SORE, could attenuate sorafenib resistance. The transportation of exosomal circRNA-SORE can spread drug resistance in HCC cells. Through the circPTGR1-miR-449a-MET axis, exosomal circPTGR1 from highly metastatic HCC cell lines can enhance the migratory and invasive abilities of low metastatic HCC cell lines,[56] which makes it a potential biomarker for monitoring HCC tumor progression. These studies showed that exosomal circRNAs could be novel biomarkers for diagnosis and predicting the recurrence and therapeutic strategy of HCC.

Diagnostic and Therapeutic Potentials of circRNA in HCC

As already mentioned, the tissue-specific expression and highly stable loop structure suggest that circRNA may function as a biomarker. Some particular circRNAs may have high accuracy in diagnosis and prognosis through receiver operating characteristic (ROC) curve analysis. Recent studies have also revealed a correlation between circRNA expression and clinical characteristics, such as tumor size, TNM stage, and overall survival.[24,45] The expression of has_circ_0005075 is higher in HCC tissues than in adjacent tissues. Validation in 60 samples (30 HCC tissues and 30 normal tissues) showed an association between tumor size ($p = 0.042$) and AUC = 0.94, suggesting its potential role as a biomarker.[59] Compared with the traditional biomarkers AFP and carcinoembryonic antigen (CEA), exo_circ_0006602 has a better AUC. The combination of exo_circ_0006602 and serum AFP can improve the accuracy of HCC diagnosis.[60] However, these circRNAs still require large sample sizes and the inclusion of different HCC subtypes for validation.

Compared with tissue samples, the liquid biopsy is largely non-invasive, and circRNAs enriched in can be ideal biomarkers. For example, exosomal circANTXR1 is associated with the clinical features (TNM stage and tumor size) and poor prognosis in HCC patients, and the inhibition of HCC progression mediated by circANTXR1/miR-532-5p/XRCC5 axis may be an effective strategy for treatment.[58] And for the association between high expression of exosomal circAKT3 and worse prognosis,[61] circAKT3 could be the monitoring biomarker to detect recurrence earlier.

Besides the difficulty in the early diagnosis of HCC, the drug resistance and the lack of therapeutic targets also contribute to the poor prognosis of HCC patients. CircRNA-SORE, which was up regulated in sorafenib-resistant cells, promoted sorafenib resistance by activating the Wnt/β-catenin pathway.[46] Some suppressor circRNAs, such as circRNA_101505, are also related to drug resistance. CircRNA_101505 was decreased in cisplatin-resistant HCC tissues and cells and could sensitize HCC cells to cisplatin by miR-103/NOR1 signaling axis.[52] These findings make circRNAs potential targets for clinical intervention in advanced HCC patients.

It has also been reported that decreased circRNAs are involved in the tumor microenvironment (TME). Through the miR-6852-3p/ICAM-1 axis, has_circ_0007456 can regulate the susceptibility of HCC to natural killer (NK) cells, which is associated with poor prognosis.[62] And NK cell dysfunction induced by exosomal circUHRF1 could drive the resistance to anti-PD1 immunotherapy in HCC patients. Both of these suggested new clues in clinical applications of HCC immunotherapy.

Bioinformatics Facilitating the Discovery and Annotation of circRNAs in HCC

The identification, quantification, and proper annotation of circRNAs are associated with some challenges. The use of bioinformatics as a powerful in silico tool was launched in the 2010s. RNA-seq is used as the main technology for sequencing, which has led to the discovery of thousands of circRNAs across different tissues and species. In addition to RNA-seq, microarray is efficient and sensitive for the detection of known circRNAs and less expensive.[63] Although not suitable for the detection of novel circRNAs, it is useful in circRNA profiling.[49] Meanwhile, the advance in bioinformatics approaches is also essential for the detection of low-abundance circRNAs and exploration of the internal structure of circRNAs. Therefore, we have summarized some algorithms and databases that facilitate the discovery and annotation of circRNAs.

Algorithms Based on Long-Read Sequencing Reveal the Full-Length circRNAs

By utilizing reverse transcription and rolling circle amplification (RCA) to increase the abundance of circRNA, the full-length sequence of circRNA can be detected by two algorithms called CIRI-long[64] and isoCirc.[65]

With the long-read sequencing technology, Oxford Nanopore, combined with the calling of cyclic consensus sequence or consensus sequences, the full-length and isoforms of circRNA were accurately characterized.[64,65] Validation from both simulated datasets and Illumina RNA-seq data proved the reliability of this method.[64] Interestingly, intronic self-ligated circRNAs derived from the lariat intron during intron cleavage were identified with non-canonical flanking splicing signals of GT/AG,[64] which show that CIRI-long will be helpful in studies related to the biogenesis and function of circRNA. Similarly, EIcircRNAs were identified by isoCirc, which is difficult to detect by short-read sequencing.[65] In the isoCirc long-read datasets, alternative splicing events were also identified for the full-length circRNA reconstruction ability of isoCirc.

Accurate quantification of circRNAs was also with challenges. CIRIquant was developed as a novel algorithm for the accurate quantification of circRNAs and one-stop differential expression analysis.[66] For the construction of pseudo-circular reference to re-align RNA-seq reads and the process to correct RNase R treatment biases, there has been advancement in circRNA quantification among current tools. In HCC patient samples, linear-circular isoform switching (LC-switching) and circular transcript usage switching (CTU-switching) circRNAs were found, which provide novel insights into the biogenesis of circRNAs.

CircRNA Related Databases and Regulatory Network Prediction

In parallel with the development of bioinformatics tools. The circRNA-related databases also facilitate a better understanding of circRNAs. For example, CircAtlas is an integrated database, with 1070 samples across six vertebrate species and provides full-length sequences of 81.3% circRNAs. The cross-species and different tissues and different cell lines

Table 2 CircRNA-Related Databases

Ref	Database Name	Url	Description	Lasted Update Time	Note
[73]	circBase	http://www.circbase.org/	Multiple species circRNAs with putative sequence	Jul-2017	
[13]	CircAtlas	http://circatlas.biols.ac.cn/	Large sample size based circRNA database across six vertebrate species	Mar-2020	
[74]	circRNADb	http://reprod.njmu.edu.cn/circrnadb	Database with protein-coding annotations	Oct-2016	
[75]	circBank	http://www.circbank.cn/	Human annotated circRNAs from different source	Apr-2019	
[76]	ENCORI	https://starbase.sysu.edu.cn/	Comprehensive RNA interactome database, previously called starBase	2020	
[77]	exoRBase	http://www.exorbase.org/	Extracellular vesicles (EVs) derived long RNAs based annotation	Nov-2021	
[78]	CSCD	http://gb.whu.edu.cn/CSCD	Cancer-specific circRNAs	Jan-2018	
[79]	CircInteractome	https://circinteractome.nia.nih.gov/	circRNA interactome database	Jan-2020	
[80]	CIRCpedia	https://picb.ac.cn/rnomics/circpedia/	Comprehensive circRNA annotation from over 180 RNA-seq datasets across six different species	Aug-2018	
[81]	MiOncoCirc	https://mioncocirc.github.io/	Extensive clinical, cancer-centric resource of circRNAs.	Feb-2019	
[14]	TSCD	http://gb.whu.edu.cn/TSCD	Comprehensive view of TS circRNAs in human and mouse	Nov-2017	
[82]	DeepBase	http://rna.sysu.edu.cn/deepbase3/index.html	Interactive display and analysis of the expression, evolution, and functions of various ncRNAs by deeply mining thousands of high-throughput sequencing data from tissue, tumor and exosome samples	Nov-2020	
[83]	CircFunBase	http://bis.zju.edu.cn/CircFunBase/	Functional circRNA database with visualization of circRNA-miRNA interaction networks	Oct-2019	
[84]	CircNet	https://awi.cuhk.edu.cn/~CircNet	An updated database for exploring circular RNA regulatory networks in cancers	Nov-2021	

(*Continued*)

Table 2 (Continued).

Ref	Database Name	Url	Description	Lasted Update Time	Note
[85]	Circ2Traits	http://gyanxet-beta.com/circdb/	Comprehensive knowledgebase of potential association of circular RNAs with diseases in human	Dec-2013	NA
[86]	CircR2Disease	http://bioinfo.snnu.edu.cn/CircR2Disease/	A comprehensive resource for circRNA deregulation in various diseases	May-2018	NA

Abbreviation: NA, not accessible.

also enable a more accurate determination of the conservation score[13] and exploration of expression patterns. Recent databases related to circRNAs are listed in Table 2.

Several circRNA-miRNA-mRNA regulatory networks have also been identified in HCC through the analysis of related samples from Gene Expression Omnibus (GEO) or The Cancer Genome Atlas (TCGA) to obtain the critical circRNAs involved in pathogenesis or as therapeutic targets.[67–69] These predictions show the potential mechanisms and pathways associated with the pathogenesis of HCC, but further validation is necessary.

Limitations in circRNA-Related Databases and Functional Annotation

The existing databases have some limitations: the limited overlap, the different updating conditions and availability of access, and the different naming systems cause ambiguous nomenclature of circRNA.[70] Moreover, some challenges may be encountered with the use of in silico data without experimental validation for candidate circRNA screening. Therefore, the selection of candidate circRNAs with experimental validation or the well-studied circRNAs in the different databases will prevent some issues in the investigation of circRNAs.

Conclusion and Perspectives

CircRNAs have been detected in different tumor tissues. The dysregulated expression of circRNAs in HCC shows their potential as a biomarker and their involvement in tumorigenesis and metastasis. Many HCC studies have demonstrated that circRNAs can act as a suppressor or promoter, mediated by ceRNA mechanism or interaction with RBPs. Peptides encoded by circRNAs are also involved in HCC progression. But, the regulatory mechanism of circRNA biogenesis and its downstream effect are still not clearly understood. And it is critical to all cancer types. With the development of in silico tools, we can obtain the full-length sequences of circRNAs, and the different circRNA databases can provide us with detailed annotations. But, the inclusion criteria of circRNAs differs between databases, the in silico predictions need experimental validation. And different nomenclature systems between databases still cause some confusion.

Currently, HCC is usually diagnosed at the late stage, and it is associated with high metastasis and drug resistance; hence, the prognosis is poor. Several circRNAs have shown high accuracy in the diagnosis of HCC, although validation is required with a larger sample size before clinical application. And the accuracy of circRNA quantification still needs improvement before clinical application. The recent studies elucidate the involvement of exosomal circRNAs in drug resistance and HCC development, which shows the potential of a novel therapeutic strategy for HCC and a monitoring biomarker for metastasis. We believe the growing findings of circRNA research in HCC will give us more insight into the initiation and development of HCC, which could facilitate the development of effective therapy.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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