Circular RNA in Hepatitis

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Abstract

Circular RNAs (circRNAs) are a newly validated type of noncoding RNAs recently found to be deregulated in several human cancers(1). circRNA is a type of endogenous RNA that serve a crucial role in disease development and aberrantly express in a number of types of cancer(2). In the eukaryotic transcriptome, the evolutionary conserved circular RNAs naturally occur from the family of noncoding RNAs. Circular RNAs possess a unique feature to interact with nucleic acids and ribonucleoproteins and are establishing themselves as an obligatory composition for the regulatory messages which are In the eukaryotic transcriptome, the evolutionary conserved circular RNAs naturally occur from the family of noncoding RNAs. Circular RNAs possess a unique feature to interact with nucleic acids and ribonucleoproteins and are establishing themselves as an obligatory composition for the regulatory messages which are encoded by the genome. The back-splicing mechanism leads to the formation of circularized RNA, and because of this they become resistant to exonuclease-mediated degradation. The differential and aberrant expression of circular RNAs can be detected with the help of various profling methods by using serum, plasma, and tissue samples(3) Circular RNAs (circRNAs) were recently described as a novel class of cellular RNAs. Due to their elevated stability in comparison to linear RNA, circRNAs may be an interesting tool inmolecular medicine and biology(4) Circular RNAs (circRNAs) represent a class of endogenous noncoding RNAs that have recently been recognized as important regulators of gene expression and pathological networks. However, their transcriptional activities and functional mechanisms in cancer remain largely unknown (5). Circular RNAs (circRNAs) have been reported as effective diagnostic and therapeutic biomarkers in many diseases, but the potential of using this easy‐to monitor and highly stable materials for diagnosing Community‐acquired pneumonia (CAP) remains unexplored (6). More accurate and specific noninvasive biomarkers are strongly needed for better diagnosis and prognosis of hepatocellular carcinoma (HCC). Hepatocellular carcinoma (HCC), one of the most common type of cancers, is highly refractory to most systemic therapies. Understanding the genomic dysregulations, in particularly non-coding RNA (ncRNA) dysregulations, in HCC may provide novel strategies to HCC treatment(7). Circular RNAs (circRNAs) have been emerged as an indispensable part of endogenous RNA network. However, the expression significance of circRNAs inhepatocellular carcinoma (HCC) is rarely revealed. The global circRNA expression profile in HCC was measured by circRNA microarray(8). Hepatitis is a kind of liver dysfunction and usually refers to a variety of pathogenic factors. Circular RNA (circRNA) participates in diverse diseases(9). Alcoholic hepatitis (AH) is a widely prevalent liver-related disease that results from long-term alcohol consumption. However, there is still a lack of eﬀective treatment. Previous studies have reported that circular RNAs (circRNAs) are related to the development of various diseases (10). Circular RNAs (circRNAs) play an important role in pathogenesis and development of hepatocellular carcinoma (HCC) (11) Hepatocellular carcinoma (HCC)is the leading cause of cancer-related deaths worldwide. Despite advances in the diagnosis and treatment of HCC, incidence, and mortality continue to rise. For accurate diagnosis and treatment of HCC, there is an urgent need to precisely understand the molecular mechanisms underlying HCC tumorigenesis and progression. Accumulating evidence showed that circRNAs , which are normally produced by scrambling of exons at the splicing process, are recognized as a novel class of endogenous noncoding RNA, which have microRNA sponging properties (12). To explore whether plasma circular RNAs (circRNAs) can diagnose hepatitis B virus (HBV)-related hepatocellular carcinoma(HCC), microarray and qPCR were used to identify plasma circRNAs that were increased in HBV-related HCC patients compared to controls (including healthy controls, chronic hepatitis B and HBV-related liver cirrhosis)(13). Circular RNAs (circRNAs), often dysregulated in a variety of human diseases, participate in the initiation and development of cancers. Recently, circMTO1 (a circRNA derived from *MTO1* gene), identified as a tumor suppressor, has been shown to contribute to the suppression of hepatocellular carcinoma. The present study aimed to explore the clinical significance and roles of circMTO1 in liver fibrosis. Data from RNA pull‐down assay further confirmed that circMTO1 interacted with miR‐17‐5p. The inhibitory effects of circMTO1 on HSC ativation were suppressed by miR‐17‐5p mimics. Further studies showed that Smad7 was a target of miR‐17‐5p. Moreover, circMTO1‐inhibited HSC activation was also blocked down by loss of Smad7.(14) Until recently, little has been known about the expression, regulation, and biological function of circRNAs in both health and chronic hepatitis B (CHB)(15).

Introduction

The role of circular RNA is still unclear, but some circular RNA play a major character in gene regulation as well as in pathophysiological processes by conducting itself as miRNA sponge, exporter of RNA, and binding protein molecules. they also play a key role in the normal homeostasis, for example, in regulation and control of cell cycle, development of embryo, regulation of metabolic activities, and stress condition of cell. Maintenance of conventional homeostasis is very important for normal functioning of living organisms(6). The circumstances under which circular RNAs are formed are quite different from those of the linear ones because circular RNAs form a covalent closed-loop for circularization, and it is possible because they lack 5′ (cap) and 3′ (polyadenylation) end. Due to the circularization process, they possess resistance to exonuclease-mediated degradation. The unique feature makes the circular RNA highly stable and allows its interaction to many molecules including miRNAs (miRNA sponges) and spliceosomes complex (RNAprotein complex) which further helps in the transcription process. The splicing mechanism of circular RNA is mediated by alternative and back-splicing of primary mRNA which leads to the formation of circular RNA in which the exon part gets shuffed and forms different protein products. In back-splicing, the donor splice site is joined to acceptor splice site which exists at the upstream region and forms circRNAs as product, whereas in case of normal splicing, the donor splice site is usually joined to downstream acceptor splice site. Most of the circRNAs can be procured from exonic or intronic forms, as well as from 5′-3′ untranslated regions. The difference between the exonic and intronic circRNAs is that the former one connects the exons and forms truncated but functional protein products, whereas the intronic circRNAs formed by the joining of introns is meagre in eukaryotes. During the intronic splicing, the lariat structure formed is different from exonic splicing because of the formation of 2′-5′ carbon linkage at the splicing junction. Later on, it was observed that the lariat structure formed from intronic RNAs is very stable and possesses the properties to degrade the 3′ appendages and leave the remains behind. This devised lariat products are known as circular intronic RNAs, while the RNAs which exhibit 3′-5′ junctions are known as circular exonic RNAs(3).

In 1979, circRNAs were primarily observed in mammalian cells with the help of electron microscopy. Further, the presence of circRNA was reported in yeast and viroid viruses, but till date, there are very few circular RNAs reported for humans. In the 1990s, the circRNAs were frst identifed from DCC transcript study in human cells. The circular RNAs were frst experiential in Sry gene of mouse adult testis. This gene plays a vital role in the sex determination of embryo. Many experimental assays were performed including RT-PCR and RNAase protection assays to confrm the presence of circular RNA, and it was concluded that the circular RNAs were highly profuse in testis. These circulars are RNAs differentially expressed at the time of infection or disease. This distinctive characteristic of circular RNA makes them unique and can be used as potential biomarker for the evaluation of human diseases or infections. The high stability and expression of circular RNAs in blood or other body fuids make them unique biomarkers. Many clinical trials have been conducted to identify the role of remarkable circular RNAs in various disease forms, from the clinical serum samples(3). In many diseased conditions including cardiovascular diseases, neurological disorders, cancer, and infectious diseases, the differential expression of circRNAs has been observed. For instance, ciRS-7 in Alzheimer’s disease was seen to be upregulated which helps in the degradation of amyloid peptides. Secondly, it was observed that the circular RNAs are lavishly present in the heart tissues. During the clinical trials, it was identifed that the patients who suffered from ischemia disease had upregulated hsa\_circ\_0124644 in comparison to healthy individuals. In case of gastric cancer condition, has\_circ\_0001649 gets downregulated in the serum and tumor tissue samples and is responsible for the development of metastasis and consequently can be used as noninvasive prognostic biomarker. Further, in hepatocellular carcinoma circRNA, hsacirc\_0001649 is downregulated as the tumorigenic condition intensifes. The infectious hepatitis B and cancerous hepatocellular carcinoma (HCC) are interrelated to each other. The circRNA\_100338 regulates the expression levels of miR-141-3p which is a disease-relevant miRNA and proliferates the metastasis condition. Thus, the overall differential and tissue-specifc expression of circular RNAs in diseased as well as normal condition makes them conventional biomarkers for the diagnosis and prognosis purpose(3). Circular RNAs (circRNAs) have recently been discovered as a large class of ubiquitously expressed, tissue-specific, mainly noncoding RNA. They are produced by the canonical splicing machinery by a process termed “backsplicing”, where a donor splice site is spliced to an upstream instead of a downstream acceptor site. They are mostly located in the cytoplasm and appear to be generally more stable than linear RNA due to their resistance to exonucleolytic degradation .The first described function for cellular circRNAs was serving as microRNA (miRNA) sponges. Two circRNAs, CDR1as/ciRS-7 and SRY, were found to contain highly conserved binding sites for miRNA-7 or miRNA-138, respectively .CDR1as/ciRS-7 is highly expressed in brain and functionally suppresses miRNA-7 activity, thereby de-repressing natural miRNA-7 targets. Recently it was shown that CDR1as/ciRS-7 is essential for normal brain function, and knockout caused dysfunctional synaptic transmission in mice .miRNA-122 was therefore already utilized as a drug target in anti-HCV therapy. The first antimiR-drug Miravirsen was successfully tested in phase II clinical trials .Miravirsen

is a locked-nucleic-acid (LNA)/DNA-mixmer oligonucleotide that is complementary to miRNA-122, and

tightly binds and functionally sequesters the miRNA. In patients, virus titers were decreased to non-detectable levels after four weeks of subcutaneous administration .Recently a second anti-miRNA-122 drug was clinically tested. RG-101, an N-acetylgalactosamine-conjugated antimiRNA-122 oligonucleotide substantially reduced viral load in combination with direct-acting antiviral drugs (4).

Globally, hepatocellular carcinoma (HCC) is the most common type of hepatic malignancies, accounting for approximately 90% of primary liver cancer. It ranks as the second most significant cause of cancer-related deaths in men, 50% of the cases and deaths occurred in China .It is disappointing that most HCC patients were diagnosed at advanced stages with metastasis, missing the best opportunity for curative therapy, such as resection, transplantation or ablation .The early diagnosis is urgent for prognosis of HCC.The risk of HCC increases with liver fibrosis stages .Many studies revealed that the intimate relationship between cirrhosis and HCC .In general, anyone with cirrhosis should be screened for HCC .In recent years, circular RNAs (circRNAs) have emerged as a new star in noncoding RNA (ncRNA) world, representing a class of endogenous RNAs existing in mammalian cells and featuring stable structure and high cell-type-specific, tissue-specific and developmental-specific expression.By interacting with microRNAs (miRNAs) or other molecules, circRNAs regulate gene expression at the transcriptional or post-transcriptional level .Compared to linear RNAs, circRNAs have the outstanding feature of non-canonical splicing without a free 3’ and 5’end, which enables them to resist RNA exonucleases .As a result, they might be suitable as potential biomarkers and targets for novel therapeutic approaches for human diseases. Recently, researchers have found that circRNAs are linked to several cancers, such as gastric cancer, colorectal cancer, HCC, pancreatic ductal adenocarcinoma and ovarian cancer(8). Circular RNAs (circRNAs) ,widely expressed in tissue and developmental-stage speciﬁc patterns that regulate gene expression in mammals. CircRNAs are a novel class of widespread and diverse endogenous RNAs characterized by the presence of a covalent bond linking the 30 and 50 ends generated by back splicing. The majority of circRNAs are conserved across species, are stable, and are resistant to RNase . Functional circRNAs have been shown to act as cytoplasmic microRNA (miRNA) sponges and RNA binding protein sequestering agents as well as nuclear transcriptional regulators, illustrating the relevance of circRNAs as participants in the regulatory networks governing gene expression . MicroRNAs (miRNAs), a class of small (18–24 nucleotides) noncoding RNAs, which regulated target mRNA at post transcriptional level . A large number of experimental results exhibited that miRNAs involved in a number of critical biological processes, such as: cell development, differentiation and apoptosis . CircRNA may also serve as a novel potential biomarker for HCC diagnosis and prognosis . Chronic hepatitis B virus (HBV) infection is a dominant risk factor in the pathogenesis of hepatocellular carcinoma (HCC) . HBV carcinogenesis through integrating into the host genome, leading to the widespread instability . Aberrant expression of genes, which can involve RNA, is a key node for the occurrence and development of HCC. However, the hepatic expression of circRNAs in HCC tissues remains fully unknown(11). Community‐acquired pneumonia (CAP) is one of the most common infectious diseases globally and is a widespread and ever‐present public health threat. Despite ongoing advances in the development of effective new treatments for CAP, this disease still causes great mortality and morbidity, particularly among sensitive populations like the elderly. There are a variety of limitations in current practice for the diagnosis, pathogen detection, evaluation, and prediction of CAP, and there have been multiple biomarkers reported for CAP diagnosis to date. Nevertheless, the sensitivity, specificity convenience, and diagnostic performance of these various biomarkers—variously including metabolic products and mRNA profiles, among others—are problematically variable or cumbersome and are largely insufficient for widespread deployment in public health contexts. Therefore, the development of diagnostic biomarkers for CAP that are simultaneously highly sensitive and convenient would be highly welcomed (6). Hepatocellular carcinoma (HCC) is the leading cause of cancer related deaths worldwide . Despite advances in the diagnosis and treatment of HCC, incidence and mortality continue to rise. For accurate diagnosis and treatment of HCC, there is an urgent need to precisely understand the molecular mechanisms underlying HCC tumorigenesis and progression. Currently, alpha fetoprotein (AFP) is widely used clinical biomarker for HCC diagnosis, while its sensitivity is only about 60% . Recently, sorafenib is approved as one of the few available targeted drugs recommended by deﬁnitive guides in clinical practice , for advanced HCC, however, it is still limited in improving the overall survival of HCC patients .In addition, other targeted drugs, such as sunitinib , brivanib , and everolimus , have been tested in clinical trials in the late years, but all failed in the third phase . It is well-recognized that HCC is a heterogeneous disease of complicated etiology due to acquired gene mutations , epigenetic alterations , and dysregulation of coding or noncoding genes . For example, TERT promoter (54–60%), p53 (12–48%), β-catenin (11–37%), and Axin (5–15%) , have been identiﬁed as recurrently mutated genes in HCC. Moreover, DNA methylation proﬁle of HCC revealed that MMP2, MMP9, and MMP12 were hypo-methylated in liver cancer using pyrosequencing . In addition ,non-coding RNAs ,such as long non-coding RNA (lncRNA) and microRNA (miRNA), have been widely recognized to contribute to HCC . Particularly, the long non-coding RNAs could provide signals of malignant transformation by interacting with chromatin, proteins and RNAs (12) .Alcoholic hepatitis (AH) is a common type of liver injury with high morbidity that results from chronic alcohol abuse. Although the interaction between the direct toxic eﬀects of alcohol and its metabolites is generally accepted as the central etiology during AH pathogenesis, the causal molecular mechanism remains elusive (Louvet and Mathurin, 2015). circRNAs are highly stable in vivo, are predominantly located in the cytoplasm and can be sorted into exosomes (Xu et al., 2015). Due to these characteristics, circRNAs have become good candidates as diagnostic molecular biomarkers for cancers ( Arnaiz et al., 2018). They regulate target gene expression which act as miRNAs sponges and RNA-protein sponges (Cai et al., 2019; Du et al., 2017; Liu et al., 2019; Zhang et al., 2019). However, there is still a lack of direct evidence for the function of circRNAs in AH(14).Fruitful investigations have illustrated that non-coding RNAs (ncRNAs), play key roles in diverse human diseases and physiological or pathological processes . For instance , circRNA-MTO1, which was notably poor expressed in hepatitis patients, inhibited liver ﬁbrosis via interacting with miR-17-5p . hsa\_circ\_0000650 had some connections with the development of chronic hepatitis B (CHB) through interacting with transforming growth factor-β (TGFβ2), which was mediated by miR-6873-3p . These data suggested that circRNAs had possibilities to get involved in mediating the occurrence of hepatitis or liver ﬁbrosis. CircRNA-4099 (hsa\_circRNA\_100759), which is a pivotal circRNA located on chromosome 11, has been turned out to be overexpressed in degenerated nucleus pulposus (NP) tissues, and it exhibited important roles in the intervertebral disc degeneration (IVDD) process miRNAs, about 20nt in length, regulate genes expression by silencing speciﬁc target messenger RNAs (mRNAs) at post-transcriptional levels . Abnormal expression of miRNAs is associated with diverse liver diseases including hepatic ﬁbrosis, viral hepatitis and fatty liver disease. Wang et al. found that the abnormal expression of miR-455-3p was signiﬁcantly connected with the sensitivity of hepatic stellate cells (HSCs) and thus aﬀected liver ﬁbrosis in mice . miR193a/b-3p repressed collagen Iandalpha smooth muscle actin (α-SMA) to restrain the proliferation of HSCs, and so as to be conductive to the attenuation of liver ﬁbrosis . What's more, one recent research illustrated that miR-706 inhibited the production of ﬁbrosis-related protein α-SMA, which was induced by oxidative stress in vivo . Generally, circRNAs regulate biological procedures by acting as a sponge of miRNAs, and the circRNA-miRNA axis has been extensively investigated to reveal the functions of circRNAs. Nevertheless, there was no clear evidence about the functions and mechanisms of circRNA4099 and miR-706 in hepatitis or liver ﬁbrosis. The direct relationship between the circRNA-4099 and miR-706 was still waiting for further elucidating. (9).

In contrast to other linear RNAs, such as mRNAs or microRNAs (miRNAs), whose functions have been intensively studied in the past decades, little is known about circRNAs, and even less is understood. Recent studies from two independent groups showed that one human circRNA derived from the antisense strand of the human Cerebellar Degeneration-Related protein 1 (CDR1) locus contains more than 70 endogenous miR-7 target recognition sites, thereby serving as a miR-7 sponge to “sponge up” or sequester the biological impacts of endogenous miR-7. This striking feature enables this circRNA, named CiRS-7 (Circular RNA Sponge for miR-7) or CDR1as (antisense), to function as a negative regulator of miRNA. Consistently, perturbation of CiRS-7 levels in both cell culture and neuronal tissues leads to an inverse change in endogenous miR-7 and dramatic changes in transcriptome profiles or developmental processes. Similarly, the testis-specific circRNA Sry functions as a miR-138 sponge . These findings suggest that circRNAs play a crucial role in regulating gene expression and that alteration of circRNA expression may contribute to the pathogenesis of many diseases, including cancer. In recent years, the impacts of ceRNA (competing endogenous RNA) interplay on the course of cancer initiation and progression have gradually emerged, and ceRNAs have been documented in various types of cancer, including prostate, liver and breast cancers . Given that circRNAs are potential ceRNAs, understanding circRNA transcriptional activities in cancer would greatly facilitate the study of cancer pathogenesis and provide potential novel targets for cancer therapeutics. As one of the most malignant and common cancers worldwide, hepatocellular carcinoma (HCC) is the third leading cause of cancer mortality and has steadily spread from the eastern to western countries . The development of HCC is a complex process that involves accumulation of gene regulation alteration at multiple levels, and molecules such as transcriptional factors, histone modifiers, microRNAs, lncRNAs and ceRNAs have been identified to play adominant role. However, the exact roles of circRNAs in cancer and the underlying molecular mechanism of circRNA-mediated gene regulation during HCC development remain elusive. The development of a circRNA microarray has greatly facilitated the understanding of circRNA expression in diverse biological contexts(6). Hepatocellular carcinoma (HCC) is the sixth common cancer and the second leading cause of death from cancer worldwide.The American Cancer Societyʼs estimates for deaths by primary liver cancer and intrahepatic bile duct cancer in the United States for 2018 are 30 200.HCC incidence in Egypt has increased sharply over the last decade. due to the high prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection among Egyptians.Indeed, liver cancer is the most frequent cancer in both men and women in Egypt. Although there are diagnostic and treatment strategies available for HCC, it still cannot be detected at early stages efficiently. The current diagnostic methods fail to detect HCC in many patients(1). Hepatitis B virus (HBV) and hepatitis C virus (HCV) are primary causes of HCC. Chronic HBV infection is a dominant risk factor in the majority of areas of Asia and Sub‑Saharan Africa that have a high incidence of HCC. The majority of patients with HCC whoexperience HBV infectionexhibit cirrhosis, secondary to the chronic necroinfammation. HBV, an oncogenic virus, promotes HCC via indirect (necroinfammation and regeneration injury) and direct (integration of its DNA in the host genome) pathways. The aberrant expression of genes and regulatory RNA moleculesare key nodes for the occurrence and development of HCC(2). The interaction between circRNAs and disease‑associated miRNAs indicates that circRNAs are important for disease regulation. CircRNAs serve crucial roles in the development of diseases, including nervous system disorders and atherosclerosis. In addition, circRNAs have been demonstrated to be involved in the neoplastic process; however, the molecular mechanisms underlying the association of circRNAs with cancer remain unclear. To the best of our knowledge, a large‑scale microarray screening of HCC and the focus of circRNAs as biomarkers of HCC has not been previously reported(2). Many research studies have been done for analyzing the dysregulated expression circular RNAs during the diseased conditions. Research investigation by Shichang Cui et al. revealed that a total of 24 circRNAs were upregulated, while 23 circRNAs were downregulated. Among these the top five upregulated circRNAs were hsa\_circRNA\_104351, hsa\_circRNA\_102814, hsa\_circRNA\_103489, hsa\_circRNA\_102109, and hsa\_circRNA\_100381. Furthermore, the top fve downregulated circRNAs were hsa\_circRNA\_100327, hsa\_circRNA\_101764, hsa\_circRNA\_101092, hsa\_circRNA\_001225, and hsa\_circRNA\_102904. Whereas, other researchers have detected the dysregulated expression of some other circRNAs. The four circRNAs- circMTO1, hsa\_circ\_0001649, circZKSCAN1, and hsa\_circ\_0004018 were downregulated, while three circRNAs named, hsa\_circ\_0005075, ciRS-7(Cdr1as), and circRNA\_100338 got upregulated during HCC condition. CircMTO1 is responsible for repression of HCC progression by sponging miR-9 that in turn leads to increased expression of p21 gene. CiRS-7 targets miR-7 and leads to enhancement of cell proliferation and invasion by promoting CCNE1, and PIK3CD expression CircZKSCAN1 is responsible for inhibiting the HCC cell growth, migration, and invasion by regulating cancer cell signaling pathways. CircRNAs, hsa\_circ\_0004018, circRNA\_100338, and circRNA\_000839, play roles in HCC development. CircRNAs regulate cancer development through a number of mechanisms, including miRNA sponges, modulating epithelial-mesenchymal transition, Wnt signaling pathway, the p53 PIK3CA, and β-catenin gene mutation. Literature survey has suggested that circular RNAs are initially present in viruses as unique noncoding RNA molecules(3). During the course of infection, these circRNAs are transferred to the host. These CircRNAs are stable structure and have tissue-specifc expression and are widely present in the cytoplasm of eukaryotic organisms, in the circular form. They are also responsible for developing the disease by regulating gene expression by competing with the endogenous RNAs of the cells. It modulates the function of miRNAs, by terminating the suppression from their targets, which in turn leads to modulated expression levels of other associated RNA molecules. The interaction between circRNAs and disease-associated miRNAs indicates that circRNAs are important for disease regulation. The different available diagnostics methods are Liver Imaging Reporting and Data System (LIRADS), CT, MRI, contrast imaging, ultrasound, etc. These aforesaid diagnosis procedures are somewhat time consuming, less sensitive, require validation, and expensive. Because of the drawbacks of above discussed diagnostic methods, the circular RNAs as biomarkers come into light with unique feature to diagnose the diseased condition primarily(3). Owing to recent advances in high-throughput sequencing and bioinformatics, the functions of circRNA have been reexamined. Studies have revealed that circRNAs can serve as microRNA (miRNA) sponges to sequester miRNAs from their bound target genes. As a result, circRNAs can inhibit miRNA functions and could play important roles in various cellular activities and disease processes. In addition, studies have shown that circRNAs might also act as biomarkers for many types of cancers , including HCC. For instance, the circRNA MTO1 was signifcantly downregulated in HCC tissues, and the low expression of circRNA MTO1 was considered as a poor prognosis marker for HCC patients. Recently, Conn et al. have shown that levels of hsa\_circ\_0001445 (also named circSMARCA5) were signifcantly increased with a minimal change in the levels of linear mRNA during epithelial-to-mesenchymal transition (EMT). As a well-known crucial step of HCC, EMT accelerates tumor progression by enhancing metastasis(19). Hepatocellular carcinoma (HCC), largely attributable to chronic hepatitis B virus (HBV) infection, is the second most common gastrointestinal solid tumors and remains the second leading cause of cancer-related death in China. The high mortality of HCC is due partly to the fact that early-stageHCC shows no obvious symptoms and the diagnostic accuracy of AFP (alpha-fetoprotein, a serum biomarker for the diagnosis of HCC in clinical use) and other potential serum biomarkers (such as DCP [des- γ-carboxyprothrombin], GPC3 [glypican-3], and microRNAs) is unsatisfactory. The sensitivities and specificities of high-serum AFP for HCC were reported to range from 39 to 64% and76–91%, respectively.A meta-analysis showed that the sensitivity and specificity of DCP for the diagnosis of HCC were 71% and 84%, respectively. The sensitivities and specificities of GPC3 in diagnosing HCC ranging from 36 to 65% and 65–100%, respectively. A multicenter, retrospective study showed that the sensitivities and specificities of Cmi (the combination of seven serum microRNAs) in diagnosing HCC ranging from 70 to 86% and 80–91%, respectively. Therefore, a novel biomarker for the detection of HCC, especially early-stage HCC, need to be identified.(13)

Previously, the data from circRNA expression profile revealed down‐regulation of circRNA circMTO1 (a circRNA derived from mitochondrial tRNA translation optimization [*MTO1*] gene, hsa\_circ\_0007874) in HCC tissues.14 C ircMTO1 h as b een d emonstrated to play an inhibitory role in HCC progression. Particularly, fluorescence in situ hybridization analysis indicated the location of circMTO1 in liver tissues. Therefore, circMTO1 may be involved in liver fibrosis and hepatic stellate cell (HSC) activation. In this study, the roles of circMTO1 in liver fibrosis and the clinical significance of serum circMTO1 in patients with liver fibrosis were explored(20). Over the last two decades, several new cutting-edge technologies, such as next-generation sequencing and microarray technologies ,have emerged, leading the search for biomarkers into a new era of ‘omics'.Using these technologies, the analysis of tens of thousands of molecular targets has become affordable and operable. Currently, numerous circulating markers and tissue markers have been identified .For instance, we recently identified a plasma microRNA panel, which has considerable clinical value in diagnosing earlystage HCC(10).

HBV is not directly hepatocytotoxic in the natural course of CHB; however, the inflammatory changes in liver resulting in immune responses against the virus cause unpredictable disease progression and may affect treatment response in CHB. This underscores the importance of understanding the mechanism of host hepatocyte inflammation and HBV entry. A large number of studies has shown that host miRNA play a vital role in the interaction between virus and host, affecting the occurrence and progression of CHB and its related diseases (13-16). CircRNA, as regulatory factors of miRNA, may affect the occurrence and development of CHB(15).

Chronic hepatitis B (CHB) affects more than 2 billion people worldwide, particularly in the Asia-Pacific region, and accounts for about 650,000 deaths annually .Chronic hepatitis B virus (HBV) infection can lead to serious liver diseases, including fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), with subsequent effects on multiple other organs. Although hepatitis B vaccination rates have increased in recent years and the rate of HBV infection has decreased, the population of CHB patients remains high. Moreover, the unpredictability of CHB progression hinders CHB treatment .Chronic HBV infection is caused by an interplay among the virus, host, and environment .Clinically, CHB has the characteristics of prolonged treatment time, poor treatment effect, and poor prognosis, thus has a negative impact on overall human health .However, the precise host mechanisms of CHB pathogenesis and progression remain unclear.

Circular RNAs (circRNAs) were recently identified as a novel class of noncoding RNAs (ncRNAs) widely expressed in various cells .In fact, circRNAs are generated by back-spliced exons (connecting the 5’ splice site of upstream- splice donor and the 3’ splice site of downstream- splice acceptor) at the pre-mRNA stage. Compared with linear RNAs, circRNAs form covalently closed loops without 5’ caps and 3’ tails. Therefore, circRNAs can resist RNAse R, which digests linear RNAs .Several lines of evidence have suggested that circRNAs are involved in cell division, differentiation, growth, and transcriptional regulation .Similar to competing endogenous RNAs (ceRNAs), circRNAs act as microRNA sponges and regulate the expression of miRNA-targeted mRNA in many biological processes(15).

To achieve a functional sequestration of miRNA-122 from HCV, a molecular sponge needs to compete with the viral binding sites. These reside at the 5 0-end of the HCV plus strand RNA genome and follow the canonical principles of miRNA-mRNA interactions.To design a molecular sponge, three different miRNA-122 binding sites were analyzed: an experimentally validated endogenous binding site from the IGF1R mRNA 3 0-UTR .a bulged binding site lacking complementarity at nucleotides 10–12 and a perfectly complementary binding site, which is thought to be cleaved by the miRNA-122-RISC complex .Four copies of these binding sites, corresponding seed mutant versionsand unrelated 30 -UTRs without miRNA-122 binding sites (derived from LAPTM4A, HNRNPK and KPNB1 mRNAs) were inserted into the firefly luciferase reporter 3 0-UTR of a dual-luciferase reporter system. The reporter constructs were transfected into HuH-7.5 cells that express high levels of miRNA-122, and luciferase activity was monitored in cell lysates. The IGF1R binding sites did not repress luciferase expression, whereas the wildtype bulged and both perfectly complementary sites did.In the latter, the seed mutation is not sufficient to completely abolish repression of luciferase expression. The reduced luciferase activity may not only be due to translational repression but also cleavage and/or destabilization of the luciferase reporter RNA as apparent from semiquantitative RT-PCR analysis(4).

Results

Marwa Matboli and etal said that The malignant group showed higher serum levels of the expression of cirR\_000224 and AFP concentration and lower expression of cirR\_00156 and cirR\_000520 (P < 0.001). There was a significant association of the serum has\_cirR\_00156 expression levels in the malignant group with cirrhosis (P = 0.02); has\_cirR\_000224 expression with mean size of the tumor (P = 0.013;). Most importantly, significant associations were found between has\_cirR\_00156, hsa\_cirR\_00224, and hsa\_cirR\_000520, and aspartate transaminase, alanine transaminase, total bilirubin, direct bilirubin, albumin, and international normalized ratio in the malignant group of the study (P < 0.05; Table 2). A significant negative correlation was found between hsa\_cirR\_00156 and hsa\_cirR\_000224 expression (r = −0.218 and P < 0.001) and between has\_cirR\_000224 and hsa\_cirR\_000520 (r = −0.579 and P < 0.001). Furthermore, there was a significant positive correlation between hsa\_cirR\_00156 and hsa\_cirR\_000520 (r = 0.348 and P < 0.001). When they are comparing patients with HCC with healthy controls, the best discriminating cutoff values of hsa\_cirR\_00156, hsa\_cirR\_000224, hsa\_cirR\_000520, and AFP were 0.9, 1.27, 1.4, and 13.15, respectively. Accordingly, the sensitivities were 73.5%, 95.6%, 97.1%, and 77.9%, respectively, indicating that these thresholds could be used to discriminate patients with HCC from healthy subjects. When combined, the three circRNA biomarkers showed remarkably high sensitivity (100%) and specificity slightly higher than that of AFP (83.3%;). The positivity rates of the serum (has\_ciR\_00156, has\_ciR\_000224, has\_ciR\_000520, and AFP) were found to be 73.5%, 95.6%, 97.1%, and 77.9%, respectively, in the malignant group (P < 0.001) By following up all the study cases, the recurrence rate was 38% of the patients with HCC. In univariate analysis, HCC cancer patients with negative hsa\_circ\_000520, hsa\_cirR\_00156, or hsa\_circ\_000224 had relatively longer RFS (Supporting Information). The Kaplan‐Meier analysis revealed a significant decrease in RFS and an increase in cumulative hazards among hsa\_circ \_00520 patients with HCC (logrank test; chi‐square, 14.4; P = 0.05;). The results of Cox multivariate analyses showed that hsa\_circ\_000520 was an independent prognostic factor of RFS.

SHICHANG CUI and etal had these two groups of results: circRNA expression profles. A total of 5,396circRNAs were scanned and the array image of each sample was demonstrated. Quantile normalization of raw data and subsequent data processing were performed using the R software package. The data demonstrated that 222,567,556 circRNAs were upregulated (fold‑change ≥2) and 125,439,219 circRNAs were downregulated (fold‑change ≥2). Differentially expressed circRNAs. The differentially expressed circRNAs with statistical signifcance between the two groups (HCC tissues group vs. NT group) were identifed through using volcano plot fltering. A total of 24 upregulatedcircRNAs and 23 downregulated circRNAs were identifed to be signifcant in HCC tissues compared with NTs (fold‑change ≥2; P≤0.05; Fig. 2; Tables II and III). The top fve upregulated circRNAs were hsa\_circRNA\_104351, h s a \_ c i r c R N A \_ 10 2 814, h s a \_ c i r c R N A \_ 10 3 4 8 9, hsa \_circR NA \_102109 and hsa \_circR NA \_10 0381.Furthermore, the top five downregulated circRNAs were hsa\_circRNA\_100327, hsa\_circRNA\_101764, hsa\_circRNA\_101092, hsa\_circRNA\_001225 and hsa\_circRNA\_102904. Annotation for circRNA/miRNA interactions. The circRNA/miRNA interaction was predicted using the miRNA target prediction software. All differentially expressed circRNAs (fold‑change ≥2; P≤0.05) were annotated in detail using the circRNA/miRNA interaction information. The most upregulated circRNA, hsa\_circRNA\_104351, adjusts its MREs: hsa‑miR‑490‑5p, hsa‑miR‑876‑5p, hsa‑miR‑619‑3p, hsa‑miR‑619‑3p, hsa‑miR‑331‑3p and hsa‑miR‑411‑3p. Similarly, the most downregulated circRNA, hsa\_circRNA\_100327, targets the following MREs: Hsa‑miR‑637, hsa‑miR‑326, hsa‑miR‑330‑5p, hsa‑miR‑646 and hsa‑miR‑24‑3p.

Shaling Li etal had these results:

* In a small sample size verification in 15 paired tumor (T) and non-cancerous (N) tissue samples, the expression of circRNA 101368 was significantly upregulated in tumor samples. Thus, circRNA 101368 was selected for further experiments.
* circRNA 101368 is overexpressed in HCC tissues and cell lines and is correlated with poorer prognosis
* circRNA 101368 knockdown suppressed the cell migration and HMGB1/RAGE signaling in HCC cell lines
* the effect of circRNA 101368 knockdown was partially attenuated by miR-200a inhibition, suggesting that circRNA 101368 exert its effect on HCC cell migration through miR-200a and downstream HMGB1/RAGE signaling.
* HMGB1 mRNA expression was significantly upregulated whereas miR-200a expression was downregulated in tumor tissue specimens. In tissue specimens, miR-200a was negatively correlated with HMGB1 and circRNA 101368, respectively; HMGB1 was positively correlated with circRNA 101368

Xianwei Zhang etal said that: The results showed that the expression of hsa\_circ\_0001445 was signifcantly lower in HCC tissues compared to that in the adjacent nontumor tissues (P < 0 001). their data suggest that hsa\_circ\_0001445 might serve as a tumor suppressor in HCC. Furthermore, plasma hsa\_circ\_0001445 levels could also be used to distinguish HCC patients from cirrhosis. Their data supported that hsa\_circ\_0001445 might potentially serve as a novel diagnostic biomarker for HCC detection. Tain zhao and et al said to investigate the diagnostic value of these four circRNAs (hsa\_circ\_0018429; B,hsa\_circ\_0026579; hsa\_circ\_0099188; has\_circ\_0012535) as candidate biomarkers of CAP.We found that hsa\_circ\_0018429 (AUC=0.8216; 95% CI, 0.7122‐0.9311; P<0.0001) exhibited the best performance in terms of specificity reached to 80%, while hsa\_circ\_0125357 (AUC=0.7730; 95% CI, 0.6516‐0.8943; P<0.001) performed the best in terms of sensitivity reached to 82%. Analysis based on the combination of all four circRNAs yielded an AUC value of 0.8776 (95% CI, 0.78840.9667; P<0.0001), and sensitivity and specificity reached diagnostic performance as a panel of biomarkers for CAP. Our KEGG enrichment analysis of the attendant predicted miRNA genes suggest functional roles in hepatitis B infection and in HTLV ‐1 infection. As hsa ‐miR‐199a, hsamiR‐484,and hsa‐miR‐638 are all potential binding partners of hsa\_circ\_0026579, we also tested the pathogenic diagnosis value of hsa\_circ\_0026579. The result showed that the expression level of hsa\_circ\_0026579 was higher in viral patients with CAP than those with nonviral (bacterial or bacterial/viral coinfection) pneumonia, while the other three circRNAs showed no significant difference.

Shanshan Wanga , and et al said Based on the microarray data, we found signiﬁcantly up-regulation of 24 circRNAs and down-regulation of 23 circRNAs in the HCC samples compared to non-tumorous (NT) samples (fold change > 2.0 and P < 0.05). Of them , 6 candidate circRNAs (hsa\_circRNA\_102814, 100381, 103489, 101764, 100327, and 103361) were veriﬁed by qRT-PCR. Of them, hsa\_circRNA 100381, 103489 up-regulation and 101764 down-regulation were found to be signiﬁcantly different in the 10 validation HCC tissue. Clusters of circRNAs were aberrantly expressed in HCC compared with NT samples. CircRNA\_101764 was the largest nodes in circRNA/microRNA co-expression network, especially co-expression with hsa-miR-181 family, which plays an important role in cell network. Annotation of circRNA/miRNA interactions indicated that the biological effects of circRNA may be achieved by binding of miRNAs. GO analysis revealed that numerous target genes were involved in the biological processes, cellular component and molecular function. There was nearly 30 target genes enrichment on KEGG pathways analysis , PI3K-Akt signaling pathway which the most number of genes involved.

Hongwu Menga had these results all the EtOH-fed mice were characterized by immune cell activation, injury and steatosis in the liver. Firstly, the degree of liver injury was evaluated by hematoxylin eosin (H&E) staining. Histopathological analysis showed that the degree of liver damage in EtOH-fed mice (model) was more severe than control diet fed (control) mice .

Accumulating evidence indicated that apoptosis of hepatocytes is a prominent feature of the initiation and progression stages of AH (Sun et al., 2018; Yin et al., 2016). Therefore, we continue to explore whether mm9\_circ\_018725 is associated with alcohol-induced hepatocyte apoptosis in vitro .We knocked downmm9\_circ\_018725 with small interfering RNA, and qRT-PCR results showed that small interfering RNA could signiﬁcantly reduce the expression of mm9\_circ\_018725 in ethanol-stimulated hepatocytes. Western blot results showed that silencing mm9\_circ\_018725 signiﬁcantly reduced alchol-induced hepatocyte apoptosis.

In this experiment we continue to explore whether mm9\_circ\_018725 is associated with inﬂammatory factors secreted by Raw264.7cells. First we knocked down mm9\_circ\_018725 in Raw264.7cells . When mm9\_circ\_018725 was silenced, the release of pro-inﬂammatory factors was signiﬁcantly reduced . Western blot results showed that knockdown of mm9\_circ\_018725 signiﬁcantly reduced TNF-α and IL-6 expression .

Yuling Lia and et al had result : H2O2 induced inhibition of viability and promotion of apoptosis, ROS production and cell ﬁbrosis as well as keap1/Nrf2 and p38MAPK cascades on L02 cell line. circRNA-4099 was stimulated by H2O2. Plentiful circRNA-4099 augmented H2O2-resulted damage by inhibiting miR-706. miR-706 mimic partly abolished the inﬂuence of circRNA-4099 on L02 cells. Meanwhile, circRNA-4099 silence exerted opposite eﬀect on these elements above. circRNA-4099 aggravated H2O2-induced injury by inhibiting miR-706 through triggering keap1/ Nrf2 and p38MAPK in the L02 cells.

Xiu-Yan Huang and et al had these result CircRNA-100338 Is Up-Regulated in HCC Tissues and Promotes Tumor Proliferation. Finally, identiﬁed RHEB (Ras homolog enriched in brain) as the target of miR141-3p in HCC ( Spearman correlation coeﬃcient < −0.6), suggesting that circRNA-100338 may act as a ceRNA by competing with RHEB. Like circRNA-100338, RHEB was also up-regulated in tumor tissues . These results suggested that miR-141-3p may negatively regulate RHEB, therefore, as circRNA-100338 may competitively bind with miR141-3p, the upregulation of this circRNA would increase the RHEB RNA level. On the contrary, when circRNA-100338 was suppressed, miR-141-3p expression may be increased, which in turn increased the probability of its binding with RHEB, thus decreased RHEB expression.

We then selected two HCC cell lines with high metastatic potential, MHCC97H, and SMMC7721, and two HCC cell lines with low metastatic potential, BEL7402, and Hep3B to investigate the regulatory relationship between circRNA-100338, miR-141-3p, and RHEB. We found that RHEB mRNA expression was signiﬁcantly downregulated in MHCC97H (CI: 0.32 ± 0.04, n = 3) and SMMC7721 (CI: 0.22 ± 0.01, n = 3) cell lines with miR141-3p mimics (P < 0.05, Figure 2C), as compared with controls (CI: 0.65 ± 0.02, n = 3 for MHCC97H, and CI: 0.51 ± 0.03, n = 3 for SMMC7721), respectively. Moreover, the RHEB mRNA expression was signiﬁcantly upregulated in BEL7402 (CI: 0.74 ± 0.01, n = 3) and Hep3B (CI: 0.48 ± 0.03, n = 3) cell lines with miR-141-3p inhibitor (P < 0.05, Figure 2D), as compared with the controls (CI: 0.36 ± 0.02, n = 3 for BEL7402, and CI: 0.23 ± 0.01, n = 3 for Hep3B), respectively. These results demonstrated that RHEB was a target of miR-141-3p. In accordance with HCC cell lines with overexpression of circRNA100338, hepatitis B-related HCC tissues in circRNA-100338-high group also showed high activity of mTOR signaling pathway, further demonstrating that circRNA-100338 could promote activation of mTOR signaling pathway. activation of

mTOR signaling pathway by circRNA-100338 could result in high probability of pulmonary metastasis and/or vascular invasion, further suggesting that the mTOR signaling pathway activated by circRNA-100338/miR-141-3p/RHEB may promote HCC pulmonary metastasis.

Liyun Fu and et al said As Table 1 indicates, hsa\_circ\_0004018 level was correlated with serum alpha-fetoprotein (AFP) level, tumor diameters, differentiation, Barcelona Clinic Liver Cancer (BCLC) stage and Tumor-node-metastasis (TNM) stage. To confirm the results of hsa\_circ\_0004018 in HCC patients, we selected cirrhosis and the chronic hepatitis biopsy tissues. Intriguingly, we revealed that the levels of hsa\_circ\_0004018 in HCC tissues were significantly lower than those of cirrhosis (F=4) (*P*<0.001); and its levels in cirrhosis tissues were significantly lower than those in chronic hepatitis tissues (F=0-3) (*P*<0.001). Hsa\_circ\_0004018 expression levels exhibited HCC-stage-specific characteristics.

Wei Wang and et al said It was found that with the increasing fibrosis scores, serum circ‐MTO1 was significantly down‐regulated. Similarly, with the increasing HAI scores, lower serum circMTO1 was observed. Moreover, in comparison with patients with normal ALT, there was lower circMTO1 expression in those with elevated ALT, indicating that serum circMTO1 expression was associated with inflammation and liver damage. Based on these, circ‐MTO1 is reduced in CHB patients and negatively correlated with liver fibrosis progression.

Discussion

In Our study circRNAs, a class of noncoding RNAs that are abundant in body fluids and can act as miRNA sponges to regulate gene expression and that are more stable than miRNAs on account of the resistance to RNA exonuclease activity conferred by their unique circularized structures, are increasingly appreciated as attractive potential diagnostic biomarkers.hsa‐miR‐199a and hsa‐miR‐484 show a strong association with adaptive immune responses and have been implicated in immunology‐related functions. hsa‐miR‐199a was identified as a biomarker for hepatocellular carcinoma related with hepatitis B virus, and hsa‐miR‐638 has been reported to have antiviral effects against the hepatitis B virus . Based on circRNAs was more stable than miRNA and LncRNA and therefore ,they may be promising as diagnostic or predictive biomarkers

There are an increasing number of circRNAs found to function as miRNA sponges in human diseases such as certain cancers, diabetes. It was reported that hsa\_cirRNA\_0054633 was abnormally expressed in gestational diabetes mellitus (GDM) patients. However, the speciﬁc role of circRNAs in AH is rarely reported . In addition, knockdown of mm9\_circ\_018725 alleviates hepatocyte apoptosis in EtOH-induced Aml-12cells and mm9\_circ\_018725 inhibition reduces the expression of pro-inﬂammatory factors produced by EtOHstimulation in Raw264.7cells, which may improve our understanding of the pathogenic mechanisms in AH and help ﬁnd new molecular targets for the clinical treatment of AH.

the keap1/Nrf2 and p38MAPK signaling cascades had pivotal impacts on H2O2-induced L02 damage or hepatitis. Overproduction of circRNA-4099 further triggered these cascades by enforcing the phosphorylation of relative proteins.

HCC is a heterogeneous disease of complicated etiology. The molecular basis of HCC about protein-coding genes has largely been studied in the context of tumorigenesis, progression, and metastasis. circRNA-100338 functions as an endogenous sponge for miR-141-3p, an integrated analysis of circRNA-100338, miR-141-3p, and target genes was conducted . RHEB as the target of miR-141-3p in HCC, suggesting that circRNA-100338 may act as a ceRNA by competing with RHEB, which could activate the protein kinase activity of mTORC1, thereby play a key role in the regulation of mTOR signaling.

in vitro invasion assays in MHCC97H cells, a metastatic liver cancer cell line, provided direct evidence of the involvement of circRNA\_100338 and miR-141-3p in regulation of metastasis in liver cancers. Given than each miRNA targets multiple downstream genes, it would be very interesting to identify the downstream miR-141-3p target genes that are responsible for the regulation of cancer cell metastasis. Even though MTSS1 is widely known as a metastasis suppressor gene that is involved in regulation of cell mobility and consequently cancer metastasi, recent studies surprisingly indicated that MTSS1 also acts as an oncogene and a driver of metastasis in melanoma tumours and breast cancers. This evidence indicates that MTSS1 may also serve as a metastasis driver in HCC patients and that circRNA\_100338 regulates HCC metastasis though a potential circRNA\_100338-miR141-3p-MTSS1 interaction pathway.

three circRNAs in the CircPanel proved to be secreted by HCC cells, and their expression in plasma was positively correlated with that in HCC tissues, though the correlation coefficient was relatively low. In addition, the CircPanel showed higher accuracy than AFP in distinguishing individuals with HCC or Small-HCC from the controls and performed well in diagnosing AFP-negative HCC and AFP-negative Small-HCC. All these findings make the CircPanel a compelling diagnostic biomarker.

References

1. Marwa Matboli1 | Ayman E Shafei2 | Mahmoud A Ali2 | Ahmed M Ashry2 |Kamal M Kamal2 | Mohammed Ali Agag2 | Ibrahim Reda2 | Eman Fathy Tash |Marwa Ali: circRNAs (hsa\_circ\_00156, hsa\_circ \_000224, and hsa\_circ \_000520) are novel potential biomarkers in hepatocellular carcinoma
2. SHICHANG CUI1, ZHILING QIAN1, YUHAN CHEN2, LEI LI2, PENG LI2 and HUIGUO DING2: Screening of up‑ and downregulation of circRNAs in HBV‑related hepatocellular carcinoma by microarray
3. Rupal Ojha, Raj Nandani, Nina Chatterjee, and Vijay Kumar Prajapati: Emerging Role of Circular RNAs as Potential Biomarkers for the Diagnosis of Human
4. Functional sequestration of microRNA-122 from Hepatitis C Virus by circular RNA sponges

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Comprehensive circular RNA profiling reveals the regulatory role of the circRNA-100338/miR-1413p pathway in hepatitis B-related hepatocellular carcinoma

1. Tian Zhao1 | YaLi Zheng2 | DengZai Hao1 | Xuesong Jin1 | QiongZhen Luo2 | YaTao Guo2 | DaiXi Li2 | Wen Xi2 | Yu Xu2 | YuSheng Chen3 | ZhanCheng Gao2 | Yan Zhang1 Blood circRNAs as biomarkers for the diagnosis of community‐acquired pneumonia
2. Lia, Huimin Gua, Yan Huanga, Qian Pengb, Rongrong Zhoua, Panpan Yia, Ruochan Chena, Zebing Huanga, Xingwang Hua, Yun Huangc, and Daolin Tangd: Circular RNA 101368/miR-200a axis modulates the migration of hepatocellular carcinoma through HMGB1/RAGE signaling
3. Screening differential circular RNA expression profiles reveals hsa\_circ\_0004018 is associated with hepatocellular carcinoma

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1. Yuling Lia,1, Xingjuan Gaob,1, Zhihua Wangc,1, Wei Liua, Fang Xua, Yejia Hua, Yanuo Lia, Lei Shia,⁎

Circular RNA 4099 aggravates hydrogen peroxide-induced injury by downregulating microRNA-706 in L02 cells

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Circular RNA expression proﬁle of liver tissues in an EtOH-induced mouse model of alcoholic hepatitis

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Screening and bioinformatics analysis of circular RNA expression proﬁles in hepatitis B-related hepatocellular carcinoma

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CircRNA-100338 Is Associated With mTOR Signaling Pathway and Poor Prognosis in Hepatocellular Carcinoma

1. Plasma circular RNA panel to diagnose hepatitis B virus-related hepatocellular carcinoma: A large-scale, multicenter study, Jian Yu1,2,3\*, Wen-bing Ding1,2,3\*, Meng-chao Wang1,2,3\*, Xing-gang Guo1,2,3\*, Jian Xu4\*, Qing-guo Xu1,2,3,Yuan Yang1,2,3,Shu-han Sun5,6, Jing-feng Liu7, Lun-xiu Qin8, Hui Liu1,2,3, Fu Yang5,6 and Wei-ping Zhou 1,2,3
2. CircMTO1 inhibits liver fibrosis via regulation of miR‐17‐5p and Smad7

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1. Differential expression profile of hepatic circular RNAs in chronic hepatitis B

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1. Xianwei Zhang ,1 Hu Zhou ,2 Wei Jing ,1 Ping Luo,1 Shili Qiu ,1 Xuefang Liu,1 Man Zhu ,1 Chunzi Liang ,1 Mingxia Yu ,1 and Jiancheng Tu 1: The Circular RNA hsa\_circ\_0001445 Regulates the Proliferation and Migration of Hepatocellular Carcinoma and May Serve as a Diagnostic Biomarker
2. Plasma hsa\_circ\_0027089 is a diagnostic biomarker for hepatitis B virus-related hepatocellular carcinoma

Kai Zhu1,2, Hao Zhan1, Yuanfei Peng1, Liuxiao Yang1, Qiang Gao1, Hao Jia3, Zhi Dai1,Zhaoyou Tang1, Jia Fan1,2,4 and Jian Zhou1,2,4,\*