The circular RNA circMAST1 promotes hepatocellular carcinoma cell proliferation and migration by sponging miR-1299 and regulating CTNND1 expression

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Abstract
Circular RNAs (circRNAs) are a class of non-coding RNAs with a loop structure; however, their functions remain largely unknown. Growing evidence suggests that circRNAs play a pivotal role in the progression of malignant diseases. However, the expression profiles and function of circRNAs in hepatocellular carcinoma (HCC) remain unclear. We investigated the expression of microtubule-associated serine/threonine kinase 1 (MAST1) circRNA (circMAST1) in HCC and healthy tissues using bioinformatics, quantitative real-time PCR (qRT-PCR), and fluorescence in situ hybridization. Luciferase reporter assays were performed to assess the interaction between circMAST1 and miR-1299. Proliferation assays, colony formation assays, flow cytometry, transwell assays, and western blotting were also performed. A mouse xenograft model was also used to determine the effect of circMAST1 on HCC growth in vivo. CircMAST1 was upregulated in HCC tissues and cell lines; silencing via small interfering RNA inhibited migration, invasion, and proliferation of HCC cell lines in vitro as well as tumor growth in vivo. Furthermore, the expression of circMAST1 was positively correlated with catenin delta-1 (CTNND1) and negatively correlated with microRNA (miR)-1299 in HCC clinical samples. Importantly, circMAST1 sponged miR-1299 to stabilize the expression of CTNND1 and promoted tumorigenic features in HCC cell lines. We found that circMAST1 may serve as a novel biomarker for HCC. Moreover, circMAST1 elicits HCC progression by sponging miRNA-1299 and stabilizing CTNND1. Our data provide potential options for therapeutic targets in patients with HCC.

Introduction
Hepatocellular carcinoma (HCC) is one of the most common malignant tumors globally and constitutes the third leading cause of cancer-related deaths worldwide. In 2017, there were 953,000 cases of liver cancer and 819,000 deaths globally. HCC is clinically characterized by its invasiveness, poor prognosis, and limited therapeutic options. Despite the advances in the clinical understanding of the mechanisms of HCC, the 5-year survival rate of patients with this disease remains low. Presently, surgery is the most common intervention for patients with HCC, but most patients with multifocal development and distant metastases are ineligible for curative surgical treatment. Therefore, a deeper understanding of the molecular mechanisms underlying HCC progression is of paramount importance.

Circular RNAs (circRNAs) are a newly discovered type of non-coding RNAs. Unlike canonical linear RNAs,
Fig. 1 (See legend on next page.)
circRNAs are highly conserved and are characterized by covalently linked closed-loop structures with neither 5′-3′ caps nor polarity; they also have no polyadenylated tails, which makes them more stable than linear RNAs. The biological function of circRNAs has been extensively investigated and can be grouped into five categories; sponging of microRNAs (miRNAs) to suppress their function, transcriptional and translational regulation, influencing alternative splicing of pre-miRNAs, interacting with RNA-binding proteins to regulate gene expression, and potentially, encoding proteins. These features collectively indicate pivotal functions for circRNAs in biological and pathological processes.

A growing body of literature shows that circRNAs are differentially expressed in HCC. Some studies have demonstrated that circRNAs act as oncogenes in HCC, while others showed that they act as HCC tumor suppressors. As such, circRNAs are implicated in the onset and development of HCC. CircRNAs are also highly abundant and stable, suggesting that they are ideal biomarkers and promising therapeutic targets for patients with HCC. However, compared with other non-coding RNAs such as miRNAs and long non-coding RNAs, the study of circRNAs in HCC is just beginning. To date, only a small quantity of functional circRNAs have been discovered and characterized in HCC; a large number remain to be explored or identified.

In this study, we aimed to find out if circMAST1 can serve as a biomarker as well as a potential therapeutic target for patients with HCC, by analyzing the expression profile of circRNAs in HCC tissues. We determined that the circRNA of microtubule-associated serine/threonine kinase 1 (MAST1), or circMAST1, was significantly upregulated in HCC tissues and was closely related to tumor progression through a novel route.

**Results**

**Profiles of circRNAs in HCC**

A total of 4451 circRNAs were detected in three pairs of HCC tissue samples (3 HCC tissues and three matching non-tumor liver tissues) using circRNA microarray analysis from the microarray dataset GSE78520. Using the “limma” package of the R software and selecting a false discovery rate of less than 0.05 and log2-fold-change greater than 1 as cut-off criteria, we identified 257 differentially expressed circRNAs, of which 213 and 44 were upregulated and downregulated, respectively (Additional file 6: Supplementary Table S5). Volcano and scatter plots showed the variation in circRNA expression between the HCC tissues and non-tumor liver tissues (Fig. 1A). A heatmap representing the differentially expressed circRNAs values was generated to distinguish human liver cancer from adjacent healthy liver tissues (Fig. 1B). Afterwards, the parental genes of differentially expressed circRNAs were subjected to Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis; the top ten entries are shown in Fig. 1C. These parental genes regulate cell division, mitotic nuclear division, sister chromatid cohesion, chromosome segregation, DNA repair, replication initiation, DNA replication, DNA synthesis involved in DNA repair, regulation of transcription involved in the G1/S transition of the mitotic cell cycle, and G1/S transition itself.

Next, we detected ten circRNAs expressed in both HCC tissues and paired non-tumor tissues from 15 patients using qRT-PCR. Among them, we found that has_circRNA_102459 (hsa_circ_0049613, circMAST1) expression was persistently and significantly increased in HCC compared to that of the matching adjacent normal liver tissues (Fig. 1D). We also detected the existence of circMAST1 in the serum of HCC patients and healthy controls. The results indicated that the serum levels of circMAST1 were significantly higher in patients with HCC than that of healthy controls (Additional file 7: Supplementary Fig. S1A). Thus, we focused on investigating the role of circMAST1 in HCC progression. Notably, circMAST1 was derived from exons 9–11 of MAST1 located on chromosome 19p13.2 and independent experiments were performed to determine its circular structure. We first inserted the PCR products of circMAST1 into a T vector for Sanger sequencing (Fig. 1E), which showed consistency with the back spliced
Fig. 2 (See legend on next page.)
shown in Fig. 1f, the linear and circular transcripts of MAST1 were amplification. The data demonstrate both the presence and circular transcripts of MAST1 were resistant to degradation by RNase R, while the circular transcripts of MAST1 were resistant to degradation. The data demonstrate both the presence and circular structure of circMAST1.

The subcellular localization of circRNA determines its primary mode of action. The FISH analysis revealed that circMAST1 was highly expressed in tumor tissues compared to the matching non-tumor counterparts (Fig. 2a). Moreover, comprehensive assessments of circMAST1 expression in the HCC cell lines HepG2, SK-HepG1, Huh7, and HCCLM3, as well as in healthy liver L02 cells, were performed using qRT-PCR. The expression levels of circMAST1 in all HCC cell lines were generally higher than that of L02 cells, the highest observed in HCCLM3 cells and lowest in Huh7 cells (Fig. 2b). To further investigate the regulatory role of circMAST1, we designed three circMAST1 small interfering RNAs (siRNAs) to specifically target different binding sites on the back splice junction sequence of circMAST1; in both the HCCLM3 and HepG2 cell lines, siRNA-1 and siRNA-3 effectively silenced the expression of circMAST1 and were used for subsequent experiments (Fig. 2c). Moreover, circMAST1 was predominantly located in the cytoplasm as confirmed by FISH (Fig. 2d, e). The results indicate that circMAST1 is a highly stable cytoplasmic circRNA derived from exons 9–11 of the MAST1 locus.

circMAST1 is mainly located in the cell cytoplasm

In general, the subcellular localization of circRNA determines its primary mode of action. The FISH analysis revealed that circMAST1 was highly expressed in tumor tissues compared to the matching non-tumor counterparts (Fig. 2a). Moreover, comprehensive assessments of circMAST1 expression in the HCC cell lines HepG2, SK-HepG1, Huh7, and HCCLM3, as well as in healthy liver L02 cells, were performed using qRT-PCR. The expression levels of circMAST1 in all HCC cell lines were generally higher than that of L02 cells, the highest observed in HCCLM3 cells and lowest in Huh7 cells (Fig. 2b). To further investigate the regulatory role of circMAST1, we designed three circMAST1 small interfering RNAs (siRNAs) to specifically target different binding sites on the back splice junction sequence of circMAST1; in both the HCCLM3 and HepG2 cell lines, siRNA-1 and siRNA-3 effectively silenced the expression of circMAST1 and were used for subsequent experiments (Fig. 2c). Moreover, circMAST1 was predominantly located in the cytoplasm as confirmed by FISH (Fig. 2d, e). The results indicate that circMAST1 is a highly stable cytoplasmic circRNA derived from exons 9–11 of the MAST1 locus.

circMAST1 is likely required to sustain the cell cycle progression of HCC cells

Using the back splice junction-specific siRNA, we successfully silenced circMAST1 expression in HCCLM3 and HepG2 cells. We then investigated whether circMAST1 affected HCC cell cycle progression using flow cytometry. Silencing circMAST1 increased the proportions of HCCLM3 and HepG2 cells in G0/G1 phase significantly while decreasing the proportions of these cells in the G2 phase (Fig. 3a, b). Furthermore, circMAST1 was found to strongly affect the post-translational levels of the cell cycle-related proteins cyclin A and cyclin E as well as the cyclin-dependent kinases (CDKs) 1 and 2 in these cells (Fig. 3c, d). The WST-1 assay showed that circMAST1 silencing reduced HCCLM3 and HepG2 cell proliferation (Fig. 4a, b). Notably, proliferating cell nuclear antigen (PCNA) levels in these cells were initially elevated but attenuated after transfection with the circMAST1 back splice junction-specific siRNA (Fig. 4c). Meanwhile, colony formation assays revealed that circMAST1 was positively associated with the proliferation of HCCLM3 and HepG2 cells (Fig. 4d). Moreover, HCCLM3 and HepG2 cell migration were suppressed by circMAST1 silencing (Fig. 4e), as was the cell invasion through the Matrigel (Fig. 4f). We generated Huh-7 cells stably overexpressing circMAST1 by transducing them with the lentivirus of circMAST1. In comparison with the controls, circMAST1 overexpression increased the proliferation, migration, and invasion of Huh-7 cells (Fig S2A-C). These results suggest that circMAST1 is likely required to sustain the proliferation, migration, and invasion of HCC cells in vitro.

circMAST1 is likely required to sustain HCC tumor growth in vivo

HCCLM3 cells were injected subcutaneously into BALB/c nude mice for 12 days to create tumor xenografts to examine the role of circMAST1 in HCC tumorigenesis further. Twelve days later, we commenced the injection of 10 OD cholesterol-modified circMAST1 siRNA or negative control siRNA every three days subcutaneously at the tumor site for 24 days (Fig. 5a). Following 36 days of observation, the mice that had received circMAST1 siRNA exhibited markedly decreased tumor volumes and weights than those that had received control siRNA (Fig. 5b, c), suggesting that circMAST1 promoted HCC cell growth in vivo. These results further support a role for circMAST1 in HCC tumorigenesis and development. At the same time, we examined the expression of PCNA protein as well as that of the cell cycle-related proteins cyclin A, cyclin E, CDK1, and CDK2 in the tumor tissues of circMAST1 siRNA- and control siRNA-injected mice; all were significantly lower in the circMAST1 siRNA group than the control siRNA group (Fig. 5d). Moreover, circMAST1 silencing significantly reduced the Ki-67 proliferation index as well as the number of CD31-positive intratumoral microvessels (Fig. 5e, f). These
results verify that circMAST1 is likely required to sustain HCC growth in vivo.

circMAST1 serves as a sponge for miR-1299 in HCC cells

Since circRNAs that are predominantly located in the cytoplasm are usually associated with miRNA sponging, we further explored whether circMAST1 could bind to miRNAs (Fig. 6a). Three miRNAs associated with circMAST1 (miR-663b, miR-1281, and miR-1299) were predicted to be relevant by miRanda, RNAhybrid, and regRNA; miR-1299 was selected as a candidate miRNA for subsequent experiments (Fig. 6b). Figure 6c illustrates the predicted RNA secondary structure; the yellow region indicates the predicted 'RNAfold' structure of the motif.
using calculated pair probabilities; the minimum free energy = −34.02. Previous studies showed that miR-1299 is downregulated in HCC tissues and functions as a tumor suppressor and that the low expression of miR-1299 in HCC tissues predicts poor prognosis (Fig. 6d). Pearson’s correlation analysis of circMAST1 and miR-1299 expression levels revealed a negative correlation (Fig. 6e). Additionally, luciferase reporters using either a
Fig. 5 (See legend on next page.)
Collectively, these results demonstrated that circMAST1 is required to sustain HCC cell tumorigenicity. miR-1299 targets CTNND1, which is required to sustain HCC cell tumorigenicity. The miranda, miRDB, TargetScan, and miRWALK prediction tools revealed high scores for miR-1299 targeting the 3′ untranslated region of the CTNND1 (Fig. 7a). Pearson correlation analysis revealed a negative correlation between miR-1299 and CTNND1 expression levels (Fig. 7b). We found that miR-1299 inhibition significantly increased CTNND1 protein levels and that miR-1299 mimetic agents reduced the expression of CTNND1 in HepG2 and HCCLM3 cells (Fig. 7c). The miR-1299-CTNND1 interaction was confirmed via luciferase reporter assays, where miR-1299 significantly reduced the activity of the luciferase reporter compared to the negative control, for the wildtype CTNND1 sequence. However, such reductions were not observed when the binding sites of miR-1299 were mutated (Fig. 7d). These results indicated that miR-1299 negatively regulates the expression of CTNND1.

Furthermore, miR-1299 inhibition promoted the proliferation, cell cycle progression, migration, and invasion of HCC cells. Importantly, however, these enhancements were not observed in cells co-transfected with siRNA-CTNND1 and miR-1299 inhibitor (Fig. 7e–k). These results suggested that miR-1299 targets CTNND1 and inhibits the proliferation, cell cycle progression, migration, and invasion of HCC cells.

circMAST1 expression is positively correlated with CTNND1 expression

To further evaluate CTNND1 expression levels, we performed qRT-PCR and western blotting in HCC and matching healthy tissues. The expression of CTNND1 was higher in HCC tissues than that of the matching healthy counterparts (Fig. 8a, b). Our aforementioned finding that the 3′ untranslated region of CTNND1 contained a miR-1299 binding site that was identical to that of circMAST1 suggested that circMAST1 might regulate CTNND1 expression by competively binding to this miRNA. In fact, a positive correlation between circMAST1 and CTNND1 mRNA levels was found (Fig. 8c). Immunohistochemical staining of xenografted tumors revealed that the circMAST1-silenced group showed significantly inhibited CTNND1 expression when compared to the negative control group (Fig. 8d). Western blotting results were consistent with immunohistochemical staining (Fig. 8e). These results demonstrated that circMAST1 is likely required to sustain the growth of HCC in vivo partly by regulating CTNND1. Consistent with this premise, we found that the circMAST1/miR-1299 axis also regulated CTNND1 expression, thereby influencing HCC cell proliferation, cell cycle progression, migration, and invasion (Fig. 8f).
Fig. 6 (See legend on next page.)
Discussion

Our study demonstrated that circMAST1 functions as a tumor promoter and induces HCC cancer cell proliferation and invasion through the miR-1299/CTNND1 axis, suggesting that circMAST1 is a potential biomarker and therapeutic target for HCC. This is supported by our findings: (1) circMAST1 is highly expressed in HCC tissues, and HCC cell lines (e.g., HepG2 and HCCLM3); (2) silencing circMAST1 in a murine xenograft model significantly reduces the growth of HCC; (3) circMAST1 is likely required to sustain the cell cycle progression, proliferation, migration, and invasion of HCC cell lines; (4) circMAST1 is a miR-1299 sponge, and silencing circMAST1 inhibits cell growth significantly; (5) circMAST1 sponges miR-1299 to promote CTNND1 expression and is required to sustain cancer progression. Our study thus identified a previously unrecognized role for circMAST1 in promoting HCC.

CircMAST1 (Hsa_circ_0049613) was derived from the MAST1. MAST1, also known as SAST170, belongs to a family of four members (MAST1–MAST4). MAST1 rearrangement has consistently been observed in breast cancer cell lines and tissues, and overexpression of MAST1 fusion genes enhances the proliferation of breast cancer both in vitro and in vivo. MAST1 was also identified as the main driver of cisplatin resistance in human cancer. There is clinical evidence that expression of MAST1, both de novo and cisplatin-induced, contributes to platinum resistance and worse clinical outcome. The aforementioned findings indicate that MAST1 plays a vital role in cancer progression. To date, however, there have been no investigations of circMAST1 and whether it plays a similar role as its parent gene in promoting the progression of cancer. In our study, we found that circMAST1 was derived from exons 9–11 of MAST1 located on chromosome 19p13.2 and that it was dramatically upregulated in HCC cell lines and tissues relative to non-tumor tissues. Even after RNase R treatment, circMAST1 was still detected with a little degradation. Our research confirmed that circMAST1 has the same role as its parent gene in promoting HCC progression, although it is more stable.

CircMAST1 was highly expressed in HCC cell lines and tissues (most markedly in HCCLM3). More importantly, silencing circMAST1 in a murine xenograft model significantly reduced the growth of HCC. KEGG and gene ontology analyses were used to define the functional pathways of the differentially expressed circRNA host genes; these parental genes mainly participated in DNA replication and the regulation of G1/S transition. Previous studies have shown that circRNAs play an essential role in cell cycle progression and proliferation. We provided evidence that the ectopic expression of circMAST1 is likely required to sustain cell proliferation and cell cycle progression at the G2/M phase. Concerning the specific function of circMAST1 in cell proliferation, we found that cyclin A, cyclin D, and CDK1, CDK2 in HCCLM3 and hepG2 cells by Western-blot. Bar graph showed the results of the expression of PCNA, cyclin A, cyclin D and CDK1, CDK2 in HCCLM3 and hepG2 cells (P<0.05; **P<0.01; ***P<0.001; n=4).

Although the mechanisms, through which circRNA regulates carcinogenesis and cancer progression have not been fully elucidated, the “circRNA-miRNA-mRNA” axis, also known as the “miRNA sponge”, is frequently cited. In our study, we confirmed that circMAST1 is a miR-1299 sponge and that silencing circMAST1 increased the expression of miR-1299 significantly, which in turn inhibited the proliferation, migration, and invasion of HCC cell lines. We also confirmed a direct correlation between miR-1299 and circMAST1. Consistent with our results, other studies have shown that circRNAs act as a sponge during the development and progression of HCC; Yu et al. also found that the circRNA cSMARCA5 sponges miR-17 and miR-181b to...
Fig. 7 (See legend on next page.)
Our study demonstrated that circMAST1 is upregulated in HCC cell lines and tissues and that its high expression is associated with HCC progression. CircMAST1 is required to sustain the proliferation and invasion of HCC by directly binding to miR-1299 and impeding its suppression of CTNNBD1. Our findings suggest that circMAST1 is potentially a novel biomarker and therapeutic target for HCC.
Fig. 8 circMAST1 promotes HCC by miR-1299/CTNND1 axis. 

a The protein expression level of CTNND1 in 10 paired HCC and normal tissues (**P < 0.01; n = 10). 
b Relative expression of CTNND1 in HCC and normal tissue pairs were measured by qRT-PCR (**P < 0.01; n = 10). 
c Pearson's correlation analyses showing the correlation of CTNND1 and circMAST1 expression (n = 10). 
d CTNND1 expression levels are shown in representative xenograft tumors by IHC (**P < 0.01; n = 4). 
e The protein expression of level of CTNND1 in xenograft model (**P < 0.01; n = 4). 
f Schematic diagram shows that circMAST1 promotes HCC cells proliferation, migration and invasion through miR-1299/CTNND1 axis.
**Patient selection**

A total of 39 HCC samples were obtained from the clinical sample bank of the First Affiliated Hospital, Harbin medical university. The collection of human specimens was approved by the Biomedical Ethics Committee of the Harbin medical university. First Affiliated Hospital and written informed consent was obtained from each patient. Inclusion criteria for patient selection were curative hepatectomy performed between 2017 and 2018. This study was performed in compliance with the Declaration of Helsinki and was approved by the Institutional Review Board of the Harbin Medical University.

**Animal studies**

All protocols were approved by the Harbin Medical University Animal Care and Use Committee. This study was also approved by the ethics review board of Harbin Medical University.

**Statistical analyses**

All statistical analyses were performed using SPSS version 21.0 (IBM SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 6.0 (GraphPad Software, LaJolla, CA, USA) software. Categorical variables are expressed as a count or percentage and tested using chi-square or Fisher’s exact tests, as appropriate. Continuous data are reported as mean ± standard deviation (SD) and compared using Student’s t-test, the one-way analysis of variance (ANOVA) test or Mann-Whitney test as appropriate. Correlations were calculated using Pearson’s correlation analysis. \( P < 0.05 \) was considered statistically significant.

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**Conflict of interest**

The authors declare that they have no conflict of interest.

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