Hsa_circ_0005100 regulates tumorigenicity of colorectal carcinoma via miR-145-5p/MACC1 axis

Tongtong Zhang | Suyang Yu | Shipeng Zhao

Department of Gastrointestinal Surgery, The Third Hospital Affiliated to Hebei Medical University, Shijiazhuang, China

Correspondence
Shipeng Zhao, Department of Gastrointestinal Surgery, The Third Hospital Affiliated to Hebei Medical University, No. 139 Ziqiang Road, Qiaoxi District, Shijiazhuang 050051, China. Email: ztthwx@163.com

Abstract
Background: Circular RNAs (circRNAs) are a kind of RNA molecules involved in the regulation of cancer progression, including colorectal carcinoma (CRC); nevertheless, their regulation mode is blurry. In the present work, we attempted to reveal the characteristics of hsa_hsa_circ_0005100 in CRC.

Methods: Differential expressions of hsa_circ_0005100, FMN2 mRNA, microRNA-145-5p (miR-145-5p), and MACC1 were indicated by qRT-PCR and Western blot. The capacities of cell growth and motility were validated by the MTT assay, flow cytometry assay, EdU assay, colony formation assay, and transwell assay. Moreover, the targeted relationship of miR-145-5p and hsa_circ_0005100 or MACC1 was distinguished by dual-luciferase reporter assay. The animal experiment was implemented to confirm the influence of hsa_circ_0005100 on tumorigenesis in vivo.

Results: Hsa_circ_0005100 and MACC1 expression levels were increased, but miR-145-5p expression level was diminished in CRC. Hsa_circ_0005100 knockdown repressed cell proliferation, cell cycle, migration, and invasion, while expedited cell apoptosis in CRC cells. Furthermore, miR-145-5p was disclosed to block CRC via overturning MACC1. Hsa_circ_0005100 targeted miR-145-5p to modulate MACC1. Additionally, hsa_circ_0005100 knockdown also attenuated tumorigenesis in vivo.

Conclusion: Hsa_circ_0005100 was a vital regulator in the development of CRC by miR-145-5p/MACC1 axis, which deepened the understanding of CRC pathogenesis from circRNA insights.

KEYWORDS
colorectal carcinoma, hsa_circ_0005100, MACC1, miR-145-5p

INTRODUCTION

Colorectal carcinoma (CRC) is strictly associated with people's chronic inflammation, diet habits, genetic factors, and so on. Clinically, the 5-year survival rate for local CRC was about 90%, and it could drop sharply to 10% if distant metastasis occurred. At present, the effective measures to prevent CRC are mainly colonoscopy. Therefore, novel treatment strategies are impending.

Circular RNAs (circRNAs) are classified into non-coding RNAs, but evidence reveals that certain circRNAs have potential...
protein-coding ability.\textsuperscript{5–8} CircRNAs are imperative participators in various cancers, including CRC.\textsuperscript{9,10} For instance, circLONP2 could enhance CRC invasion and metastasis.\textsuperscript{11} CircRNA\textsubscript{103809} could participate in the progression of CRC.\textsuperscript{12} Hsa\_circ\_0005100 might function as potential diagnostic and prognostic indicators for CRC detection.\textsuperscript{13} Hsa\_circ\_0005100 could trigger the malignant phenotypes of prostate cancer cells.\textsuperscript{14} and it also promoted cancer cell proliferation in CRC.\textsuperscript{15} Hsa\_circ\_0005100 is generated by back-splicing from formin 2 gene (FMN2), also known as circFMN2. Nevertheless, the detailed monitoring mode of hsa\_circ\_0005100 in CRC was not legible.

MicroRNAs (miRNAs) are small RNAs that regulate various cellular biological functions.\textsuperscript{5,6} For instance, miR-145-5p regulated stemness in glioma.\textsuperscript{16} In addition, miR-145-5p prevented the evolution of breast cancer.\textsuperscript{17,18} Besides, miR-210, miR-21, and miR-126 could act as diagnostic markers in CRC.\textsuperscript{19} Moreover, miR-212 could suppress the progression of CRC.\textsuperscript{20} Yet, the definite upshot of miR-145-5p in CRC was vague.

Metastasis-associated in colon cancer-1 (MACC1) situated on human chromosome 7 (7p21.1) was an important biomarker for predicting distant metastasis of colon cancer.\textsuperscript{21} Meanwhile, the level of MACC1 was faithfully correlated to the recurrence of many cancers.\textsuperscript{21–24} MACC1 promoted the proliferation of cancer cells.\textsuperscript{21} In addition, MACC1 could also affect the angiogenesis of gastric cancer,\textsuperscript{26} but the functional effects of MACC1 in CRC were still uncertain.

Herein, we revealed the functions of hsa\_circ\_0005100 in CRC cells. Hsa\_circ\_0005100 might expedite CRC progression via miR-145-5p/MACC1. Our conclusions will afford original perceptions into the monitoring mode of hsa\_circ\_0005100 in CRC evolution.

2 | MATERIALS AND METHODS

2.1 | Clinical samples

The experiment was sustained by the Third Hospital Affiliated to Hebei Medical University. Forty-three pairs of CRC tissues and para-carcinoma tissue were collected from the Third Hospital Affiliated to Hebei Medical University, and written informed consent was attained from all subjects. Then, all samples were frozen. CRC patients who had never received any therapies against CRC (such as chemotherapy and radiotherapy) and had no other types of cancers or severe systemic diseases were included in our study. The characteristics of included CRC patients are listed in Table 1.

2.2 | Cell lines and transfection

We chose CRC cell lines HCT116 and SW480, using the NCM460 as a non-cancer control. All cells were acquired from Chuan Qiu Biotechnology and cultured in 37°C incubators with 5% CO\textsubscript{2}.

| Parameters                       | No. of cases | Circ\_FMN2 expression (n) | p-value |
|----------------------------------|--------------|---------------------------|---------|
| Age (years)                      |              |                           |         |
| ≤60                              | 26           | 15                        | 11      | 0.2895  |
| >60                              | 17           | 7                         | 10      |
| Gender                           |              |                           |         |
| Female                           | 23           | 14                        | 9       | 0.1721  |
| Male                             | 20           | 8                         | 12      |
| Lymph node metastasis            |              |                           |         |
| Yes                              | 23           | 16                        | 7       | 0.0096* |
| No                               | 20           | 6                         | 14      |
| TNM stage                        |              |                           |         |
| I–II                             | 20           | 7                         | 13      | 0.0480* |
| III                              | 23           | 15                        | 8       |
| Tumor size (cm)                  |              |                           |         |
| ≤5                               | 18           | 6                         | 12      | 0.0472* |
| >5                               | 25           | 16                        | 9       |
| Tumor location                   |              |                           |         |
| Colon                            | 18           | 10                        | 8       | 0.6249  |
| Rectum                           | 25           | 12                        | 13      |

\textsuperscript{a}Chi-square test.

\textsuperscript{*}P < 0.05 indicates statistical difference.

| Parameters               | No. of cases | Circ\_FMN2 expression (n) | p-value |
|--------------------------|--------------|---------------------------|---------|
| Age (years)              |              |                           |         |
| ≤60                      | 26           | 15                        | 11      | 0.2895  |
| >60                      | 17           | 7                         | 10      |
| Gender                   |              |                           |         |
| Female                   | 23           | 14                        | 9       | 0.1721  |
| Male                     | 20           | 8                         | 12      |
| Lymph node metastasis    |              |                           |         |
| Yes                      | 23           | 16                        | 7       | 0.0096* |
| No                       | 20           | 6                         | 14      |
| TNM stage                |              |                           |         |
| I–II                     | 20           | 7                         | 13      | 0.0480* |
| III                      | 23           | 15                        | 8       |
| Tumor size (cm)          |              |                           |         |
| ≤5                       | 18           | 6                         | 12      | 0.0472* |
| >5                       | 25           | 16                        | 9       |
| Tumor location           |              |                           |         |
| Colon                    | 18           | 10                        | 8       | 0.6249  |
| Rectum                   | 25           | 12                        | 13      |

\textsuperscript{a}Chi-square test.

\textsuperscript{*}P < 0.05 indicates statistical difference.
The si-hsa_circ_0005100, sh-hsa_circ_0005100, the control (si-NC and sh-NC), miR-145-5p mimics, miR-145-5p inhibitors and controls, MACC1 overexpression (MACC1), and control (pcDNA) were acquired from Sangon Biotech. CRC cells were transfected with oligonucleotides or vectors using Lipofectamine 2000 reagent (Invitrogen).

2.3 | RNA extraction and qRT-PCR

TRizol Reagent (Invitrogen) was enforced to isolate total RNA. The qRT-PCR was implemented by SYBR Green kit (Takara), GAPDH or RNU6 (U6) was applied as an endogenous control. The $2^{-\Delta\Delta C_t}$ method was enforced to analyze relative expression. The primers were listed in Table 2.

2.4 | Western blot

The process of Western blot was performed as recounted previously.27 The antibodies were listed as follows: anti-MACC1 (ab226803; 1:1000; Abcam), anti-PCNA (ab92552; 1:1000; Abcam), and anti-GAPDH (ab9485; 1:2500; Abcam).

2.5 | RNase R digestion assay

Total RNA from the experimental cells was dealt with RNase R (Sigma-Aldrich). Finally, the hsa_circ_0005100 and FMN2 mRNA contents were revealed by qRT-PCR.

2.6 | MTT assay

After post-transfection, CRC cells (2 × 10^3 per well) were seeded in 96-well plates. The 20 μl of MTT (Sigma) solution was supplemented and incubated. Then, the absorbance values were measured.

2.7 | Flow Cytometry assay

CRC cells (1 × 10^6 per well) were planted in 6-well plates. Annexin V-FITC/PI kit (Sigma) and PI Flow Cytometry Kit (Abcam) were implemented to distinguish the cell apoptotic and cycle in line with the instructions. Finally, the cells were examined by a flow cytometer (Beckman Coulter, Miami, FL, USA).

2.8 | Cell proliferation assay

CRC cells were cultured in 96-well plates (2 × 10^4/well). Next, the EdU Apollo In Vitro Imaging Kit (Sigma) was employed in line with the guide. In brief, cells in 96-well plates were cultured for 48 hours and then co-cultured with EdU for another 8 h. After EdU labeling, cell fixing was performed using the fixative solution from Kit, and then, cell nucleus was stained with DAPI. The number of EdU-positive cells was observed by light microscopy (Nikon).

2.9 | Colony formation assay

CRC cells were plated in 6-well plates (300 cells/well). The cell culture medium was changed every 3 days for 2 weeks. Subsequently, the colonies were washed with PBS, fixed by 4% paraformaldehyde, and then stained with 0.5% crystal violet for 15 min. A light microscope was used to observe the colonies.

2.10 | Transwell assay

After post-transfection, CRC cells were assessed by a transwell with 8-μm pore polycarbonate membrane (BD Biosciences). In brief, 4 × 10^5 transfected CRC cells, resuspended in 100 μl DMEM without serum, were planted into the top chamber. Then, the lower chamber of the transwell contained 500 μl of DMEM and 10% FBS. Next, the cells on the inferior surface of the membrane were stained. The same method was enforced to detect the invasion ability with the chamber was precoated with matrigel (BD Biosciences). Eventually, a light microscope was performed to validate the count of cells.

| Name | Primers for PCR (5′-3′) |
|------|-------------------------|
| circ_FMN2 | AGAACCACCGAGACCTTTTTTA |
|         | GAGACCTTGAAGGGTCTCAG   |
| MACC1  | GTGATGGCTGTGGGAGAAGA   |
|         | TTTCCAACAACGGGCTTCA    |
| miR-145-5p | AGGGGGTCCAGTTTTCCCAGG |
|         | GTGCGTGTCGTGGAGTCG     |
| GAPDH  | TCCCATACCATCTTGAGAGA   |
|         | GTGCGTGTCTGGAGTCG      |
| U6     | GTGCGTGTCTGGAGTCG      |
| FMN2   | CTCGGCTCCGGCACAGCATGATC |
2.11 | Dual-luciferase reporter assay

The targeted relationship of miR-145-5p and hsa_circ_0005100 or MACC1 was anticipated by circbank and starbase. Then, the pmirGLO vector was used to construct luciferase reporter vectors, and the hsa_circ_0005100 or MACC1 wild-type (WT) and mutant-type (MUT) reporter vectors were produced by Sangon Biotech (hsa_circ_0005100-WT, MACC1-WT or hsa_circ_0005100-MUT, MACC1-MUT). Luciferase activity was quantified using dual-luciferase assay kit (Sigma) along with the directives.

2.12 | In vivo tumorigenicity

The Animal Care and Use Committee of the Third Hospital Affiliated to Hebei Medical University supervised the whole test process. These nude mice (female; 6-week-old; 18–22 g) were gotten from Shanghai Laboratory Animal Company (SLAC, Shanghai, China). HCT116 cells (5 × 10⁶ cells per mouse) infected with the sh-hsa_circ_0005100 or the sh-NC were vaccinated in mice (n = 6/group). The volume (mm³) = length × width² × 0.5. Next, the tissues were used for examination.

2.13 | IHC assay

The cleaved caspase-3 (ab90437; 1:1000; Abcam) and Ki67 (ab92742; 1:1000; Abcam) contents in tumor were distinguished by IHC assay. The detailed procedures were conducted as reported by Zou et al. Briefly, tumor tissues from mice were cut into 4-μm thickness slides, followed by dewaxing, rehydration, and antigen retrieval. Then, the slides were challenged with the antibodies targeting cleaved caspase-3 and Ki67. After incubation of matched secondary antibody, the slides were stained using the DAB kit from Abcam. The positive staining was observed by light microscopy.

2.14 | Statistical assay

The data were investigated by GraphPad Prism 7. The experiment was reiterated at least three times. Pearson’s correlation analysis was enforced to quantity the correlation between two groups. Student’s t test and ANOVA were implemented to detect the difference. p < 0.05 was significant.
FIGURE 2  Hsa_circ_0005100 downregulation inhibits CRC. (A, B) The hsa_circ_0005100 contents were assessed. (C, D) The cell viability was assessed. (E, F) The cell mitotic cycle was assessed. (G, H) The Edu-positive cell was detected. (I) The PCNA level was detected. (J, K) The cell migration and invasion were validated. (L) The apoptosis of CRC cells was observed. *P < 0.05
3 | RESULTS

3.1 | Hsa_circ_0005100 abundance was elevated in CRC

To scrutinize the possible role of hsa_circ_0005100 in CRC, its abundance was confirmed in CRC by qRT-PCR. First of all, we reconnoitered that hsa_circ_0005100 level was elevated in CRC (Figure 1A,B). As exposed in Figure 1C,D, the FMN2 mRNA was significantly reduced after RNase R treatment, while hsa_circ_0005100 was basically not altered, verifying the cyclic structure of hsa_circ_0005100. Moreover, hsa_circ_0005100 was mainly distributed in the cytoplasm relative to the nucleus. (Figure 1E,F). These outcomes exposed that hsa_circ_0005100 was elevated in CRC. Additionally, hsa_circ_0005100 was substantiated to have a circular structure.

3.2 | Downregulation of hsa_circ_0005100 restrained CRC development

To reconnoiter the effect of hsa_circ_0005100 in CRC cells, HCT116 and SW480 cells were transfected with si-NC or si-hsa_circ_0005100. Hsa_circ_0005100 content was elevated in CRC cells after si-hsa_circ_0005100 transfection (Figure 2A,B). Moreover, hsa_circ_0005100 downregulation lessened the cell vitality (Figure 2C,D). Besides, si-hsa_circ_0005100 transfection considerably hindered CRC cells in the G0/G1 phase (Figure 2E,F). Hsa_circ_0005100 deficiency diminished the cell proliferation of CRC cells (Figure 2G). Furthermore, the consequences presented the downregulated hsa_circ_0005100 reduced the amount of colonies (Figure 2H). PCNA was demonstrated to be connected with cell proliferation. Herein, we substantiated that si-hsa_circ_0005100 abridged PCNA level in CRC cells (Figure 2I). Silencing of hsa_circ_0005100 reserved migration and invasion of CRC cells.
Besides, hsa_circ_0005100 deficiency tempted cell apoptosis in CRC cells (Figure 2L). Our consequences directed that down-regulated hsa_circ_0005100 prevented CRC.

3.3 MiR-145-5p targeted hsa_circ_0005100

To confirm whether hsa_circ_0005100 served as a miRNA sponge, the possible target of hsa_circ_0005100 was predicted and assessed. Circbank was employed to envisage that miR-145-5p bound to hsa_circ_0005100 (Figure 3A). Besides, the luciferase activity was diminished in hsa_circ_0005100-WT with miR-145-5p transfection, but there was no alteration in the hsa_circ_0005100-MUT group (Figure 3B,C). Additionally, we exposed that miR-145-5p was amplified by silencing hsa_circ_0005100 (Figure 3D). The miR-145-5p content was lesser in CRC (Figure 3E,G). In addition, Pearson’s correlation analysis indorsed that miR-145-5p level was negatively linked with hsa_circ_0005100 in CRC (Figure 3F).
3.4 | Hsa_circ_0005100 expedited CRC by targeting miR-145-5p

In consideration that miR-145-5p was a target of hsa_circ_0005100, we hypothesized that hsa_circ_0005100 regulated the development of GRC cells via miR-145-5p. Primarily, miR-145-5p content was increased by si-hsa_circ_0005100, whereas declined by anti-miR-145-5p in CRC cells (Figure 4A). Besides, hsa_circ_0005100 downregulation reduced the cell vitality; nevertheless, the inhibitory cell viability was recovered by anti-miR-145-5p (Figure 4B,C). Moreover, silence of hsa_circ_0005100 could considerably hinder CRC cell cycle in the G0/G1 phase, whereas this outcome was damaged by downregulated miR-145-5p (Figure 4D,E). In the meantime, the results exposed that hsa_circ_0005100 knockdown weakened the cell proliferation, while this upshot was reduced by anti-miR-145-5p (Figure 4F,G). Furthermore, miR-145-5p inhibitors reserved the influences of hsa_circ_0005100 knockdown on diminished PCNA level in CRC cells (Figure 4H). Transwell assay revealed that si-hsa_circ_0005100 transfection diminished the cell migration and invasion, yet this consequence was decreased by miR-145-5p deficiency (Figure 4I,J). Furthermore, downregulation of hsa_circ_0005100 prompted cell apoptosis, while this influence was debilitated by anti-miR-145-5p (Figure 4K). Our discoveries verified that si-hsa_circ_0005100 repressed CRC cell behaviors by targeting miR-145-5p.
3.5 | MiR-145-5p targeted MACC1 in CRC cells

MiRNAs could regulate tumor progression by targeting mRNAs. Consequently, the imaginable target genes of miR-145-5p were foretold. The targeted sites of miR-145-5p in MACC1 3’UTR were displayed in Figure 5A. The luciferase activity of MACC1 3’UTR-WT was retarded after miR-145-5p treatment. Yet, the MACC1 3’UTR-MUT group was not reformed (Figure 5B,C). Additionally, miR-145-5p content was increased by miR-145-5p mimics and reduced by anti-miR-145-5p (Figure 5D). However, the expression of MACC1 was lessened by miR-145-5p mimics and augmented by anti-miR-145-5p (Figure 5E,F). Additionally, the MACC1 content was upregulated in CRC (Figure 5G,H). As well, Pearson's correlation analysis corroborated that miR-145-5p level was negatively linked with MACC1 mRNA content (Figure 5I). Nevertheless, the MACC1 content was positively linked with hsa_circ_0005100 (Figure 5J). Figure SK,L exhibited that MACC1 was upregulated in CRC cells (HCT116 and SW480) when compared to NCM460 cells. Furthermore, miR-145-5p inhibitors alleviated the influences of hsa_circ_0005100 silencing on reduced content of MACC1 in CRC cells (Figure SM,N). As a group, these sightings advocated that miR-145-5p bound to MACC1.

3.6 | MiR-145-5p blocked CRC by regulating MACC1

To uncover whether miR-145-5p affected CRC progression via MACC1, recovery tests were implemented. Firstly, the MACC1 content was declined by transfection with miR-145-5p, but this influence was partly impaired by MACC1 overexpression in CRC cells (Figure 6A,B). Afterward, miR-145-5p confined the cell viability; nevertheless, this influence was weakened by MACC1 (Figure 6C,D). The miR-145-5p impeded CRC cell cycle in the G0/G1 phase, while this consequence was diminished by MACC1 (Figure 6E,F). Besides, miR-145-5p diminishes the cell proliferation of CRC cells, while MACC1 overexpression recovered miR-145-5p-depleted cell proliferation...
Figure 6G,H). Figure 6I established that MACC1 reversed the influence of miR-145-5p mimics on dwindled PCNA level in CRC cells. Moreover, miR-145-5p weakened the cell migration and invasion; conversely, this consequence was weakened by MACC1 (Figure 6J,K).

Successively, we observed that miR-145-5p expedited cell apoptosis in CRC cells, and the effect was limited by MACC1 (Figure 6L). In summary, all facts demonstrated that miR-145-5p controlled CRC development via MACC1.

3.7 | Silencing hsa_circ_0005100 constrained tumorigenesis in vivo

To reconnoiter the clinical application of hsa_circ_0005100 on CRC in vivo, the xenograft model was implemented. The sh-hsa_circ_0005100 constrained tumor volume and weight (Figure 7A,B). Furthermore, hsa_circ_0005100, MACC1, and Ki67 were apparently abridged, but miR-145-5p and cleaved caspase-3 were exceptionally amplified in sh-hsa_circ_0005100 group (Figure 7C–G). These consequences pointed out that silencing hsa_circ_0005100 repressed tumorigenesis via miR-145-5p/MACC1 axis.

4 | DISCUSSION

Studies have found the mortality of CRC was snowballing. The growth of CRC is associated with lifestyle factors, such as smoking, lack of exercise, obesity, red meat consumption, and excessive alcohol consumption. CRC has become a challenge for people. Meanwhile, there were many circRNAs that were singularly expressed in CRC. Nevertheless, the characteristics of these circRNAs in CRC were still uncertain. Hence, our study inspected the part of hsa_circ_0005100.

Preceding readings have discovered that many circRNAs are vital for CRC. For example, hsa_circ_102958 encouraged tumorigenesis of CRC. Besides, circCAMSAP1 promoted tumor growth in CRC. In our study, our outcomes designated that downregulation of hsa_circ_0005100 prevented CRC. In addition, our in vivo study further discovered that knockdown hsa_circ_0005100 impaired tumor growth. The circRNAs could control targeted genes and bound to miRNAs. For example, hsa_circ_102958 bound to miR-585 and circCAMSAP1 could sponge miR-328-5p in CRC. Herein, hsa_circ_0005100 impelled CRC via miR-145-5p, which was comparable to former discoveries.
cancer, and studies declared that miR-145-5p exerted the inhibitory effects on cancer cell proliferation, migration, and invasion, and the stimulative effects on cell apoptosis and cell cycle via controlling its target genes. 34−36 Here, we demonstrated that miR-145-5p played a curbed part in CRC by binding MACC1. MACC1 was reported to be highly upregulated in gastric cancer and acts as a vital role in gastric cancer by enhancing immune killing. 37 MACC1 was also overexpressed in osteosarcoma, and its silencing arrested cell cycle in G0/G1 phase and induced cell apoptosis of osteosarcoma cells. 38 Moreover, MACC1 deficiency blocked cervical cancer cell proliferation through interfering cell mitosis and cell cycle progression. 39 In this study, MACC1 expression was enhanced in CRC. We witnessed that miR-145-5p retarded CRC cell growth, arrested cell cycle, blocked cell migration/invasion, and induced cell apoptosis; however, these anticancer effects caused by miR-145-5p were considerably diminished by MACC1. miR-145-5p knockdown attenuated the restrained outcome of downregulated hsa_circ_0005100 on MACC1 expression in CRC cells. These consequences sustained the monitoring mode of the hsa_circ_0005100/miR-145-5p/MACC1 in CRC.

There are still some limitations in the present study. For example, the amount of clinical samples is not enough, and more samples should be used to identify hsa_circ_0005100 expression in future work. Besides, we only focus on the miR-145-5p/MACC1 axis downstream of hsa_circ_0005100, and other miRNA/mRNA signals targeted by hsa_circ_0005100 should be further identified.

In summary, hsa_circ_0005100 and MACC1 levels were enhanced and miR-145-5p level was lessen in CRC. Additionally, our study firstly demonstrated that hsa_circ_0005100 deficiency suppressed CRC malignant progression via miR-145-5p/MACC1 axis. We provided perception into the monitoring network in CRC and presented new thinking for curing CRC patients.

CONFLICT OF INTEREST
The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT
The data used to support the findings of this study are available from the corresponding author upon request.

ORCID
Shipeng Zhao https://orcid.org/0000-0003-1238-0218

REFERENCES
1. Lasry A, Zinger A, Ben-Neriah Y. Inflammatory networks underlying colorectal cancer. Nat Immunol. 2016;17(3):230-240.
2. Ostuni R, Kratochvill F, Murray PJ, Natoli G. Macrophages and cancer: from mechanisms to therapeutic implications. Trends Immunol. 2015;36(4):229-239.
3. Richter JM, Campbell EJ, Chung DC. Interval colorectal cancer after colonoscopy. Clin Colorectal Cancer. 2015;14(1):46-51.
4. Allen JI. Quality measures for colonoscopy: where should we be in 2015? Curr Gastroenterol Rep. 2015;17(3):10.
5. Ambros V. The functions of animal microRNAs. Nature. 2004;431(7006):350-355.
6. Garzon R, Marcucci G, Croce CM. Targeting microRNAs in cancer: rationale, strategies and challenges. Nat Rev Drug Discov. 2010;9(10):775-789.
7. Li Z, Ruan Y, Zhang H, Shen Y, Li T, Xiao B. Tumor-suppressive circular RNAs: mechanisms underlying their suppression of tumor occurrence and use as therapeutic targets. Cancer Sci. 2019;110(12):3630-3638.
8. Lu Y, Li Z, Lin C, Zhang J, Shen Z. Translation role of circRNAs in cancers. J Clin Lab Anal. 2021;35(7):e23866.
9. Greene J, Baird AM, Brady L, et al. Circular RNAs: biogenesis, function and role in human diseases. Front Mol Biosci. 2017:4:38.
10. Sheng JQ, Liu L, Wang MR, Li PY. Circular RNAs in digestive system cancer: potential biomarkers and therapeutic targets. Am J Cancer Res. 2018;8(7):1142-1156.
11. Han K, Wang FW, Cao CH, et al. CircLONP2 enhances colorectal carcinoma invasion and metastasis through modulating the maturation and exosomal dissemination of microRNA-17. Mol Cancer. 2020;19(1):60.
12. Bian L, Zhi X, Ma L, et al. Hsa_circRNA_103809 regulated the cell proliferation and migration in colorectal cancer via miR-532-3p / FOXO4 axis. Biochem Biophys Res Commun. 2018;505(2):346-352.
13. Zhang J, Cai A, Zhao Y. Three circRNAs function as potential biomarkers for colorectal cancer. Clin Lab. 2020;66(12). doi:10.7754/Clin.Lab.2020.191265
14. Shan G, Shao B, Liu Q, et al. circFMN2 sponges miR-1238 to promote the expression of LIM-homeobox gene 2 in prostate cancer cells. Mol Ther Nucleic Acids. 2020;12:133-146.
15. Li Y, Li C, Xu R, Wang Y, Li D, Zhang B. A novel circFMN2 promotes tumor proliferation in CRC by regulating the miR-1182/hTERT signaling pathways. Clin Sci (Lond). 2019;133(24):2463-2479.
16. Chen J, Chen T, Zhu Y, et al. circPTN sponges miR-145-5p/miR-330-5p to promote proliferation and stemness in glioma. J Exp Clin Cancer Res. 2019;38(1):398.
17. Gao W, Zhang C, Li W, et al. Promoter methylation-regulated miR-145-5p inhibits laryngeal squamous cell carcinoma progression by targeting FSCN1. Mol Ther. 2019;27(2):365-379.
18. Tang W, Zhang X, Tan W, et al. miR-145-5p suppresses breast cancer cell proliferation by inhibiting SOX2. J Surg Res. 2019;236:278-287.
19. Sabry D, El-Deek SEM, Maher M, et al. Role of miRNA-210, miRNA-21 and miRNA-126 as diagnostic biomarkers in colorectal carcinoma: impact of HIF-1alpha-VEGF signaling pathway. Mol Cell Biochem. 2019;454(1-2):177-189.
20. Mou TY, Zhang RR, Wang YN. MiRNA-212 acts as a tumor-suppressor in colorectal carcinoma through targeting SOX4. Eur Rev Med Pharmacol Sci. 2019;23(24):10751-10760.
21. Stein U, Walther W, Arit F, et al. MACC1, a newly identified key regulator of HGF-MET signaling, predicts colon cancer metastasis. Nat Med. 2009;15(1):59-67.
22. Shimokawa H, Uramoto H, Onitsuka T, et al. Overexpression of MACC1 mRNA in lung adenocarcinoma is associated with postoperative recurrence. J Thorac Cardiovasc Surg. 2011;141(4):895-898.
23. Wang G, Kang MX, Lu WJ, et al. MACC1: a potential molecule associated with pancreatic cancer metastasis and chemoresistance. Oncol Lett. 2012;4(4):783-791.
24. Sattler M, Salgia R. C-met and hepatocyte growth factor: potential as novel targets in cancer therapy. Curr Oncol Rep. 2007;9(2):102-108.
25. Lederer A, Herrmann P, Seehofer D, et al. Metastasis-associated in colon cancer 1 is an independent prognostic biomarker for survival in Klatzkin tumor patients. Hepatology. 2015;62(3):841-850.
26. Wang L, Wu Y, Lin L, et al. Metastasis-associated in colon cancer-1 upregulation predicts a poor prognosis of gastric cancer, and promotes tumor cell proliferation and invasion. Int J Cancer. 2013;133(6):1419-1430.
27. Hou W, Zhang Y. Circ_0025033 promotes the progression of ovarian cancer by activating the expression of LSM4 via targeting miR-184. Pathol Res Pract. 2021;217:153275.
28. Zou T, Duan J, Liang J, et al. miR-338-3p suppresses colorectal cancer proliferation and progression by inhibiting MACC1. *Int J Clin Exp Pathol*. 2018;11(4):2256-2267.

29. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011;61(2):69-90.

30. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016;66(2):115-132.

31. Center MM, Jemal A, Smith RA, Ward E. Worldwide variations in colorectal cancer. *CA Cancer J Clin*. 2009;59(6):366-378.

32. Li R, Wu B, Xia J, Ye L, Yang X. Circular RNA hsa_circRNA_102958 promotes tumorigenesis of colorectal cancer via miR-585/CDC25B axis. *Cancer Manag Res*. 2019;11:6887-6893.

33. Zhou C, Liu HS, Wang FW, et al. circCAMSAP1 promotes tumor growth in colorectal cancer via the miR-328-5p/E2F1 Axis. *Mol Ther*. 2020;28(3):914-928.

34. Liang H, Sun H, Yang J, Yi C. miR1455p reduces proliferation and migration of hepatocellular carcinoma by targeting KLF5. *Mol Med Rep*. 2018;17(6):8332-8338.

35. Jin C, Wang A, Liu L, Wang G, Li G, Han Z. miR-145-5p inhibits tumor occurrence and metastasis through the NF-kappaB signaling pathway by targeting TLR4 in malignant melanoma. *J Cell Biochem*. 2019;120:11115-11126. doi:10.1002/jcb.28388

36. Guan X, Guan Y. miR-145-5p attenuates paclitaxel resistance and suppresses the progression in drug-resistant breast cancer cell lines. *Neoplasma*. 2020;67(5):972-981.

37. Tong G, Cheng B, Li J, et al. MACC1 regulates PDL1 expression and tumor immunity through the c-met/AKT/mTOR pathway in gastric cancer cells. *Cancer Med*. 2019;8(16):7044-7054.

38. Zhang K, Tian F, Zhang Y, et al. MACC1 is involved in the regulation of proliferation, colony formation, invasion ability, cell cycle distribution, apoptosis and tumorigenicity by altering Akt signaling pathway in human osteosarcoma. *Tumour Biol*. 2014;35(3):2537-2548.

39. Chai H, Yang Y. Effects of MACC1 siRNA on biological behaviors of HeLa. *Arch Gynecol Obstet*. 2014;289(6):1271-1280.

How to cite this article: Zhang T, Yu S, Zhao S. Hsa_circ_0005100 regulates tumorigenicity of colorectal carcinoma via miR-145-5p/MACC1 axis. *J Clin Lab Anal*. 2022;36:e24533. doi: 10.1002/jcla.24533