Circ_cse1l Inhibits Colorectal Cancer Proliferation by Binding to eIF4A3

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Background: Circular RNAs (circRNAs) are involved in the growth of many tumors. However, the expression and possible role of circ_cse1l (hsa_circ_0060745) in colorectal cancer (CRC) are unclear. The present study was designed to explore the role of circ_cse1l in CRC.

Material/Methods: The levels of circ_cse1l expression in cancer tissues and serum samples of 50 patients with CRC and in control subjects were analyzed by quantitative reverse transcription-polymerase chain reaction (qRT-PCR). CCK-8, colony formation, transwell and wound healing assays were performed to assess the functions of circ_cse1l in CRC cell lines after overexpression. The relationship between circ_cse1l and eIF4A3 during cell proliferation was analyzed by western blotting and RNA-binding protein immunoprecipitation (RIP).

Results: qRT-PCR assays showed that the levels of expression of circ_cse1l were lower in CRC cell lines and in tissue and serum samples from patients with CRC than in control samples. The expression of circ_cse1l in CRC tissues had clinical significance, as its level of expression was inversely associated with the depth of tumor invasion. Overexpression of circ_cse1l in HT29 and HCT116 cells markedly reduced cell proliferation and metastasis. Western blotting showed that circ_cse1l overexpression downregulated the expression of PCNA protein. RIP results demonstrated that circ_cse1l inhibited the proliferation of CRC cells by binding to eIF4A3.

Conclusions: The expression of circ_cse1l is downregulated in CRC. Furthermore, circ_cse1l downregulated PCNA expression by binding to eIF4A3, inhibiting the proliferation of CRC cells.

MeSH Keywords: Biological Markers • Cell Proliferation • Colorectal Neoplasms • Diagnosis • DNA, Circular • Eukaryotic Initiation Factor-4A

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Background

Colorectal cancer (CRC) is the third most common type of cancer worldwide [1], with nearly 2 million persons newly diagnosed with CRC and nearly 900,000 patients dying of this disease in 2018 [2]. The rate of distant metastasis in CRC patients is about 40%, and the recurrence rate in the absence of lymph node metastasis is about 25% [3,4]. Despite improvements in its diagnosis and treatment and the elucidation of some of the molecular mechanisms of CRC, CRC incidence and mortality rates remain high [5]. At present, the molecular markers commonly used in the clinical diagnosis of CRC include carcinoembryonic antigen (CEA), CA199 and markers of inflammation such as NLR and PLR. These markers, however, are relatively insensitive and are therefore used as markers of tumor recurrence [6–8]. Therefore, it is necessary to identify biomarkers effective in the diagnosis of CRC.

Circular RNA (circRNA) is a series of functional molecules involved in many physiological and pathological processes. CircRNAs are mainly formed by RNA splicing at the 5' end of the upstream exon and the 3' end of the downstream exon [9]. Compared with conventional linear RNA, the structure of circular RNA is more stable [10]. Moreover, circRNAs may be potential biomarkers in tumors. Studies have shown that several circRNAs, including Circ_0104631 and circZNF609, are abnormally expressed in CRC and may have biological functions in these tumors [11–12]. However, the biological function of most circular RNAs in CRC is still unclear.

CSE1L, originally isolated from breast cancer cells [13], has been associated with the invasion, metastasis and proliferation of many tumors, including bladder [14], lung [15], breast [16] and colorectal [17] cancers. Knock-down of CSE1L was found to inhibit the expression of CRC cells and promote their apoptosis [18]. The biological properties of the circRNA derived from CSE1L has not yet been assessed in CRC. The present study assessed the expression, function and mechanism of action of circ_cse1l in CRC.

Material and Methods

Patients and sample collection

The study was approved by the ethics committee of our institution, and informed consent was obtained from each patient. Between March 2018 and July 2018, tissue and serum samples were obtained from 50 CRC patients diagnosed and treated at our center. Patients were included if they were pathologically confirmed as having primary CRC, if radical resection was feasible, if their clinicopathological data were complete, and if they had not received radiotherapy, chemotherapy or any other neoadjuvant therapy before surgery. Tissue and serum samples were obtained within 20 minutes after surgery and stored in an ultra-low temperature freezer. As controls, peripheral blood samples were obtained from 50 healthy individuals. Clinical characteristics of all patients were recorded.

Cell culture and transfection

The FHC, HT29, HCT116, and LoVo cell lines were obtained from the American Type Culture Collection (ATCC; Manassas, VA, USA). FHC cells were cultured in complete DMEM (Invitrogen, USA), and the other cell lines were cultured in McCoy’s 5A complete medium containing 10% serum. All cells were cultured in a CO₂ incubator at constant temperature, and the medium was changed regularly. The circ_cse1l overexpression vector was constructed by Sangon Biotech (Beijing, China), with the empty pCDNA3.1 vector being a negative control. HT29 and HCT116 cells were transfected with these vectors at a certain cell density.

RNA extraction and quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNA was extracted from samples using TRIzol reagent (Life Technologies, USA) and cDNA was synthesized from RNA by reverse transcription using M-MLV First Strand Kits (Beyotime, Beijing, China). qRT-PCR assays were performed using SYBR Green qPCR SuperMix-UDG (Beyotime) and primers for circ_cse1l (forward, 5'-AGGACCAGAACACGCTGACA-3'; reverse, 5'-CGAGGCAGGTATCGCTGGAA-3'), GAPDH (forward, 5'-ATCTTCCAGGAGCGAGATCCC-3'; reverse, 5'-TTTCCGAGTTCTCCACTTGC-3'), PCNA (forward, 5'-ATGCAGACACCTTGGCACTA-3'; reverse, 5'-TTTCCAGAGTTCTCCACTTGC-3'), and GAPDH (forward, 5'-ATCTTCCAGGAGCGAGATCCC-3'; reverse, 5'-TGAGTCTCTCCAGACATACCA-3'). Levels of expression of circ_cse1l and PCNA were normalized to those of GAPDH using the 2⁻ΔΔCT method.

Cell Counting Kit-8 (CCK-8) assay

Each well of a 96-well plate was seeded with about 5000 tumor cells. The cells were transfected with circ_cse1l overexpression vector or empty pCDNA3.1 vector, and cell growth was measured 24, 48, 72, and 96 h later by the CCK-8 method (APEX BIO, Houston, USA). Briefly 10 μl CCK-8 reagents were added to each well, the plates were incubated at 37°C for 2 hours, and the absorbance of cells in each well was measured at 450 nm using a microplate reader.

Colony formation assay

Transfected, logarithmically growing cells were cultured for 24 hours. Each well of a six-well plate was seeded with 500 cells, and the plates were cultured for 2 weeks. The cells were...
subsequently washed, fixed, stained, and dried. The numbers of colonies in each well were counted and photographed.

Wound healing assay

Before the experiment, a horizontal line was drawn evenly behind the six-well plate. Twenty-four hours after transfection, tumor cells were plated uniformly in six-well plates. The cells adherent to each well were scratched with a 200 µl pipette tip, and each well was washed twice with PBS to remove the detached cells. The remaining cells were cultured for 24 hours, and the area of each scratch was assessed with a microscope.

Transwell invasion assay

The invasive ability of the cells was detected using transwell chambers. Briefly, 50 µl of Matrigel (Invitrogen, USA) were spread onto the upper surface of each membrane, and the 24-well plate was cultured for 6 hours. Twenty-four hours after transfection, HT29 and HCT116 cells were starved in serum-free medium for 24 hours. After adjusting the cell concentration, 1×10⁶ cells and 200 µl serum-free medium were added to the upper chamber of each well, and an appropriate amount of McCoy’s 5A complete medium was added to the lower chamber of each Transwell. After culture for 24 hours, the cells in the upper chamber were gently wiped with a cotton swab. Finally, the invasive cells were fixed for 20 min, stained, and counted under a microscope.

Western blotting

HT29 and HCT116 cells were transfected with vector and incubated for 48 hours. Total proteins were extracted using lysis buffer, and the total protein concentration in each lysate was measured using the Lowry method. Aliquots of 30 µg protein were loaded onto each well of an SDS-PAGE gel. Following electrophoresis, the proteins were transferred to a PVDF membrane. The membranes were incubated for 2 hours in solution containing 5% skim milk to block nonspecific binding and incubated with 1: 500 dilution of primary anti-PCNA antibody (Abcam, USA) or a 1: 1000 dilution of primary anti-GAPDH antibody (Abcam, USA) at 4°C overnight with gentle shaking. After washing, the PVDF membranes were incubated with diluted secondary antibody solution for 1 hour. The membranes were scanned using a chemiluminescence imaging analyzer.

RNA immunoprecipitation assay (RIP)

RIP experiments were performed using RIP kits, according to the protocol described by the manufacturer (Millipore, USA). Cells were lysed and their lysates were cleared and incubated with magnetic beads and anti-eIF4A3 antibodies or with non-specific IgG as a control. The beads were washed for RNA extraction, and the enriched RNA was analyzed by qRT-PCR.

Statistical analysis

All data were analyzed using SPSS software 23.0 (IBM, USA). The expression of circ_cse11 in two groups was compared by t-tests, and the clinical significance of circ_cse11 expression in CRC was analyzed by independent sample t-tests. A P-value <0.05 was defined as statistically significant.

Results

Patients

This study included 50 patients, 27 men and 23 women, of median age 60 years (range 30–86 years). Of these 50 patients, 27 had rectal cancer and 23 had colon cancer. Postoperative pathological data showed that 33 patients had tumors ≤5 cm in diameter, whereas 17 had tumors >5 cm. The tumors of 41 patients were well/moderately differentiated, whereas the other nine tumors were poorly differentiated. According to TNM staging criteria, 11 patients were T1+T2 and 39 were T3+T4; 15 patients had lymph node metastasis, whereas 35 did not; and 34 patients were stage I–II and 16 were stage III–IV.

Circ_cse11 is downregulated in CRC and related to clinical characteristics

Of the 12 circRNAs from the host gene cse11 detected in CRC samples (Figure 1A), we chose the circ_cse11 located at chr20: 47688822-47689234 in the human genome (hsa_circ_0060745) as our research target. Expression of circ_cse11 was significantly lower in tissues and serum samples of the 50 CRC patients than in normal controls group (P<0.05) (Figure 1B). In addition, circ_cse11 was expressed in FHC cells and CRC cell lines (HT29, HCT116, LoVo), and we tested the effect of circ_cse11 overexpression in HT29 and HCT116 cells (Figure 1C).

Investigation of the clinical significance of circ_cse11 expression in CRC showed that its level of expression was inversely associated with the depth of tumor invasion (Table 1).

Overexpression of circ_cse11 inhibits the ability of CRC cells to migrate and invade

We evaluated the effect of circ_cse11 expression on the ability of CRC cells to migrate and invade other tissues. Wound healing experiments showed that the overexpression of circ_cse11 reduced the ability of HT29 and HCT116 cells to migrate (Figure 2A), whereas Transwell invasion experiments showed that circ_cse11 expression reduced their invasive ability (Figure 2B).
Overexpression of circ_cse1l inhibits CRC cell proliferation

CCK-8 assessment of the effect of circ_cse1l expression on CRC cell proliferation showed that circ_cse1l overexpression inhibited the proliferation of HT29 and HCT116 cells (Figure 3A). Similar findings were observed in colony formation experiments (Figure 3B). The proliferation marker PCNA is closely associated with cell DNA synthesis and the initiation of the cell proliferation process, an indicator of the development of CRC [19]. Therefore, we assessed the effects of circ_cse1l overexpression on PCNA protein expression in HT29 and HCT116 cells, finding that circ_cse1l overexpression reduced the expression of PCNA (Figure 3C).

Circ_CSE1L can control PCNA expression by binding to eIF4A3

Previous studies have found that, in addition to acting as a miRNA sponge-binding RNA, circRNA can bind to proteins to exert regulatory effects [20]. So, we used CircInteractome (https://circinteractome.nia.nih.gov/) to predict proteins that potentially bind to circ_cse1l. The RIP experiment results identified
eIF4A3 as binding to circ_cse1l (Figure 4A). EIF4A3 is a eukaryotic translation initiation factor that can monitor the quality of mRNA before it enters a translation event. Using the RIP method, we found that the level of PCNA mRNA in fraction immunoprecipitated by anti-eIF4A3 was reduced when circ_cse1l was overexpressed (Figure 4B). These findings indicate that circ_cse1l reduces PCNA expression levels by binding to eIF4A3.

**Discussion**

CRC patients are widely distributed worldwide. Despite recent progress in treatment methods, tumor recurrence and metastasis may still occur in 40% to 50% of patients, and their prognosis is poor [21]. Therefore, it is necessary to identify sensitive biomarkers for the diagnosis of CRC. CircRNA is a special type of endogenous non-coding RNA (ncRNA) [22]. circRNA is differentially expressed in various types of malignant tumor, including CRC, with its level of expression being closely related to clinical stage and prognosis [23,24].

CSE1L is highly expressed in CRC and plays important roles in tumor proliferation, invasion, migration and apoptosis [25]. The present study showed that circ_cse1l derived from the CSE1L gene is also expressed in CRC. We found that circ_cse1l expression was downregulated in CRC cell lines and that it was lower in tissue and serum samples from patients with CRC than from normal, healthy individuals. Moreover, the level of circ_cse1l expression in patients with CRC was inversely associated with the depth of tumor invasion. In exploring the mechanism of action of circ_cse1l in CRC, we found that overexpression of circ_cse1l reduced the proliferation, migration and invasiveness of HT29 and HCT116 tumor cells in vitro, suggesting that circ_cse1l inhibits the proliferation of CRC cells.

PCNA is a marker of cell proliferation, especially in tumors. The level of expression of PCNA was found to be related to the degree of malignancy of CRC, distant metastasis and patient survival rate, and can be used as a biomarker for CRC proliferation [26]. Circ_c0137008 was shown to reduce the viability and colony-forming ability of HT29 and HCT116 tumor cells in vitro, suggesting that circ_cse1l inhibits the proliferation of CRC cells.

CircRNA can not only bind miRNA and act as a “miRNA sponge”, but can also directly regulate molecular mechanisms through interaction with RNA-binding proteins, especially in tumors.

| Clinical parameter            | Group | No. of patients | Mean±S.E. | t-value | P-value |
|------------------------------|-------|----------------|-----------|---------|---------|
| Gender                       |       |                |           |         |         |
| Male                         | 27    | 5.033±2.190    | 0.74      | 0.466   |         |
| Female                       | 23    | 5.582±2.952    |           |         |         |
| Age (years)                  |       |                |           |         |         |
| ≤60                          | 19    | 5.047±2.381    | 0.51      | 0.611   |         |
| >60                          | 31    | 5.432±2.685    |           |         |         |
| Tumor size (cm)              |       |                |           |         |         |
| ≤5                           | 33    | 5.136±2.783    | 0.57      | 0.571   |         |
| >5                           | 17    | 5.576±2.094    |           |         |         |
| Histology/differentiation    |       |                |           |         |         |
| Well+Moderate                | 41    | 5.363±2.637    | 0.45      | 0.652   |         |
| Poor                         | 9     | 4.933±2.252    |           |         |         |
| Depth of invasion            |       |                |           |         |         |
| T1+T2                        | 11    | 5.581±2.046    | 2.65      | 0.011*  |         |
| T3+T4                        | 39    | 5.766±2.343    |           |         |         |
| Lymph node metastasis        |       |                |           |         |         |
| Negative                     | 35    | 5.485±2.797    | 0.98      | 0.332   |         |
| Positive                     | 15    | 4.821±1.881    |           |         |         |
| Tumor stage                  |       |                |           |         |         |
| I–II                         | 34    | 5.601±2.755    | 1.43      | 0.161   |         |
| III–IV                       | 16    | 4.618±1.988    |           |         |         |
| Tumor location               |       |                |           |         |         |
| Colon                        | 23    | 4.826±2.357    | 1.19      | 0.239   |         |
| Rectum                       | 27    | 5.677±2.696    |           |         |         |

* P<0.05.
Overexpression of circ_cse1l inhibits the ability of CRC cells to migrate and invade. HT29 and HCT116 cells were transfected with a circ_cse1l overexpression vector and an empty vector (NC). Overexpression of circ_cse1l reduced the (A) migration and (B) invasion of HT29 and HCT116 cells. *P<0.05, ** P<0.01.

Overexpression of circ-Foxo3 resulted in a greater degree of binding HIF1α and FAK, inhibiting their function and accelerating the process of cell aging [28]. Circ_0014717 was found to inhibit CRC tumors by affecting p16 protein expression [29]. Moreover, circ-0075804 was found to promote the proliferation of retinoblastoma cells by combining with HNRNPK to improve the stability of E2F3 [30]. Using CircInteractome, we predicted that eIF4A3 was a protein that could bind to circ_cse1l and confirmed this binding of eIF4A3 to circ_cse1l by RIP experiments.
Figure 3. Overexpression of circ_cse1I inhibits CRC cell proliferation while reducing PCNA expression. HT29 and HCT116 cells were transfected with a circ_cse1I overexpression vector and an empty vector (NC). (A) CCK-8 and (B) colony formation assays, showing that overexpression of circ_cse1I inhibited the proliferation of HT29 and HCT116 cells. (C) Western blotting experiments, showing that circ_cse1I overexpression reduced the expression of PCNA protein in HT29 and HCT116 cells. * P<0.05, ** P<0.01.
The EJC formed by eIF4A3 can trigger meaningless mediated mRNA decay, affecting mRNA levels and regulating protein expression at the translational and post-translational levels [31,32]. In addition, eIF4A3 has been shown important in certain cancers. For example, circPVRL3 was found to promote the proliferation of gastric cancer cells by combining with eIF4A3 [33]. CircSEPT9, together with E2F1 and EIF4A3, has been shown to promote the occurrence and development of breast cancer through the circSEPT9/miR-637/LIF axis [34]. In addition, eIF4A3 has been reported to affect mRNA expression at the post-transcriptional level, thereby affecting the biological behavior of tumors. Long noncoding RNA H19 was found to bind to eIF4A3, thereby regulating the levels of expression of mRNAs encoding cell cycle-related factors, such as cyclin D1, cyclin E1 and CDK4, and thereby affecting the proliferation of CRC cells [35].

Our experimental results suggest that circ_cse1l binding of eIF4A3 affects the level of expression of PCNA mRNA, a finding confirmed by RIP experiments. These results are consistent previous findings [35], indicating that eIF4A3 can regulate PCNA expression at the mRNA level. To our knowledge, this study is the first to show that circ_cse1l can down-regulate the expression of PCNA by binding to eIF4A3, which in turn affected the proliferation of CRC cells. Additional studies, however, are required to further clarify the role of circ_cse1l in CRC.
Conclusions

This study showed that the expression of circ_cse1l was downregulated in CRC and that its level of expression was inversely related to the depth of tumor invasion. These results also showed that circ_cse1l could downregulate PCNA expression by binding to eilf4A3, thereby inhibiting the proliferation of CRC cells.

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