RETRACTED ARTICLE: Long noncoding RNA SNHG15 enhances the development of colorectal carcinoma via functioning as a ceRNA through miR-141/SIRT1/Wnt/β-catenin axis

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ABSTRACT
Colon cancer, also known as colorectal carcinoma (CRC), remains to be one of the most mainsprings of cancer-produced deaths entire world. We planned to grab the role and possible biological cause of a long noncoding RNA, namely, small nucleolar RNA host gene 15 (SNHG15), in CRC. The mRNA level of SNHG15 in CRC tissues and cells was detected, followed by investigating the impacts of the depression of SNHG15 on CRC cell proliferation (viability and colony-forming), apoptosis, migration, and invasion. Moreover, the association between SNHG15 and miR-141 and the correlation between miR-141 and SIRT1 were also explored. Besides, the influences of dysregulated SNHG15 on the Wnt/β-catenin signal-related proteins were determined. SNHG15 was highly expressed in CRC tissues and cells. Depression of SNHG15 depressed proliferation, enhanced apoptosis, and repressed the migration and invasion of CRC cells. In addition, SNHG15 presented a downside tendency on regulating miR-141, and the miR-141 inhibitor dramatically changeover the impacts of SNHG15 depression on tumor growth and metastasis. Moreover, SIRT1 was verified as a functional target of miR-141 in CRC cells. Besides, the suppression of SNHG15 remarkably controlled activating the Wnt/β-catenin signals, which was reversed after inhibiting miR-141 at the same time. The investigated results in this research revealed that the increased expression of SNHG15 may enhance the process of CRC by acting as a ceRNA in regulating SIRT1 expression by sponging miR-141. Thus we propose that Wnt/β-catenin signals may be a downriver regulator in mediating the impacts of SNHG15 in CRC and SNHG15-miR-141-SIRT1 axis may pave a new sight in explaining the biological processes of CRC.

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Materials and methods

Patient samples

Sixty-eight CRC patients (39 men and 19 women; the average age is 55 years) were recruited in this research from September 2014 to October 2017. Banked CRC tumor tissues and the matched nontumor tissues from the patients were chosen, which were collected in the surgery process. Then the obtained tissues were immediately frozen in liquid nitrogen and stored at −80 °C. The stage of tumor was distinguished based on the TNM classification of the 6th edition AJCC. All of the enrolled patients did not receive any treatments before surgery. The study gained the approval of the medical ethics committee of our hospital, and all patients automatically signed the informed consent.

Cell lines

Four kinds of human CRC cell lines (CaCO-2, HCT8, HCT-116, and LoVo) and the normal human intestinal mucous cell line CEC-HIE-2, which were gained from the American Type Culture Collection (Manassas, VA), were chosen for this experiment. Dulbecco’s modified Eagle’s medium (DMEM) mixed with fetal bovine serum (FBS; 10%, Sangon Biotech, Shanghai, China) and l-glutamine (2 mM; Sangon Biotech) were used for cultivating cells. The cultivate condition is at 37 °C with 10% CO₂ atmosphere.

Cell transfection

Short hairpin RNA targeting SNHG15 (sh-SNHG15) (100 nM), shNC (100 nM), miR-141 mimic (50 nM), mimic control (50 nM), miR-141 inhibitor (150 nM), inhibitor NC (150 nM), siRNA targeting SIRT1 (si-SIRT1) (50 nM), and siNC (50 Nm) were synthesized from Sangon Biotech (China). Lipofectamine® 2000 (Invitrogen) was used for the above vectors cell transfection. After incubation for 48 h, the cells were gained for the afterwards experiments.

RT-qPCR assay

We isolated the total RNA from CRC tissues and cells respectively using the specific kit of Trizol reagent (Sangon Biotech). The cDNA was synthesized via the reverse-transcription experiment using an M-MLV Reverse Transcriptase kit (Sangon Biotech). The standard SYBR Green PCR kit (Takara, Dalian, China) was chosen for carrying out the RT-qPCR assay. β-actin was chosen as confidential references for miRNAs and RNAs, respectively. 2⁻ΔΔCt method was chosen for analyzing the relative gene expression levels.

Dual-luciferase reporter test

A pMIR-REPORT-SIRT1-3’UTR-wt/mut (Obio, Shanghai, China) construct was generated and subsequently transfected into the specific cells of HCT-116, together with miR-141 mimic/mimic control. Later, transfected cells were further incubated for 48 h, Dual-Luciferase Reporter Assay System (E1910, Promega, WI) was chosen for determining the luciferase activity in each group.

Cell viability test

We chose MTT kit for the assessment of cell viability. In brief, cells (2 × 10⁴/well) were incubated in a 96-well plate for different treatments. Later, MTT (0.1 mg; Sigma-Aldrich, St. Louis) was mixed in the cells and continuously fostered at 37 °C for 4 h to produce formazan crystals. Subsequently, dimethyl sulfoxide (150 μL) was mixed in the cultured system for dissolving the crystals. Finally, we used a plate reader (MRX II; Dynex Technologies, Chantilly, VA) to measure the absorbance.

Colony-forming test

After different treatments, the incubated cells were re-suspended in the medium mixed with 10% FBS, and then seeded in a six-well plate (400 cells/well). Later, cells were incubated for 2 weeks for measuring the formation of colonies. Absolute methanol was chosen for fixing colonies, and then crystal violet was used for staining all cloning. Any colony with a diameter > 2 mm was considered statistically significant.

Cell apoptosis

The cells (1 × 10⁶ cells/mL) were harvested after different treatments, followed by being suspended again in binding buffer (100 μL). Cells were then stained in Annexin V and PI using the Annexin V-FITC Apoptosis Kit (Sangon Biotech). D LSRII Flow Cytometer System (BD Biosciences) was chosen for the assessment of the apoptotic cells. FACSDIVA Software was chosen for statistical analysis.

Cell migration and invasion assay

We chose Transwell assay for assessing the cell migration and invasion. Thereinto, Matrigel Matrix (1 mg/mL) was added the upward Transwell chamber (8 μm pore size; Costar, Switzerland) for invasion assay specifically. Transwell chambers were firstly prepared for an initial equilibrium; for that, their lower compartments were willed with medium (600 μL mixed with 10% FBS). Later, cells were incubated for another 48 h, 8 × 10⁴ cells were suspended in fresh serum-free medium (200 μL) for the other 24 h cultivation. Crystal violet (0.1%) was chosen for fixation and staining of cells adheres to the downward surface. Light microscope (BX41, Olympus, Japan) was chosen for counting the migrated/invaded cells at least in 5 randomly selected visual fields of 400× magnification.

Western blot

We lysed the cells collected from different groups using cell lysis buffer (Sangon Biotech) to isolate the total protein. The isolated protein samples (50 μg/lane) were used for assessment of 12% SDS-polyacrylamide gels. Then the separated proteins were blotted onto polyvinylidene fluoride (PVDF) membranes (Millipore, Billerica, MA) by electrotransfer.
The PVDF were then incubated with the appropriate primary antibodies (1:1000, Abcam, Cambridge, UK) overnight at 4°C and corresponding secondary antibodies (1:5000, Abcam) for 1 h at room temperature. Odyssey Infrared Imaging System (LI-COR, Lincoln, NE) was chosen for revealing the obtained signals. β-actin was chosen as an internal control.

Statistical analysis

We carried out all experiments independently with 3 times for repeat. Data are exhibited as means ± SD. SPSS Statistics 16.0 software (IBM, NY) was chosen for the statistical analysis. Two-tailed Student's t-test was used for assessment of differences between any two groups. *p < .05 was chosen for exhibiting a statistically significant.

Results

SNHG15 is highly expressed in CRC tissues and cells

SNHG15 expression was dramatically augmented in CRC tissues relative to that in the matched non-tumor tissues (p < .01, Figure 1(A)). In line with this observation, remarkable up-regulation of SNHG15 expression was also found in four CRC cell lines (CaCO-2, HCT8, HCT-116, and LoVo) in relation to the normal intestinal mucous of CCC-HIE-2 cells (all p < .05, Figure 1(B)). CaCO-2 and HCT-116 cell lines were selected for subsequent experiments as these two cell lines showed the highest expression of SNHG15.

Suppression of SNHG15 inhibits the proliferation, promotes apoptosis, and represses the migration and invasion of CRC cells

To investigate the role of SNHG15 abnormal expression in CRC, the expression of SNHG15 in CaCO-2 and HCT-116 cells was suppressed by transfection with sh-SNHG15. As shown in Figure 2(A), SNHG15 expression was strikingly decreased in CaCO-2 cells after transfection with sh-SNHG15 (p < .001), and a consistent change of SNHG15 level was also observed in HCT-116 cells with sh-SNHG15 vector (p < .01), pointing out a high transfection efficiency. Further, MTT and colony-forming assays showed that suppression of SNHG15 dramatically inhibited the viability and colony-forming abilities of CaCO-2 and HCT-116 cells (p < .05, Figure 2(B,C)). Moreover, we observed that depression of SNHG15 markedly promoted the apoptosis of CaCO-2 and HCT-116 cells (p < .001, Figure 2(D)), in accordance with the tendency of apoptotic proteins under si-SNHG15 condition, namely, the promotion on Bax/Bcl-2, pro-cleaved-caspase-3, and pro-cleaved-caspase-9 in both CaCO-2 and HCT-116 cells (all p < .05, Figure 2(E)). Besides, depression of SNHG15 obviously repressed the migration and invasion abilities of CaCO-2 and HCT-116 cells (p < .05, Figure 2(F,G)). Western blot further revealed that the depression of SNHG15 markedly affected the levels of epithelial-mesenchymal transformation (EMT)-related proteins in both CaCO-2 and HCT-116 cells, including enhanced E-cadherin, but decreased N-cadherin, vimentin, and snail (all p < .05, Figure 2(H)), indicating that the suppression of SNHG15 could inhibit epithelial-mesenchymal transformation (EMT) in CRC cells.

SNHG15 regulates tumor growth and metastasis by targeting miR-141

SNHG15 is reported to be able to sponge miR-141 in the identity of ceRNA, thereby playing a key role in osteosarcoma cells [21]. We thus investigated whether SNHG15 regulated CRC development via sponging miR-141. As displayed in Figure 3(A), miR-141 was markedly increased in both CaCO-2 and HCT-116 cells after transfection with sh-SNHG15 (p < .01), deducting a possible negative regulation pattern between SNHG15 and miR-141 in CRC cells. To verify this result, we monitored the level of miR-141 in CRC tissues and cells by different approaches, and the data presented us that miR-141 was prominently decreased in CRC tissues and the four CRC cell lines (CaCO-2, HCT8, HCT-116, and LoVo) (all p < .01, Figure 3(B,C)), confirming the inverse pattern between SNHG15 and miR-141 in CRC cells. Moreover, miR-141 was markedly enhanced by the transfection of miR-141 mimic, which was changeover by the transfection of miR-141 inhibitor (p < .001, Figure 3(D)). In order to further disclose whether the effects of SNHG15 in CRC were exerted via miR-141 regulation, HCT-116 cells were co-transfected with sh-SNHG15 and miR-141 mimic.
Figure 2. Suppression of SNHG15 inhibited the proliferation, promoted apoptosis, and repressed the migration and invasion of CRC cells. (A) SNHG15 expression in CaCO-2 and HCT-116 cells after transfection with sh-SNHG15 and sh-NC. (B) MTT showed CaCO-2 and HCT-116 cell viability in different groups. (C) Colony-forming assay showing colony-forming abilities of CaCO-2 and HCT-116 cells in different groups. (D) Flow cytometry showing the apoptosis of CaCO-2 and HCT-116 cells in different groups. (E) Western blot showing the expression of apoptosis-related proteins in CaCO-2 and HCT-116 cells in different groups. (F and G) Transwell assay showing the migration and invasion of CaCO-2 and HCT-116 cells in different groups. (H) Western blot showing the expression of epithelial-mesenchymal transformation (EMT)-markers in CaCO-2 and HCT-116 cells in different groups. The experiments were repeated three times. *p < 0.05 compared with the corresponding control.
Figure 3. SNHG15 regulated tumor growth and metastasis through negative regulation of miR-141. (A) Expression of miR-141 in both CaCO-2 and HCT-116 cells after transfection with sh-SNHG15 and sh-NC. (B) Expression of miR-141 in CRC tissues. (C) Expression of miR-141 in CRC cells. (D) Expression of miR-141 in HCT-116 cells after transfection of miR-141 mimic, miR-141 inhibitor, and corresponding controls. (E) MTT assay showing HCT-116 cell viability in different groups. (F) Colony-forming assay showing colony-forming abilities of HCT-116 cells in different groups. (G) Flow cytometry showing that the apoptosis of HCT-116 cells in different groups. (H) Western blot showing the expression of apoptosis-related proteins in HCT-116 cells in different groups. (I and J) Transwell assay showing the migration and invasion of HCT-116 cells in different groups. The experiments were repeated three times. *p < .05 compared with the corresponding control.
and miR-141 inhibitor. We observed that the impacts of SNHG15 depression on cell viability (Figure 3(E)), colony-forming ability (Figure 3(F)), apoptosis (Figure 3(G)), the level of apoptotic proteins (Figure 3(H)), migration (Figure 3(I)), invasion (Figure 3(J)) and the level of EMT related proteins (Figure 3(K)), which were changeover by the co-transfection of pc-SNHG15 and miR-141 inhibitor (all $p < 0.05$).

**SIRT1 is a downstream target of miR-141**

Previous studies have revealed that SIRT1 level is augmented in a variety of human cancers and plays an important role in tumorigenesis, including CRC [22]. We thus explored the interaction between miR-141 and SIRT1. As expected, TargetScan prediction software confirmed that there exists a binding sequence between miR-141 and SIRT1 (Figure 4(A), http://www.targetscan.org/cgi-bin/targetscan/vert_71/).

Luciferase reporter assay was subsequently performed, which confirmed that miR-141 could directly interact with SIRT1 (Figure 4(B)). Furthermore, the transfection of miR-141 mimic significantly decreased the level (mRNA and protein) of SIRT1 ($p < 0.01$), while the transfection of miR-141 inhibitor had an opposite effect ($p < 0.01$) (Figure 4(C,D)), pointing out a downside pattern between SIRT1 and miR-141. Additionally, we successfully suppressed the expression of SIRT1 in HCT-116 cells to further confirm the potential crucial role of miR-141 in CRC ($p < 0.001$, Figure 5(A)), followed by analyzing the combined impacts of miR-141 inhibitor and depression of SIRT1. We observed that the simultaneous depression of SIRT1 and inhibition of miR-141 changeover the impacts of miR-141 inhibitor alone on cell proliferation (Figure 5(B,C)), apoptosis (Figure 5(D)), the level of apoptotic proteins (Figure 5(E)), migration (Figure 5(F)), invasion (Figure 5(G)), and the level of EMT proteins (Figure 5(H)) (all $p < 0.05$).

**Impacts of SNHG15 on CRC development are through the Wnt/β-catenin signal**

Zhang and his colleagues pointed out that Wnt/β-catenin signal is frequently brisk in diversity human cancers, including CRC [23]. The relationship between SNHG15 and activation of the Wnt/β-catenin signal was also investigated. We discovered that the depressed SNHG15 resulted in a significant decrease in the Wnt/β-catenin signal associated proteins including Wnt1, C-Myc, Cyclin-D1, and β-catenin ($p < 0.01$, Figure 5(I)), implying a lessened impacts of the depressed SNHG15 on brisking Wnt/β-catenin signal. Further, the inhibition of miR-141 at the same time remarkably changeover the inhibitory impacts of the depressed SNHG15 on the levels of Wnt/β-catenin signal-related proteins ($p < 0.01$, Figure 5(I)).

**Discussion**

In this study, high level of SNHG15 was observed in CRC tissues and cells. The suppression of SNHG15 performed significant influences on cell biological processes, including depressing proliferation, migration and invasion, and augmenting apoptosis of CRC cells. Also, a downside pattern between SNHG15 and miR-141 was discovered, and miR-141 inhibitor dramatically changeover the impacts of depressed SNHG15 on tumor growth and metastasis. Moreover, SIRT1 was verified as a functional target of miR-141 in CRC cells. Besides, we observed that the depressed SNHG15 remarkably retrained the briskness of Wnt/β-catenin signals, which could be changeover by co-transfection of miR-141 inhibitor.

Consistent with the previous study reported by Jiang et al. [17], SNHG15 was found to be up-regulated in CRC tissues and cells in this research. In addition, the depressed SNHG15 markedly retrained the proliferation, migration and invasion, but promoted apoptosis of CRC cells. We therefore speculate...
Figure 5. Depression of SIRT1 reversed the effects of inhibition of miR-141 on the proliferation, promoted apoptosis, and repressed the migration and invasion of CRC cells. (A) Expression of SIRT1 in HCT-116 cells after transfection with si-SIRT1 and siNC. (B) MTT showing HCT-116 cell viability in different groups. (C) Colony-forming assay showing colony-forming abilities of HCT-116 cells in different groups. (D) Flow cytometry showing that the apoptosis of HCT-116 cells in different groups. (E) Western blot showing the expression of apoptosis-related proteins in HCT-116 cells in different groups. (F and G) Transwell assay showing the migration and invasion of HCT-116 cells in different groups. (H) Western blot showing the expression of EMT-markers in HCT-116 cells in different groups. (I) Expression of Wnt1, C-Myc, Cyclin-D1, and β-catenin in different groups. (J) The graph chart of regulatory mechanism of lncRNA SNHG15. The experiments were repeated three times. *p < .05 compared with the corresponding control.
that SNHG15 may play an oncogenic role in CRC development. Furthermore, SNHG15 was able to enhance YAP1 by holding-on miR-200a-3p at the identity of ceRNA, thereby enhanced the process of papillary thyroid carcinoma [24]. Also, SNHG15 negatively regulated miR-141 and subsequently modulated SIRT1 expression. In previous studies, miR-141 presented less effect on proliferation of CRC cells [25,26]. Furthermore, it has been reported that SIRT1 expression is elevated in several cancers, such as acute myeloid leukemia [27], prostate cancer [28], and primary colon cancer [29]. In this research, the depressed SNHG15 markedly lessened CRC cell proliferation, migration, and invasion, but enhanced apoptosis, and this kind of effect was changeover by the co-transfection of si-SNHG15 and miR-141 inhibitor. We deducted that the depressed SNHG15 may play crucial roles in mediating CRC by affecting miR-141. Further, SIRT1, a NAD-dependent histone deacetylase, is reported to play a dual role, including modifying histone protein via the following deacetylation manners, such as deacetylation of lysine residues K26 on histone H1, lysine residues K9 on histone H3, and lysine residues K16 on histone H4, acting both as an oncogene and as a tumor suppressor. Previous studies showed the pivotal effects of abnormal expression of SIRT1 in the biology of cancers including colorectal cancer [22,27,28]. There are few studies illustrating the correlation between miR-141 and SIRT1 in colon cancer. In this research, the depression of SIRT1 could ulteriorly reverse the impacts of miR-141 inhibitor alone on the tumor behaviors of CRC cells. Given the pivotal role of miR-141 and SIRT1 in tumor development, we deduct that SNHG15 could possibly promote the process of CRC via miR-141/SIRT1 axis in the identity of a ceRNA.

Furthermore, we showed initiatory evidence that suppression of SNHG15 can remarkably inhibit the brisk of the Wnt/β-catenin signals, which was changeover afterwards the inhibition of miR-141 constantly. The briskness of the Wnt/β-catenin signals is recurring encountered during the initiation and progression of CRC [30,31]. In addition, Wnt/β-catenin signal is a pivotal mediator in mediating the antitumor activity of many drugs such as magnolol [32] and resveratrol [33] in CRC cells, implying that targeting this pathway may pave a novel therapy for the treatment of CRC. Wnt/β-catenin signal is also confirmed as a downstream factor mediating the role of key IncRNAs, e.g., nuclear-enriched abundant transcript 1 (NEAT1), in promoting CRC progression [34]. Take all the findings into consideration, we ulteriorly deduct that SNHG15 may play an oncogenic role in CRC development via brisking Wnt/β-catenin signal. Nevertheless, experiments around the relationship of SNHG15 with Wnt/β-catenin signal were not presented in the current research. Further investigations are still required to confirm our findings.

In conclusion, our data revealed that high expression of SNHG15 may enhance the process of CRC through in the identity of ceRNA and regulating SIRT1 expression by sponging miR-141. The Wnt/β-catenin signal may be a downstream factor in mediating the impacts of SNHG15 in CRC. SNHG15-miR-141-SIRT1 axis may pave a promising approach for the diagnosis and treatment of CRC.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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