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SNHG14 facilitates cell proliferation in colorectal cancer through targeting KRAS via Hippo-YAP signaling

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ABSTRACT

Accumulating evidence indicates the significant role of lncRNAs in multiple biological processes and cancer progression. However, most lncRNAs in CRC remain to be excavated. In this study, we investigated SNHG14 in CRC. SNHG14 which was generally under-expressed in normal colon specimens revealed by UCSC was uncovered as markedly highly expressed in CRC cell lines. Besides, SNHG14 was a contributor to CRC cell proliferation. Additionally, we demonstrated that SNHG14 facilitated CRC cell proliferation in a KRAS-dependent manner. Moreover, the mechanistic investigations indicated that SNHG14 interacted with YAP and therefore inactivated the Hippo pathway, so as to enhance YAP-targeted KRAS expression in CRC. Furthermore, SNHG14 was explained as transcriptionally activated by FOS, a previously identified common effector molecule of KRAS and YAP. All in all, our findings elucidated a feedback loop of SNHG14/YAP/KRAS/FOS in facilitating CRC tumorigenesis, which may help develop novel effective targets for CRC patients.

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Introduction

Colorectal cancer (CRC) is a frequent gastrointestinal carcinoma that has a high rate of incidence and mortality among all cancer types (1). Worryingly, the morbidity of CRC is on the rise in recent years in China, and so is the CRC-caused deaths (2). Although the improvements in clinical therapies for CRC have extended life expectancy(3-5), the prognostic outcome of CRC patients is pessimistic (6). It is, therefore, necessary to elucidate more molecules involved in the pathogenesis of CRC.

LncRNAs belong to noncoding RNAs (ncRNAs) that are longer than 200 nucleotides(7). LncRNAs have no function to code protein due to the deficiency of open read frame (ORF) (8). LncRNAs are essential for the progress of human cancers (9), including CRC (10). Recently, the important participation of several lncRNAs in the onset and progression of CRC has been increasingly identified, such as SNHG5 (11), LINC01133(12), CCAL(13), OCC-1(14) and so on.

SNHG14 has already been elucidated as a contributor to several cancers (15-19). Importantly, SNHG14 has also been indicated as CRC progress promoters by a recent report (20). However, the precise role of SNHG14 needs clear research in CRC.

Here, we explored whether and how SNHG14 participated in the course of CRC growth.

Materials and Methods

Cell culture

The normal human colonic cell line NCM460 and five CRC cell lines including HT-29, SW620, SW480, HCT116 and LoVo, as well as HEK-293 T cells, were all obtained from ATCC (USA). The SW620 cells were grown in RPMI 1640 medium(Invitrogen, Carlsbad, USA) while others were cultured in DMEM+10% FBS (HyClone, Logan, UT, USA). Cells were all maintained at 37°C in air containing 5% CO_2.

Cell transfection

The shRNAs targeting SNHG14 (shSNHG14#1 and shSNHG14#2) and FOS (shFOS) and their scramble controls (shCtrls) were synthesized by Shanghai GenePharma, China. And the pcDNA3.1 vector purchased from Invitrogen was utilized to overexpress SNHG14 or FOS, with the empty vector acting as a negative control. Cell transfections were realized by using Lipofectamine™ 2000 (Invitrogen, USA) to treat cells for 48 h.

Quantitative Real-time PCR (qRT-PCR)

Total RNA isolation with TRizol reagent(Invitrogen, Carlsbad, CA, USA). The reverse transcription and qRT-PCR were separately executed with the Prime-Script™ one stepRT-PCR kit (TaKaRa, Dalian, China) and SYBR Green PCR kit (TaKaRa, Dalian, China). The relative

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expression was estimated with$2^{-\Delta\Delta CT}$ method by using GAPDH as the normalized control.Here are primers we used: SNHG14: 5′-GGGTGTTTACGTAGACCAGAACC-3′ (F), 5′-CTTCCAAAAGCCTTCTGCCTTAG-3′ (R); KRAS: 5′-ACAGAGAGTGGAGGATGCTTT-3′ (F), 5′-TTTCACACAGCCAGGAGTCTT-3′ (R); FOS: 5′-CAGACTACGAGGCGTCATCC-3′ (F), 5′-AGTTGGTCTGTCTCCGCTTG-3′ (R); GAPDH: 5′-AGAAGGCTGGGGCTCATTTG-3′(F), 5′-AGGGGCCATCCACAGTCTTC-3′(R).

Cell viability and proliferation assay

To assess cell viability, 3×10^3cells of each well were planted into the 96-well plates. Cells were incubated further and measured at 0, 24, 48, 72 and 96 h. After the medium was removed, the cells were washed and then incubated with CCK-8 solutions at 37°C for 2 h. Finally, a Multimode Reader (BioTek, USA) evaluated 450 nm absorbance. In respect to cell proliferation, the Cell Light EdU DNA imaging kit (Invitrogen, Carlsbad, CA, USA) was employed to conduct EdU assays.

Western blotting

Cells were lysed by protease inhibitor-contained RIPA lysis buffer (Beyotime Institute of Biotechnology, Shanghai, China). Separation of an equal amount of proteins in each sample was carried out on 12% SDS-PAGE. After transferring onto a PVDF membrane and incubating with primary antibodies and HRP-coupled secondary antibodies, and finally visualized using ECL detection reagents (Amersham Biosciences, Sweden).

RNA pull-down assay

RNAs (SNHG14 and its antisense RNA) were biotin-labeled by the use of a MaxiScript T7 kit (Ambion). Afterward, the biotin-labeled RNAs were incubated on a shaker with cell lysates overnight at 4 °C, followed by the incubation with pre-washed streptavidin-Dyna beads (Dyna beads M-280 Streptavidin, #11205D, Invitrogen). Subsequently, the precipitated proteins in beads were washed, boiled and finally examined through western blot.

RNA immunoprecipitation (RIP) assay

Cell lysates were obtained by the use of RIP buffer containing RNase inhibitor, and then incubated magnetic beads conjugated with anti-YAP (#14074, Cell Signaling Technology) or rabbit anti-IgG (negative control; Abcam). After eluting the precipitated RNAs, samples were measured by qRT-PCR.

Chromatin immunoprecipitation (ChIP)

The ChIP experiments were finished using the EZ ChIP™ Chromatin Immunoprecipitation Kit. In short, the cross-linked chromatin was fragmented into 200-1000bp by sonication. The chromatin immunoprecipitated by antibodies against YAP (#14074), FOS (#2250) or IgG (#3900; negative control) (all from Cell Signaling Technology) was estimated using qRT-PCR.

Luciferase reporter assay

KRAS and SNHG14 promoter whole sequences were sub-cloned into the pGL3-Basic luciferase vector (Promega) to yield the pGL3-KRAS promoter and pGL3-SNHG14 promoter, respectively. Transfect pGL3-KRAS promoter into SNHG14-silenced LoVo cells and SNHG14-overexpressed HT-29 cells, whereas transfect pGL3-SNHG14 promoter into FOS-depleted LoVo cells and FOS-upregulated HT-29 cells using Lipofectamine™ 2000 (Invitrogen) for 48 h, and the luciferase activities were assessed on a dual-luciferase reporter assay system.

Statistical analysis

Three independent experimental data were statistically organized using GraphPad Prism software (USA), with the results reported as means±SD. The statistical significance of differences was evaluated by Student's t-tests or one-way ANOVA. A definition of statistical significance is $p<0.05$.

Results

Stimulation of dysregulated SNHG14 on CRC cell proliferation

The role of SNHG14 was identified in CRC at first by investigating the feature of SNHG14 expression. As revealed by UCSC, SNHG14 was exhibited as low-expressed in 570normal colon specimens (Fig. 1A). However, an abnormal upregulation of SNHG14 in all five different CRC cells was detected, among which, LoVo cell and HT-29 cell had the highest and lowest level of SNHG14 expression, respectively (Fig. 1B). Based on this, the loss-of-function assays in LoVo cells and gain-of-function assays in HT-29 cells probed the precise SNHG14 function. Absolutely, we observed the noticeable abrogation of SNHG14 level in LoVo cells in response to the transfection of either shSNHG14#1 or shSNHG14#2, and overtly enhanced in HT-29 cells after SNHG14 overexpression (Fig. 1C). Im-

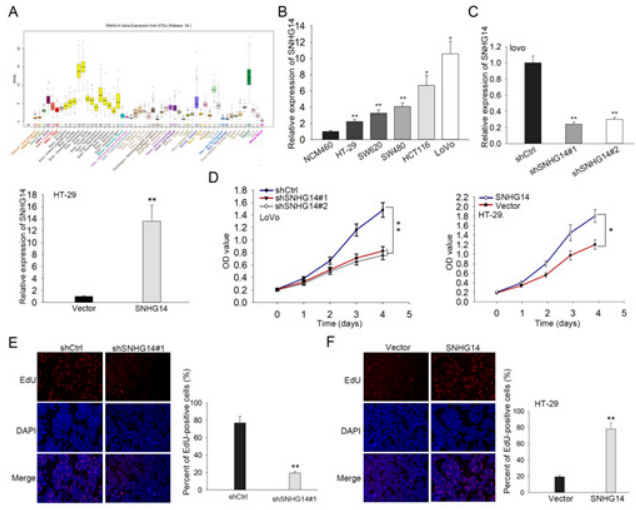

Figure 1. SNHG14 was upregulated and contributed to the malignant phenotypes in CRC cells. (A) The expression profile of SNHG14 in 53 normal tissues was revealed by UCSC. (B) qRT-PCR results of SNHG14 expression in five CRC cell lines and the normal NCM460 cells. (C-D) The level of SNHG14 in LoVo cells transfected with various shRNAs (C) and HT-29 cells transfected with pcDNA3.1 vector or vector containing SNHG14 sequences (D) was detected by qRT-PCR. (D) CCK-8 assays were performed to evaluate the viability of the above cells. (E-F) Cell proliferation in LoVo cells with or without SNHG14 silence and in HT-29 cells with or without SNHG14 overexpression was determined by conducting EdU assays. * $P< 0.05$, ** $P< 0.01$.

portantly, we uncovered that inhibition of SNHG14 by the transfection of either shSNHG14#1 or shSNHG14#2 notably reduced the viability of LoVo cells, whereas ectopic expression of SNHG14 markedly enhanced the viability of HT-29 cells on the contrary (Fig. 1D). And LoVo cells transfected with shSNHG14#1 was used in following assays due to the higher interference efficiency. Accordantly, cell proliferation was suppressed or promoted under SNHG14 silence or overexpression (Fig. 1E-F). Altogether, these results suggested that SNHG14 serves as a CRC proliferation promoter.

KRAS is a co-regulator with SNHG14 in facilitating CRC cell proliferation

KRAS is a proto-oncogene that frequently mutated as an oncogene in tumors of the colorectum(21), and the transforming protein that results participates in the development of colorectal carcinoma and other human malignancies(22). Here, we also uncovered that KRAS were distinctly elevated in CRC cells at both levels (mRNA and protein) (Fig. 2A). Besides, KRAS level was sharply decreased in responding to SNHG14 depletion in LoVo cells but robustly increased in HT-29 cells facing SNHG14 upregulation (Fig. 2B). Hence, we suspected the contribution of SNHG14 to CRC cell proliferation by regulating KRAS. As displayed in Fig. 2C-D, KRAS expression changed by SNHG14 suppression or activation was respectively offset under KRAS overexpression or silence, with a consistent alteration in the impact of SNHG14 on the KRAS-regulated AKT and ERK signaling pathways. Furthermore, enforced KRAS expression normalized the SNHG14 depletion-repressed cell proliferation, whereas the knockdown of KRAS countervailed the SNHG14 upregulation-stimulated cell proliferative ability (Fig. 2E-F). Collectively, we illustrated the CRC-facilitating role of

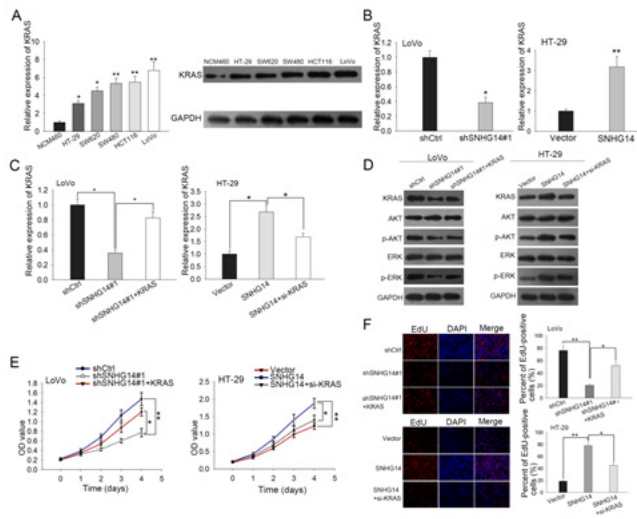

Figure 2. KRAS-mediated SNHG14-promoted CRC cell proliferation. (A) The mRNA and protein levels of KRAS in CRC cell lines and NCM460 cells were examined using qRT-PCR and western blot. (B) The impact of SNHG14 on KRAS expression in CRC cells was assessed by qRT-PCR. (C) The mRNA level of KRAS in indicated CRC cells was examined using qRT-PCR. (D) Western blot analysis for the evaluation of the protein levels of KRAS and its downstream ERK and AKT in CRC cells under different transfections. (E-F) The influence of KRAS on the SNHG14-promoted CRC cell proliferation was assessed by conducting CCK-8 and EdU assays. * P< 0.05, ** P< 0.01.

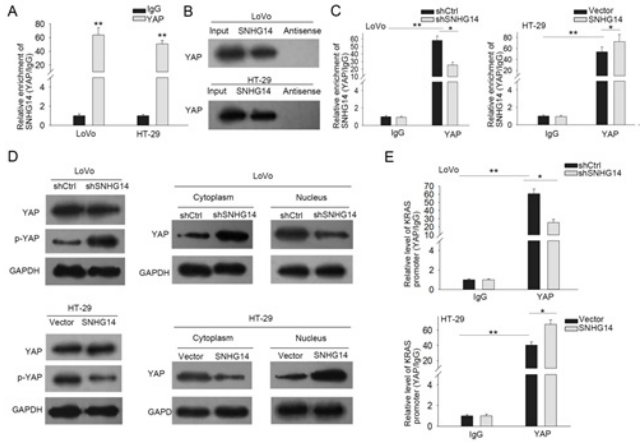

Figure 3. SNHG14 increased KRAS expression in CRC cells by inhibiting the Hippo pathway via interacting with YAP. (A-B) The interaction between SNHG14 and YAP protein was certified by RIP (A) and RNA pull-down assays (B). (C) RIP assay was performed to detect the alterations on the interaction between SNHG14 and YAP in SNHG14-depleted LoVo cells and SNHG14-upregulated HT-29 cells. (D) The protein level of YAP and p-YAP in the whole extractions and in the cytoplasm and nucleus of the indicated CRC cells was evaluated by western blot. (E) The effect of SNHG14 on KRAS transcription was determined by ChIP assays. * P< 0.05, ** P< 0.01.

SNHG14via modulating KRAS and therefore activating AKT and ERK pathways.

SNHG14 boosts KRAS expression in CRC through the Hippo-YAP pathway

Subsequently, we explored how SNHG14 affected KRAS expression.KRAS was transcriptionally regulated by YAP (23), and lncRNAs have been reported to modulate the expression of YAP-targeted genes by interacting with it recently (24). In this study, we speculated that SNHG14 enhanced KRAS level in CRC by a similar way, based on the prediction of the online RPISeq (http://pridb.gdcb.iastate.edu/RPISeq/) that SNHG14 might interact with YAP. And such interaction was further confirmed here since SNHG14 was noticeably enriched in the anti-YAP-precipitated complex and YAP was easily detected in the SNHG14-pulled down complex in both the two CRC cells (Fig. 3A-B). Intriguingly, SNHG14 depletion led to reduced SNHG14-YAP interaction and therefore induced YAP phosphorylation, activated the Hippo pathway and suppressed YAP nuclear translocation, whereas SNHG14 overexpression resulted in an opposite phenomenon in contrast (Fig. 3C-D). More importantly, we explained that the KRAS promoter binding to YAP was prominently erased in response to SNHG14 knockdown but significantly prompted in the context of enforced SNHG14 expression (Fig. 3E). By and large, the above data indicated that SNHG14 upregulates KRAS expression in CRC through inhibiting Hippo pathway via interacting with YAP.

SNHG14 is transcriptionally enhanced by FOS

Previously, FOS, a transcription factor belonging to the AP-1 family, was verified as a downstream effector of YAP1 and KRAS(25). Presently, the UCSC revealed that SNHG14 transcription might be modulated by FOS, with the binding motif obtained from JASPAR displayed in Fig.4A. Thus, we hypothesized that upregulation of KRAS and nuclear YAP1 might also affect SNHG14 ex-

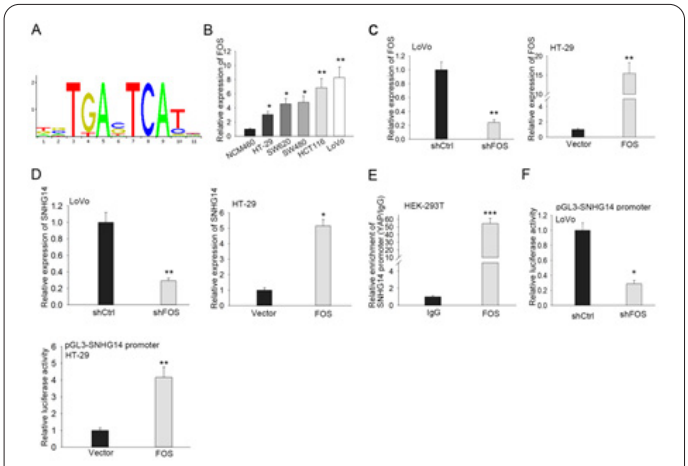

Figure 4. SNHG14 was transcriptionally stimulated by FOS. (A) JASPAR indicated the binding motif of FOS. (B) qRT-PCR result of FOS in CRC cell lines and NCM460 cells. (C-D) The expression of FOS (C) and SNHG14 (D) in LoVo cells under FOS inhibition and HT-29 cells upon FOS upregulation was detected using qRT-PCR. (E-F) The positive regulation of FOS on SNHG14 transcription was confirmed by performing ChIP and luciferase reporter assays. * P< 0.05, ** P< 0.01, *** P< 0.001.

pression in turn through FOS. Not surprisingly, the expression level of FOS was strikingly increased in CRC cells (Fig. 4B). In addition, depletion of FOS brought about reduced SNHG14 expression, whereas overexpression of FOS gave rise to enhanced SNHG14 level (Fig. 4C-D). Importantly, the results of the ChIP assay demonstrated that the SNHG14 promoter was greatly concentrated in an anti-FOS-immunoprecipitated complex (Fig. 4E). Meanwhile, SNHG14 promoter activity was weakened by FOS knockdown but evoked under FOS upregulation (Fig. 4F). To be concluded, we uncovered that SNHG14 is transcriptionally activated in CRC by KRAS/YAP-regulated FOS.

Discussion

Colorectal cancer is a common human malignancy involving both genetic and epigenetic changes(26-28). Recently, the dysregulation of lncRNAs has been increasingly suggested in the carcinogenesis of CRC (29, 30). For instance, lncRNA ST3Gal6-AS1 mediates CRC progression by modulating α-2, 3 sialylation via ST3Gal6-affected PI3K/Akt signaling(31). LncRNA CRNDE is revealed as a dominator in the proliferative activity and chemoresistance of CRC cells (32).SNHG14, a lncRNA that has different functions in human cancers (15, 18, 33), was proved to be remarkably upregulated in CRC. Moreover, the proliferation-facilitating role of SNHG14 has further demonstrated also in CRC.

Kirsten rat sarcoma (KRAS), similar to other Ras genes, regulates cell activities and processes, which is all attributed to its modulation of several signaling pathways(34, 35). Increasingly, KRASis largely implicates all processes of carcinogenesis(36, 37), including CRC (38, 39). Herein, we suggested that SNHG14 exerted the oncogenic function in CRC via a KRAS-dependent pathway, which might be eventually owing to KRAS-activated ERK and AKT signaling pathways.

Furtherly, the regulatory mechanism underlying SNHG14 upregulated KRAS was also figured out in our study. In the past decades, the emerging role of Hippo-YAP signaling has been identified in cancer development (40). A previous observation indicated that KRAS is transactivated by YAP (23). Also, lncRNAs have been proven to modulate the expression of YAP-targeted genes by interacting with them (24). Currently, we uncovered that SNHG14, by interacting with YAP protein, inactivated the Hippo pathway and promoted YAP nuclear translocation, thereby upregulating KRAS at the transcriptional level. Fascinatingly, a feedback loop was disclosed in our study that SNHG14 was a target of FOS, a common downstream effector of both YAP1 and KRAS(25).

On the whole, we unveiled for the first time that SNHG14 acts as a pro-growth factor in CRC tumorigenesis by regulating KRAS by inactivating the Hippo pathway via interacting with YAP. Meanwhile, we illustrated an in-return regulation of KRAS and YAP on SNHG14 expression through their downstream target FOS. Importantly, the findings in this study may be helpful for the development of therapeutic strategies for CRC.

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Conflicts of interest

The authors declare no conflicts of interest.

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