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LncRNA HCG11 suppresses laryngeal carcinoma cells progression via sponging miR-4469/APOM axis

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Abstract. – OBJECTIVE: Long non-coding RNAs (lncRNAs) have been reported to participate in the regulatory mechanisms of various cancers. Therefore, the aim of this study was to investigate the functional role of lncRNA HLA complex group 11 (HCG11) in laryngeal carcinoma.

MATERIALS AND METHODS: The laryngeal carcinoma cell lines SNU46, SNU899, AMC-HN-8, and normal human nasopharyngeal epithelial cells NP69 were purchased. The expression of HCG11, miR-4469, and apolipoprotein M (APOM) was detected by quantitative Real Time-PCR (qRT-PCR) in tissues and cells. Cell proliferation was detected by Cell Counting Kit-8 (CCK-8) assay and colony formation assays. The protein expression of Bax and Bcl-2 was detected by Western blot. Besides, the mechanism assays were conducted to observe the interaction between miR-449 and HCG11 or APOM. The apoptosis in each group was detected by TUNEL assay.

RESULTS: In this research, low expression of HCG11 was discovered in laryngeal carcinoma tissues and cells. Overexpression of HCG11 retarded cell proliferation and enhanced cell apoptosis. Later, we found that APOM was also downregulated in laryngeal carcinoma tissues and cell lines, and inhibited laryngeal carcinoma progression. HCG11 positively regulated APOM at the post-transcriptional level. MiR-4469 was predicted to have the binding sites of HCG11 and APOM. Furthermore, it was demonstrated that HCG11 absorbed miR-4469 to upregulate APOM expression. Finally, it was indicated that the repression of APOM rescued the effects of HCG11 overexpression on cell proliferation and cell apoptosis.

CONCLUSIONS: This study uncovered that HCG11 sponged miR-4469 to suppress laryngeal carcinoma progression by upregulating APOM expression.

Key Words:
HCG11, MiR-4469, APOM, Laryngeal carcinoma.

Introduction

Laryngeal carcinoma is a common head and neck tumor, and its survival rate is unsatisfactory[1,2]. The occurrence of laryngeal carcinoma is affected by drinking, smoking, viral infection, and environmental factors. In recent years, the overall survival of laryngeal carcinoma patients is increasing following by great improvements that have been made in surgical resection, radiotherapy, and chemotherapy[3,4], but the mortality rate is still high.

LncRNAs are a class of transcripts with a length >200 nts, without the coding ability for proteins[5,6]. It has been reported[7,8] that lncRNAs are vital mediators in the development and progression of cancers. LncRNA OECC sponges miR-143-3p to accelerate colorectal cancer development[9]. LncRNA MIR22HG represses the progression of gastric cancer by weakening NOTCH2 signaling[10]. LncRNA UCA1 activates Wnt/β-catenin signaling pathway to stimulate cell proliferation, invasion, and migration in laryngeal squamous cell carcinoma[11]. LncRNA TUG1 drives cell proliferation and migration in laryngeal cancer[12]. HCG11 has been reported to act as a tumor suppressor in multiple cancers. Importantly, lncRNA HCG11 cooperates with the miR-4425/MTA3 axis to inhibit the growth of glioma[13]. The downregulation of lncRNA HCG11 in prostate cancer is associated with poor prognosis[14]. However, the function of HCG11 in laryngeal carcinoma was not elucidated.

Accumulating mRNAs, which could transcript into corresponding proteins, have been reported to be involved in cancer progression. Apolipoprotein M (APOM), as one member of the apolipoprotein family, has been studied as an inhibitor in cancers. APOM suppresses SMMC7721 cell growth and metastasis through vitamin D re-

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ceptor signaling[15]. The overexpression of APOM repressed hepatoma cell proliferation, migration, and invasion[16]. APOM is involved in antineoplastic activity *via* upregulating VDR expression in colorectal cancer[17]. The role of APOM in laryngeal carcinoma needs to be further probed.

The purpose of this work is to explore the regulatory mechanism which was played by HCG11 and APOM in laryngeal carcinoma. In the end, we discovered that the HCG11/miR-4469/APOM axis suppressed laryngeal carcinoma progression. This finding may provide a new sight in the treatment of laryngeal carcinoma.

Materials and Methods

Clinical Samples and Cell Culture

A total of 30 pairs of laryngeal carcinoma tissues and adjacent normal tissues were gained from the Third Affiliated Hospital of Soochow University. Written informed consent was obtained from all patients. Our study obtained the approval of the Ethics Committee of the Third Affiliated Hospital of Soochow University.

Normal human nasopharyngeal epithelial cell line NP-69 and laryngeal carcinoma cell lines (SNU46, SNU899, and AMC-HN-8) were purchased from the Chinese Academy of Sciences Cell Bank (Shanghai, China). Cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM; Thermo Fisher Scientific, Waltham, MA, USA) which was added with streptomycin (100 μg/mL; Beyotime, Shanghai, China), penicillin (100 U/mL; Beyotime, Shanghai, China) and 10% fetal bovine serum (FBS; PAN-Biotech, Aidenbach, Germany). The incubation of cells was done in the humidified atmosphere of 37°C in 5% CO_2.

Cell Transfection

SNU46 or SNU899 cells were transfected with the pcDNA3.1 plasmids (Ambion; Thermo Fisher Scientific, Waltham, MA, USA) targeting HCG11 (pcDNA3.1-HCG11) or negative control (NC) by using Lipofectamine 2000 Reagent (Invitrogen, Carlsbad, CA, USA). MiR-4469 mimics, NC mimics, miR-4469 inhibitor, and NC inhibitor were all acquired from Genechem (Shanghai, China). The pcDNA3.1 plasmids expressing APOM (pcDNA3.1-APOM) and short-hairpin RNAs (shRNAs) against APOM (sh-APOM#1 or sh-APOM#2) were also transfected into SNU46 or SNU899 cells. After transfection for 48 h, these constructed cells were harvested for the next work.

Real Time-quantitative Polymerase Chain Reaction (RT-qPCR) assay

Total RNA was extracted from tissues or cells by using TRIzol Reagent (Invitrogen, Carlsbad, CA, USA). The Reverse Transcription kit (TaKaRa, Dalian, Japan) was used to reversely transcribe RNAs into cDNAs. The cDNAs were then subjected to qRT-PCR by using SYBR Premix EX Taq (TaKaRa, Dalian, Japan). The $2^{-\Delta\Delta Ct}$ method was used to obtain the relative expression. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and U6 were presented as normalized genes. The primer sequences used in qRT-PCR were as follows: HCG11 forward: 5′-GCTCTATGCCATCCTGCTT-3′ and reverse: 5′-TCCCATCTCCATCAACCC-3′; miR-4469 forward: 5′-ACACTCCAGCTAGGGCATCACATA-3′and reverse: 5′-TGGAGTCCTGGAGTCG-3′; APOM forward: 5′-GCTATCAGAAGATGCTGTTC-3′ and reverse: 5′-GTTGCTGCTGTTCAGATTTG-3′. GAPDH forward, 5'-TGCACCACCAACTGCTTAGC-3' and reverse, 5'-GGCATGCACTGTGGTCATGAG-3'; U6 forward, 5'-GCTTCGGCAGCACATATACTAAAAT-3' and reverse, 5'-CGCTTCACGAATTTGCGTGTCAT-3'.

Cell Counting Kit-8 (CCK-8) assay

After transfection, SNU46 and SNU899 cells (1×10^3 cells/well) were seeded in a 96-well plate. Each well was added with CCK-8 solution (10 μL, Dojindo Molecular Technologies, Kumamoto, Japan). Four hours later, a microplate reader (Thermo Fisher Scientific, Waltham, MA, USA) was utilized to measure the absorbance at a wavelength of 450 nm.

Colony Formation Assay

For colony formation assay, transfected SNU46 and SNU899 cells in the medium were added in 6-well plates. After 2 weeks, cell colonies were fixed, stained, and eventually counted through Image J (http://rsb.info.nih.gov/ij/) software.

TUNEL Assay

The number of apoptotic cells in transfected cells was assessed by TUNEL Apoptosis Kit (Roche, Mannheim, Germany). After ethanol dehydration, laryngeal carcinoma cells were dyed and then incubated with TUNEL reaction mixture (Roche, Mannheim, Germany). Nucleus staining was normalized by DAPI.

Western Blot Assay

After transfection, SNU46 or SNU899 cells were isolated through RIPA buffer (Thermo Sci-

entific, Waltham, MA, USA). The proteins were collected for separation by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE; Millipore, Bedford, MA, USA), and then these proteins were transferred to polyvinylidene difluoride membranes (PVDF; Bio-Rad Laboratories, Hercules, CA, USA). After blocking with 5% nonfat milk, the membranes were probed with anti-Bax (ab77566, Abcam, Cambridge, MA, USA), anti-Bcl-2 (ab182858, Abcam, Cambridge, MA, USA), anti-APOM (ab91656, Abcam, Cambridge, MA, USA), anti-CD44 (ab157107, Abcam, Cambridge, MA, USA), anti-CD133 (ab16518, Abcam, Cambridge, MA, USA), anti-Oct-4 (ab134218, Abcam, Cambridge, MA, USA), and anti-GAPDH (ab8245, Abcam, Cambridge, MA, USA) at 4°C overnight. After that, the membranes were cultivated with a secondary antibody at room temperature for 1 h. The protein bands were ultimately assessed *via* enhanced chemiluminescence kit (ECL; Bio-Rad Laboratories, Hercules, CA, USA). GAPDH served as the internal parameter.

Luciferase Reporter Assay

The wide type Luciferase reporter vectors (pmirGLO-HCG11-WT or pmirGLO-APOM-WT) and mutant type Luciferase reporter vectors (pmirGLO-HCG11-Mut or pmirGLO-APOM-Mut) were constructed by Genechem Co., Ltd. (Shanghai, China). SNU46 or SNU899 cells were separately co-transfected with Luciferase reporter vectors and miR-4469 mimics (or NC mimics). After co-transfection for 48 h, a Dual-Luciferase reporter assay system (Promega, Madison, WI, USA) was adopted to assess the relative Luciferase activity.

RNA Pull-Down Assay

Magnetic beads (Invitrogen, Carlsbad, CA, USA) conjugated to either biotinylated HCG11 probe (HCG11 probe biotin) or the negative control probe (HCG11 probe-no biotin) were mixed with cell lysate. 48 h later, the expression of miRNAs was detected by qRT-PCR analysis.

RNA Immunoprecipitation (RIP)

RIP assay was conducted with Magna RIP RNA-Binding Protein Immunoprecipitation Kit (Millipore, Billerica, MA, USA). Cell lysate was cultured with magnetic beads conjugated to either anti-Ago2 antibody (Millipore, Billerica, MA, USA) or anti-IgG antibody (Millipore, Billerica, MA, USA). The expression level of genes was examined by qRT-PCR analysis.

Statistical Analysis

All data were denoted as the mean ± standard deviation (SD) of three separate experiments. GraphPad Prism 6.0 (La Jolla, CA, USA) and Statistical Product and Service Solution (SPSS) 20.0 (IBM Corp., Armonk, NY, USA) were utilized for the statistical analysis. Student's *t*-test (for two) or one-way ANOVA (for more than two) was applied to evaluate the significance of the variance in different groups. $p < 0.05$ was defined as statistically significant.

Results

HCG11 Suppressed Laryngeal Carcinoma Tumorigenesis

It has been disclosed that lncRNA HCG11 acted as a tumor suppressor in various cancers, whereas the role of HCG11 in laryngeal carcinoma is unknown. The expression of HCG11 was initially analyzed, and we found that HCG11 was downregulated in laryngeal carcinoma tissues in comparison to adjacent normal tissues (Figure 1A). Similarly, we found that HCG11 was lower in laryngeal carcinoma cell lines (SNU46, SNU899, and AMC-HN-8) than that in normal nasopharyngeal epithelial cells (NP-69) (Figure 1B). PcDNA3.1 plasmids targeting HCG11 (pcDNA3.1-HCG11) were transfected into SNU46 and SNU899 cells, and HCG11 expression was increased after overexpressing HCG11 (Figure 1C). CCK-8 and colony formation assays indicated that HCG11 overexpression suppressed cell proliferation (Figure 1D and E). Upregulating HCG11 enhanced cell apoptosis in SNU46 and SNU899 cells (Figure 1F). Western blot assay was applied to examine cell apoptosis-related proteins (Bax and Bcl-2) and demonstrated that HCG11 overexpression increased Bax expression and decreased Bcl-2 expression (Figure 1G). Consequently, these results revealed that HCG11 acted as a tumor suppressor in laryngeal carcinoma tumorigenesis.

APOM Inhibited Laryngeal Carcinoma Tumorigenesis

APOM acts as a tumor suppressor in various cancers, whereas the role of APOM in laryngeal carcinoma is unknown. The expression of APOM was downregulated in laryngeal carcinoma tissues in comparison to adjacent normal tissues (Figure 2A). In addition, qRT-PCR revealed that APOM was lower in laryngeal carcinoma cell lines (SNU46, SNU899, and AMC-HN-8) than that in

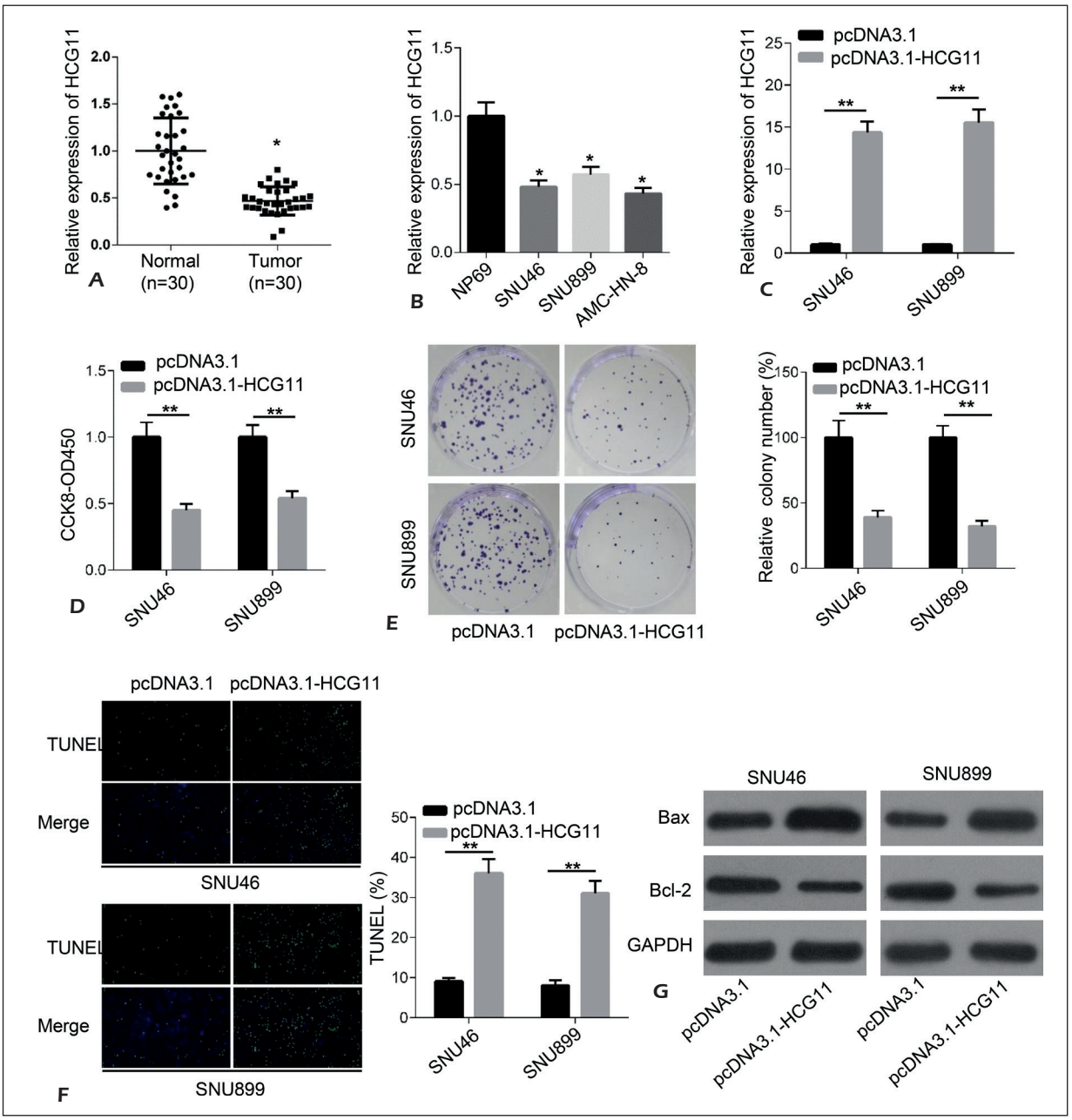

Figure 1. HCG11 suppressed laryngeal carcinoma tumorigenesis. **A**, qRT-PCR assay was conducted to detect the expression of HCG11 in laryngeal carcinoma tissues and adjacent normal tissues, n=30. **B**, qRT-PCR assay was used to measure the expression of HCG11 in laryngeal carcinoma cell lines and normal nasopharyngeal epithelium cell line. **C**, qRT-PCR assay was conducted to detect the expression of HCG11 in SNU46 and SNU899 cells after overexpressing HCG11. **D**-**E**, CCK-8 and colony formation assay were performed to detect cell proliferation by HCG11 upregulation in SNU46 and SNU899 cells (magnification ×20). **F**, TUNEL assays were performed to detect cell apoptosis by HCG11 upregulation in SNU46 and SNU899 cells (magnification ×20). **G**, Western blot assay was applied to measure the expression of cell apoptosis related proteins (Bax and Bcl-2) in SNU46 and SNU899 cells. *p<0.05, **p<0.01.

normal nasopharyngeal epithelial cells (NP-69) (Figure 2B). APOM expression was increased in SNU46 and SNU899 cells transfected with pcDNA3.1-APOM (Figure 2C). Overexpression of APOM retarded cell proliferation in SNU46 and SNU899 cells (Figure 2D and E). Moreover, the overexpression of APOM accelerated cell apoptosis (Figure 2F). Western blot assay revealed that APOM upregulation increased Bax expression and reduced Bcl-2 expression (Figure 2G). There-

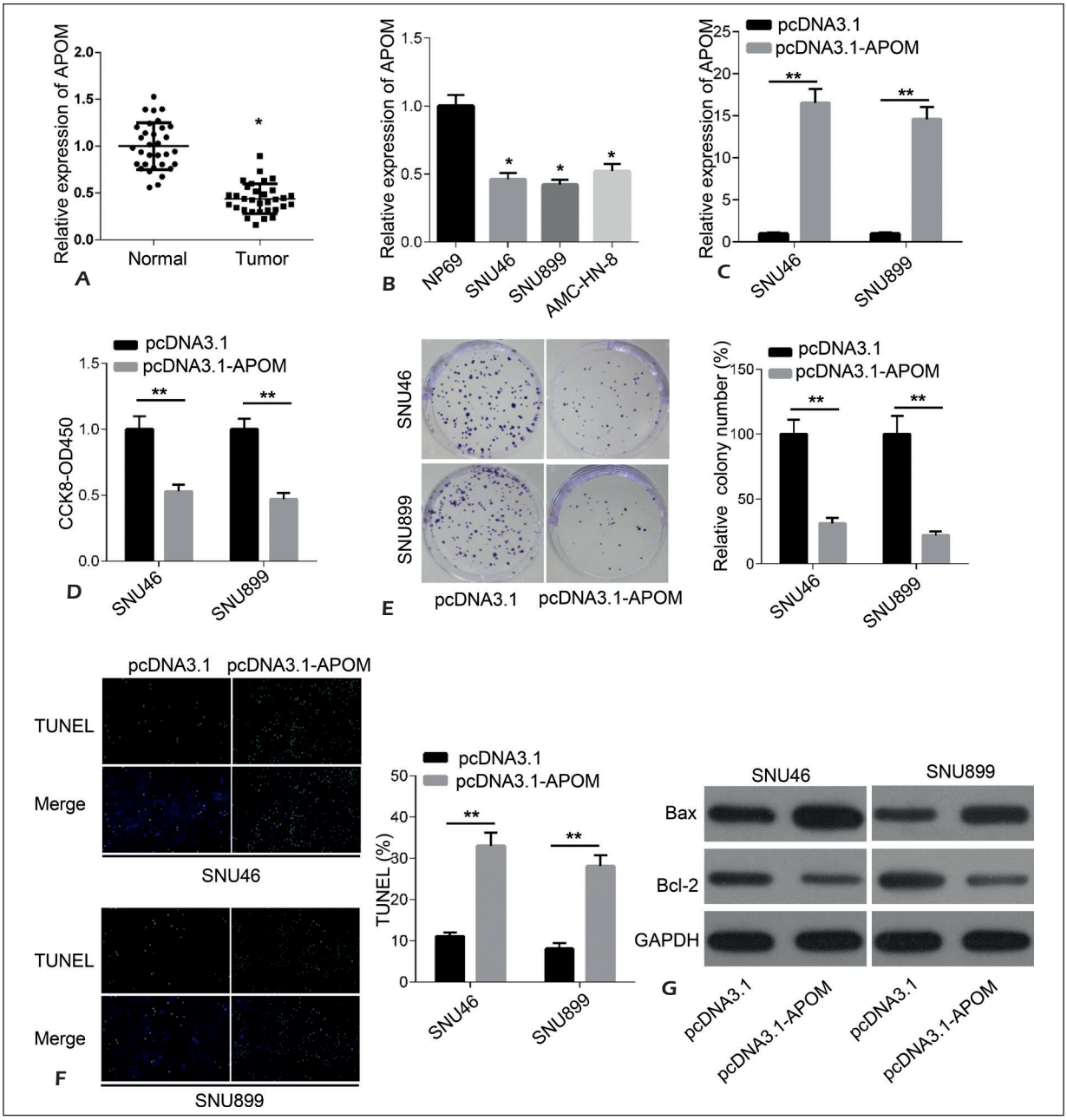

Figure 2. APOM inhibited laryngeal carcinoma tumorigenesis. **A**, The expression of APOM in laryngeal carcinoma tissues and adjacent normal tissues was detected by qRT-PCR assay. **B**, The expression of APOM in laryngeal carcinoma cell lines and normal nasopharyngeal epithelium cell line was measured by RT-qPCR assay. **C**, The expression of APOM in SNU46 and SNU899 cells after overexpressing APOM was assessed by qRT-PCR assay. **D**-**E**, CCK-8 and colony formation assay were applied to detect cell proliferation by APOM upregulation in SNU46 and SNU899 cells (magnification ×20). **F**, TUNEL assays were used to detect cell apoptosis by APOM upregulation in SNU46 and SNU899 cells (magnification ×20). **G**, Western blot assay was conducted to measure the expression of cell apoptosis related proteins (Bax and Bcl-2) by APOM overexpression in SNU46 and SNU899 cells. *p<0.05, **p<0.01.

fore, the inhibitor role of APOM in laryngeal carcinoma tumorigenesis was verified. We speculated that there may be an operation mode of ceRNA network between HCG11 and APOM.

HCG11 Sponged MiR-4469 to Upregulate APOM Expression

Venn diagram analysis discovered that 6 miRNAs (miR-2116-3p, miR-4667-3p, miR-

7113-3p, miR-3135b, miR-877-3p, and miR-4469) had the binding sites of HCG11 and APOM (Figure 3A). Through RNA pull-down assay, it was found that the accumulation of miR-4469 was the highest in HCG11 probe-biotin group (Figure 3B). MiR-4469 was high-expressed in laryngeal carcinoma cell lines (Figure 3C). The silence of miR-4469 appreciably reduced and overexpression of miR-4469 increased the expression of miR-4469 (Figure 3D). The expression of HCG11 and APOM was elevated after inhibiting miR-4469 (Figure 3E). The putative binding sequences of miR-4469 and HCG11 (or APOM) were shown in Figure 3F. The Luciferase activities of pmirGLO-HCG11-Wt and pmirGLO-APOM-Wt reporters were both weaken by miR-4469 mimics, but non-significant alteration was found in the Luciferase activities of pmirGLO-HCG11-Mut and pmirGLO-APOM-Mut reporters (Figure 3G). HCG11, miR-4469, and APOM were all existed in Ago2 complex (Figure 3H). Taken together, HCG11 absorbed miR-4469 to upregulate APOM expression in laryngeal carcinoma.

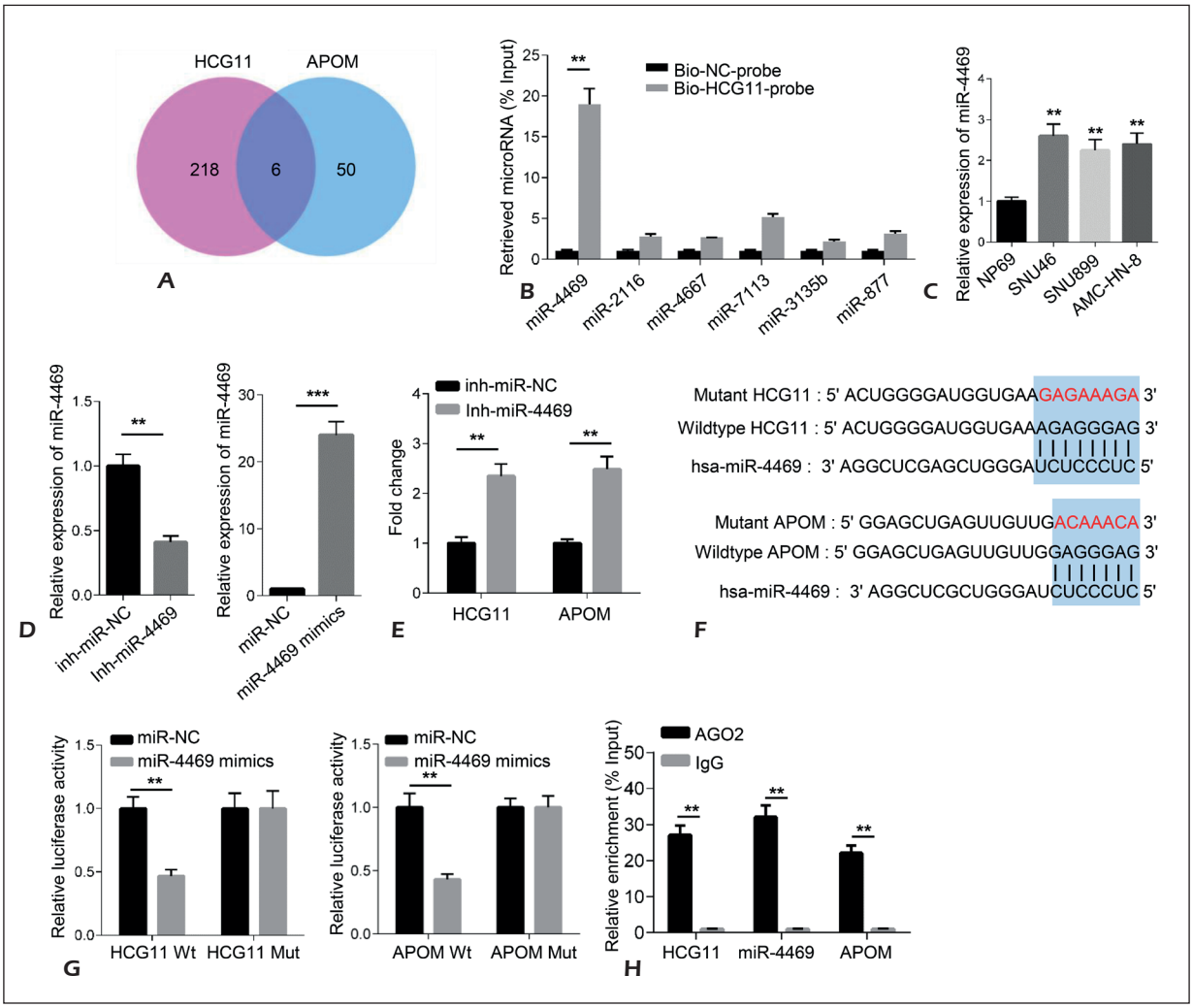

Figure 3. HCG11 absorbed miR-4469 to upregulate APOM expression. **A**, MiRNAs which had binding sites of HCG11 and APOM were showed in the Venn diagram. **B**, Through RNA pull down assay, the expression of miRNAs was assessed in HCG11 probe-biotin group and HCG11 probe-non-biotin group. **C**, The expression of miR-4469 was detected in laryngeal carcinoma cell lines. **D**, The expression of miR-4469 was measured after inhibiting or overexpressing miR-4469 in SNU46 and SNU899 cells. **E**, The expression of HCG11 and APOM was detected by suppressing miR4469. **F**, The binding sequences of HCG11 and miR-4469, as well as the binding sequences of APOM and miR-4469 were displayed. **G**, The binding sites of HCG11 and miR-4469, as well as the binding sites of APOM and miR-4469 were verified by Luciferase reporter assay. H, The interactions among HCG11, miR-4469, and APOM were further revealed through RIP assay. *p<0.05, **p<0.01.

APOM Participated in HCG11-Mediated Cell Proliferation in Laryngeal Carcinoma

Rescue assays were conducted to verify whether APOM participated in the inhibition effects of HCG11 on laryngeal carcinoma progression. The knockdown efficiency of APOM was detected by qRT-PCR (Figure 4A). HCG11 upregulation significantly retarded cell proliferation, which was restored by APOM silence (Figure 4B-C). Suppressing APOM could rescue the promotive effect of HCG11 overexpression on cell apoptosis (Figure 4D). Suppression of APOM could rescue the effects induced by overexpressing HCG11 on Bax and Bcl-2 expression (Figure 4E). In brief, these findings suggested that APOM participated in HCG11-mediated cell proliferation and apoptosis in laryngeal carcinoma.

Discussion

Many lncRNAs have been revealed that they participate in laryngeal carcinoma progression. For example, lncRNA DGCR5 interacts with miR-195 to promote the radiosensitivity of laryngeal carcinoma[18]. LncRNA SNHG3 contributes to laryngeal carcinoma proliferation and migration *via* targeting miR-384/WEE1 axis[19]. Lately, HCG11, a newly identified lncRNA, has been demonstrated to act as a tumor suppressor in several cancers. LncRNA HCG11/miR-496/CPEB3 axis inhibits the progression of glioma[20]. LncRNA HCG11 absorbs miR-543 to regulate prostate cancer progression by regulating AKT/mTOR pathway[21]. However, up to now, there are no studies about HCG11 in laryngeal carcinoma. In this work, we found the low expression of

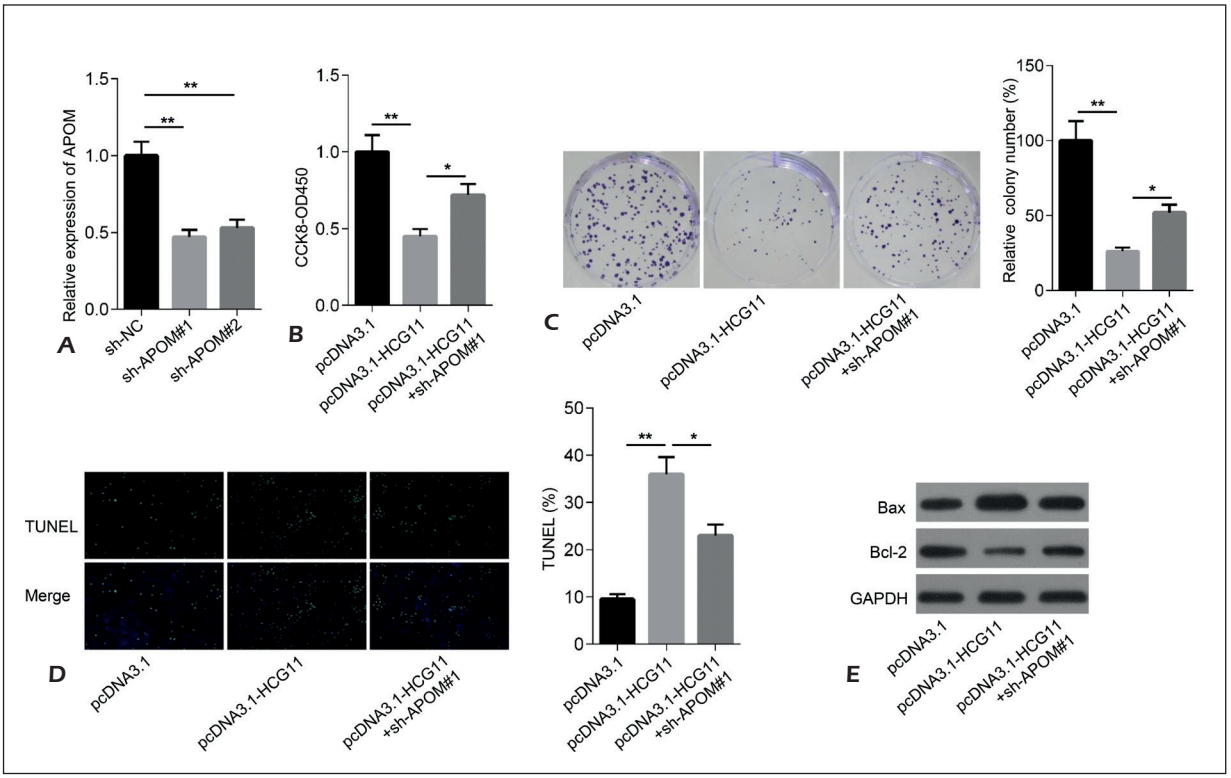

Figure 4. APOM participated in HCG11-mediated cell proliferation and apoptosis in laryngeal carcinoma. **A**, APOM expression was assessed in SNU46 cells transfected with sh-APOM#1 or sh-APOM#2. **B-C**, CCK-8 and colony formation assay were applied to detect cell proliferation in SNU46 cells transfected with pcDNA3.1, pcDNA3.1-HCG11 and pcDNA3.1-HCG11+sh-APOM#1 (magnification ×20). **D**, TUNEL assays were used to detect cell apoptosis by APOM upregulation in SNU46 cells transfected with pcDNA3.1, pcDNA3.1-HCG11 and pcDNA3.1-HCG11+sh-APOM#1 (magnification ×20). **E**, Western blot assay was conducted to measure the expression of Bax and Bcl-2 by APOM overexpression in SNU46 cells transfected with pcDNA3.1, pcDNA3.1-HCG11, and pcDNA3.1-HCG11+sh-APOM#1. *p<0.05, **p<0.01.

HCG11 in laryngeal carcinoma tissues and cell lines. Overexpression of HCG11 retarded cell proliferation and enhanced cell apoptosis.

It has been revealed that APOM served as an inhibitor in several forms of cancers. In our study, we observed that APOM inhibited laryngeal carcinoma tumorigenesis and HCG11 positively regulated APOM expression. Several ways are involved in the regulation of gene expression, such as transcriptional, post-transcriptional, translational, and post-translational control[22]. We speculated that there may be an operation mode of competitive endogenous RNA (ceRNA) network between HCG11 and APOM.

CeRNA network has been discovered to be a classical model of gene expression regulation[23]. Many researches have been reported that lncRNAs display their function of "microRNA sponge" by competitively binding to microRNAs, antagonizing the role of microRNAs in repressing specific target mRNAs. Of note, lncRNA PVT1 accelerates papillary thyroid carcinoma cell viability and invasion by functioning as a ceRNA of miR-30a *via* regulating IGF1R expression[24]. LncRNA DLX6-AS1 functions as a ceRNA by sponging miR-199a to drive cervical cancer proliferation[25]. LncRNA RP4 acts as a ceRNA to sponge miR-7-5p in colorectal cancer[26]. In the present work, miR-4469 was found to be a factor that has binding sites of HCG11 and APOM. MiRNAs are a class of micro transcripts (18-24 nts) that could not encode proteins[27,28]. MiR-4469 only has been studied in breast cancer that could induce an increase of motility[29]. In our study, we showed that HCG11 sponged miR-4469 to upregulate APOM expression. Finally, the repression of APOM rescued the effects of HCG11 overexpression on laryngeal carcinoma cell proliferation and cell apoptosis.

Conclusions

In summary, our study indicated for the first time that the HCG11/miR-4469/APOM axis suppresses the development and progression of laryngeal carcinoma. This finding might provide a new sight into the treatment of laryngeal carcinoma patients.

Availability of Data and Materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' Contributions

WB and HX designed the study. HL and TW performed the experiments. WL and HX analyzed the data and prepared the figures. WB and HX drafted the manuscript. All authors approved this manuscript.

Ethics Approval

The investigation was approved by the Ethics Committee of the Third Affiliated Hospital of Soochow University.

Conflict of Interests

The authors declare that they have no conflict of interests.

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