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Knockdown of lncRNA HCG11 suppresses cell progression in ovarian cancer by modulating miR-144-3p/PBX3

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Abstract. – OBJECTIVE: LncRNA HCG11 has been confirmed to act as a crucial role in several human cancers. Nevertheless, to our knowledge, the function of HCG11 on the progression of ovarian cancer (OC) has not been studied. This article is designed to explore the mechanism and role of HCG11 in the tumorigenesis and development of OC.

PATIENTS AND METHODS: RT-qPCR analysis was applied to detect the expression of HCG11, miR-144-3p and PBX3 in OC tissues and cell lines. MTT assay and transwell assay were opted to measure the cell viability of OC cells. The protein expression level of PBX3 was measured by Western blot assay. Dual-Luciferase reporter assay was carried out to assess the correlation between HCG11, miR-144-3p and PBX3.

RESULTS: The upregulated of HCG11 was observed in OC tissues and OC cell lines. Moreover, miR-144-3p was down expressed in OC tissues and cell lines. Functionally, the knockdown of HCG11 prevented cell viability of SKOV3 cells, while miR-144-3p inhibitor abrogated the suppressor on cell progression. Furthermore, PBX3 was verified to be a target gene of miR-144-3p. In addition, PBX3 knockdown prevented the cell progression of SKOV3 cells.

CONCLUSIONS: These data displayed that the knockdown of HCG11 prevented cell progression in OC by sponging miR-144-3p and downregulating PBX3. All results revealed that HCG11 can be a potential therapeutic target for OC therapy.

Key Words:
Ovarian cancer, HCG11, MiR-144-3p, PBX3.

Introduction

Ovarian cancer (OC) is a kind of tumors formed by the proliferation and differentiation of ovary cells under various factors. In developed countries, OC is the fourth most common female fatal tumor. Globally, approximately 220,000 women are diagnosed with OC each year. Although medical diagnosis and management technology have been improved, OC is easy to metastasize and relapse even after treatment. In addition, the current 5-year survival rate is only 25-30%[1]. Therefore, it is of great significance to find effective biomarkers for early diagnosis of OC patients.

Long non-coding RNAs (lncRNAs) can modulate the expression of genes through various pathways, thereby regulating the physiological functions. The role of lncRNAs in tumors is currently a research hotspot. With the in-depth study of lncRNAs, it was found that lncRNAs have regulatory effects on angiogenesis, cell proliferation, invasion, and migration of human cancers. LINC00662 was reported to enhance tumorigenesis and development of colon cancer by regulating miR-340-5p/CLDN8/IL22 co-expression, and motivating ERK signaling pathway[2]. LINC-PINT was confirmed to suppress cell invasion by highly conserved sequences[3]. LncRNA RAB11B-AS1 facilitated tumor angiogenesis and promoted cell invasion and migration of breast cancer cells[4].

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Inversely, in osteosarcoma, RAB11B-AS1 was down expressed and restrict cell progression[5]. In recent years, lncRNA HLA complex group 11 (HCG11) captured our attention. In breast cancer, HCG11 was upregulated and significantly related with poor overall survival[6]. In addition, Zhang et al[7] discovered that HCG11 was up expressed in gastric cancer and promoted cell proliferation and migration by modulating co-expression of miR-1276/CTNNB1. Nevertheless, the function of HCG11 in the cell progression of OC is still unknown.

MicroRNAs (miRNAs) have been observed to participate in the tumorigenesis and development of various human cancers. In breast cancer, miR-3196 prevented cell proliferation and enhanced cell apoptosis by targeting ERBB3[8]. MiR-223-3p was proved to enhance cell proliferation and invasion by regulating Arid1a in gastric cancer[9]. Many researches verified that miR-144-3p participated in various human cancers. So, Zheng et al[10] claimed that miR-144-3p was down expressed in prostate cancer and restrained cell proliferation by upregulating CEP55. Moreover, in cervical cancer, miR-144-3p was down expressed and inhibited cell viability and metastasis[11]. Although miR-144-3p has been studied in the above human cancers, its role in OC remains unknown.

In this research, we designed to explore the expression level of HCG11 in OC tissues. Then, we detected the function of HCG11 in the development of OC cells. Furthermore, the expression level and function of miR-144-3p in OC was also detected. Besides that, we clarified the effect of HCG11/miR-144-3p/PBX3 in the development of OC.

Patients and Methods

Clinical Tissues

48 OC tissues were obtained from DongDa Hospital of Shanxian. All patients did not receive OC tissues were immediately taken in a liquid nitrogen tank. Then, they were stored in a -80 °C refrigerator for further experiments. This experiment was executed according to the Declaration of Helsinki Principles. Inclusion criteria were as follows: i) Primary surgical patient, ii) complete records regarding pre-operative chemotherapy and past medical history. Exclusion criteria were as follows: i) Non-primary surgical patient, ii) missing or incomplete records regarding pre-operative chemotherapy or past medical history, iii) previous history of any malignancy. Our experiments received informed consent from all patients. The experiments were approved by the Ethics Committee of Jinan Zhangqiu District Hospital of TCM.

Cell Culture and Cell Lines

Human OC cell line OVCAR-3 was purchased from The Type Culture of the Chinese Academy of Sciences (Shanghai, China). TOV112D, A2780, SKOV3 and ISOE80 were obtained from BeNa Culture Collection (Beijing, China). OVCAR-3, TOV112D and A2780 cells were cultured with Roswell Park Memorial Institute-1640 (RPMI-1640) medium containing with 10% superior fetal calf serum (FBS). SKOV3 cells were cultured with McCoy's 5a medium at 37°C and 5% CO_2. When the cell density reaches 80-90%, the cells were digested and passaged with 0.02% Ethylene Diamine Tetraacetic Acid (EDTA) and 0.25% trypsin.

Cell Transfection

Specific small interference RNAs of HCG11 (si-HCG11), small interference RNAs of miR-144-3p (miR-144-3p inhibitor), pcDNA3.1-HCG11 (HCG11 vector), pcDNA3.1-miR-144-3p (miR-144-3p mimic), small interference RNAs of PBX3 (si-PBX3) and their corresponding negative control (NC) were synthesized by GenePharma (Shanghai, China). All were transfected into SKOV3 cells using Lipofectamine 2000.

RNA Isolation and qRT-PCR

RNAs form OC tissues and cells were isolated by using TRIzol reagent (Invitrogen, Carlsbad, CA). After adding 20 µl chloroform, the supernatant was centrifuged. Then, RNAs were precipitated by 400 µl isopropanol and washed with 75% ethanol. We finally added deionized water to dissolve the RNAs. The purity and concentration of RNAs were detected by agarose gel electrophoresis. After packing, store in a -80 °C refrigerator. LightCycle 96 Thermocycle (Invitrogen, Carlsbad, CA, USA) was carried out to investigate the relative expression of HCG11, miR-144-3p and PBX3. The expression of HCG11 and miR-144-3p was normalized to U6. PBX3 expression was normalized to GAPDH. The primer sequences were listed in Table I.

MTT Assay

SKOV3 cells were cultured with 10% fetal calf serum culture medium, then seeded into

Table I. Primer sequences in qRT-PCR.

Gene		Primers 5′-3′
HCG11	Forward	5'-GTGACCACTCTGTCGCCATT-3'
	Reverse	5'-GGTAGTACGGAGACCAACCG-3'
miR-144-3p	Forward	5'-GGCCCTGGCTGGGATATCAT-3'
	Reverse	5'-GGTGCCCGGACTAGTACATC-3'
PBX3	Forward	5'-GGACATCGGCGACATCCTC-3'
	Reverse	5'-TGATCTCACACAGGACGCTG-3'
GAPDH	Forward	5'-GACAGTCAGCCGCATCTTCT-3'
	Reverse	5'-GCGCCCAATACGACCAAATC-3'
U6	Forward	5'-GCTTCGGCAGCACATATACTAAAAT-3'
	Reverse	5'-CGCTTCACGAATTTGCGTGTCAT-3'

96-well plates. After cultured for 3-5 days, 20 µl MTT (Sigma-Aldrich, St Louis, MO, USA) was added into each well. After further incubation for 4-6 hours, we discarded the supernatant carefully and added 150 µl dimethyl sulfoxide (DMSO) to each well. Finally, they were shaken for 10 minutes to fully melt the crystals. Absorbance was detected by a microplate reader (Thermo Fisher Scientific, Waltham, MA, USA) at 490 nm.

Transwell Assay

Transwell chambers (8 µm; Millipore, Billerica, MA, USA) were performed to examine migration and invasion abilities of OC cells. Cell invasion was detected in the upper chamber with Matrigel (Corning Life Sciences, Corning, NY, USA). Cell migration was performed without Matrigel. First, 1×10^5 cells were inoculated in the upper transwell compartment. Then, 10% FBS was added into the lower compartment. After cultivation at 37 °C for 24 h, the cells were fixed and stained with 0.5% crystal violet. Finally, we counted the migrating cells numbers under an optical microscope (Olympus, Tokyo, Japan).

Dual-Luciferase Reporter Assay

HCG11-mut or HCG11-wt, miR-144-3p mimic or miR-NC and PBX3-mut or PBX3-wt were co-transfected into SKOV3 cells by Lipofectamine 2000. SKOV3 cells were cultured at 37 °C, 5% CO_2 and 95% humidity. After 48 hours of incubation, the Luciferase activity of HCG11 and PBX3 were estimated by Dual-Luciferase reporter assay kit.

Western Blot Assay

Protein samples were isolated by 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), and then, transferred to NC membrane. After incubating with 5% skimmed milk, membranes were incubated with GAPDH or U6 antibodies. The protein signals were detected by using enhanced chemiluminescence (ECL) kit Western Blotting Substrate.

Statistical Analysis

Our data were presented as mean ± SD, and analyzed by SPSS 19.0 and GraphPad Prism 6.0. Student's *t*-test was used to analyze the differences between the two groups. Moreover, multiple comparisons were analyzed by One-way ANOVA. The correlation between the expression of HCG11, miR-144-3p and PBX3 in OC tissues was assessed by Pearson's correlation analysis. $p<0.05$ was defined as statistical significance.

Results

Ectopic Expressions of HCG11 and MiR-144-3p are Found in OC Tissues and OC Cell Lines

Primarily, we verified the expression level of HCG11 and miR-144-3p in OC tissues and cell lines. The results revealed that HCG11 was remarkably higher expressed in OC tissues than in normal tissues ($p<0.01$; Figure 1A). Meanwhile, there was an increased expression of HCG11 in OC cell lines (OVCAR-3, TOV112D, SKOV3 and A2780) ($p<0.01$; Figure 1B). In addition, miR-144-3p was found to be lowly expressed in OC tissues than in normal groups ($p<0.01$; Figure 1C). Moreover, the downregulation of miR-144-3p was found in OC cell lines (OVCAR-3, TOV112D, SKOV3 and A2780) ($p<0.01$; Figure 1D). The above results indicate that abnormal expression of HCG11 and miR-144-3p may be involved in the tumorigenesis and development of OC.

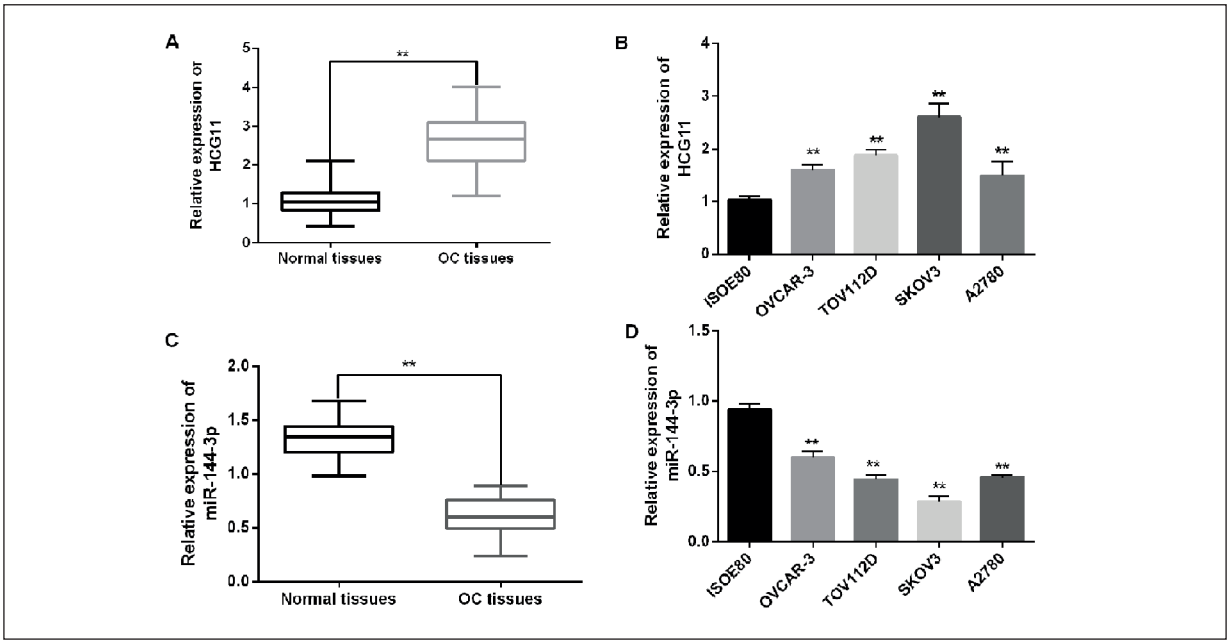


Figure 1. The dysregulation of HCG11 and miR-144-3p are found in OC tissues and OC cell lines. **A,** The expression of HCG11 in OC tissues was detected by qRT-PCR. **B,** The expression of HCG1 was higher in four human OC cell lines than normal cells. **C,** The expression of miR-144-3p in OC tissues was detected by qRT-PCR. **D,** The expression of miR-144-3p was lower in four human OC cell lines than normal cells.

HCG11 Knockdown Restrains OC Cell Viability and Cell Metastasis

Next, to explore the function of HCG11 in the progression of OC cells, HCG11 silencing was transfected into SKOV3 cells (p<0.01; Figure 2A). The cell proliferation of SKOV3 cells was measured by MTT assay. The results demonstrated that HCG11 silencing inhibited cell proliferation of SKOV-3 cells (p<0.05; p<0.01; Figure 2B). Furthermore, Transwell assay was carried out to investigate cell migration and invasion of SKOV-3 cells. We discovered that SKOV-3 cell migration and invasion ability were repressed by HCG11 silencing (p<0.01; Figure 2C, D). All results indicate that HCG11 knockdown restrains the OC cell viability.

HCG11 Acts as a Sponge of MiR-144-3p in OC

Then, StarBase software predicted that there were putative target sequences between miR-144-3p and the 3'-UTR of HCG11 (Figure 3A). Dual-Luciferase reporter assay was opted to verify this hypothesis. The results showed that miR-144-3p mimic reduced the Luciferase activity of HCG11-wt, but had no influence on HCG11-mut (p<0.01; Figure 3B). Moreover, the expression of HCG11 was reduced by miR-144-3p mimic, and accelerated by miR-144-3p inhibitor (p<0.01; Figure 3C). In addition, miR-144-3p was down regulated by HCG11 vector, but up regulated by si-HCG11 (p<0.01; Figure 3D). Besides that, miR-144-3p was demonstrated to have a negative correlation with HCG11 (R^2=0.6294; p<0.01; Figure 3E). As a consequence, we clarify that HCG11 serves as a sponge to modulate miR-144-3p expression in OC.

HCG11/MiR-144-3p Axis Regulates the Progression of OC

To explore the role of HCG11/miR-144-3p axis in the progression of OC, miR-144-3p inhibitor was transfected into SKOV-3 cells with si-HCG11. The results displayed that si-HCG11 reduced the expression level of HCG11, while miR-144-3p inhibitor impaired the inhibitory effect stimulated by si-HCG11 (p<0.01; Figure 4A). Furthermore, MTT and transwell assay were performed to assess the cell capacity of SKOV-3 cells. We found that the cell proliferation was inhibited by si-HCG11, but promoted by miR-144-3p inhibitor (p<0.01; Figure 4B). Similarly, miR-144-3p inhibitor weakened the suppression effect on SKOV3 cell migration and invasion induced by HCG11 silencing (p<0.01; Figure 4C, D). Then, RT-qPCR assay displayed that HCG11 vector suppressed

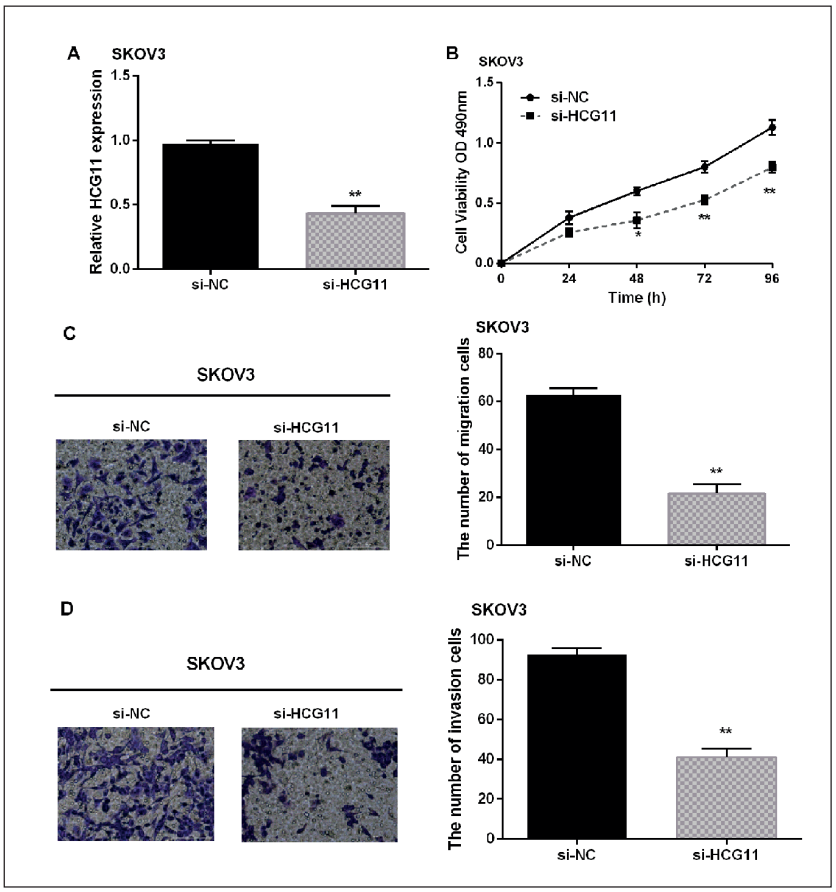


Figure 2. HCG11 knockdown restrains the cell viability in OC. **A,** The expression of HCG11 was reduced by si-HCG11. **B,** The proliferation of SKOV3 cells was indicated by MTT assay. **C, D,** Cell migration and invasion ability were detected by transwell assay (scale bar=100 μm). *p<0.05, **p<0.01.

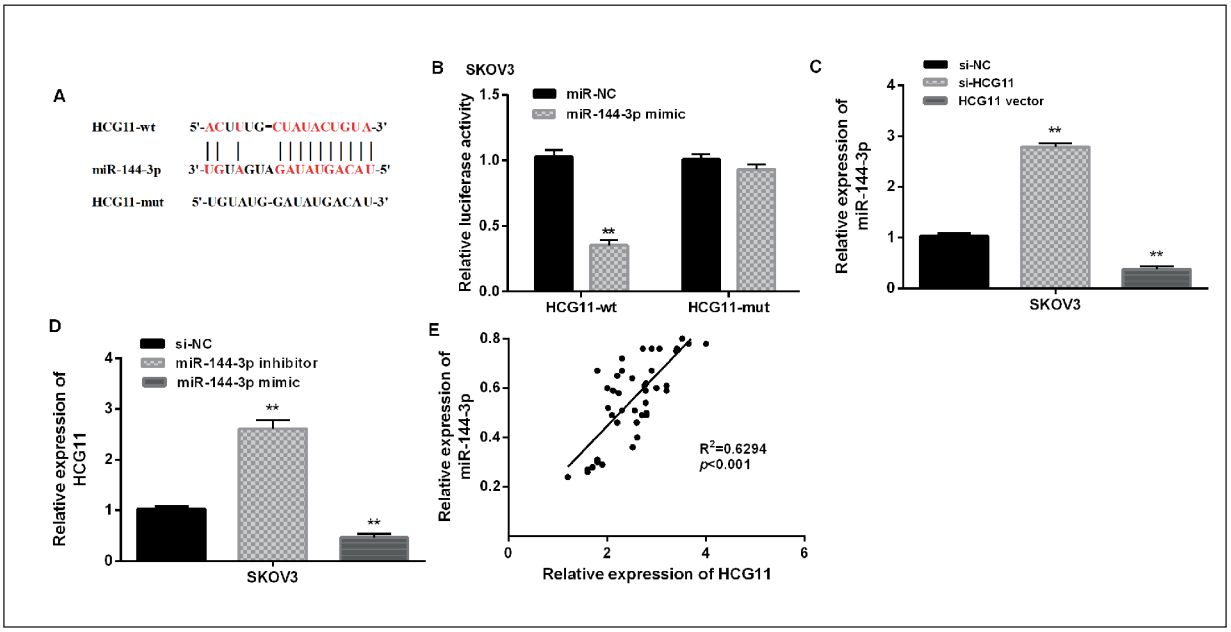


Figure 3. HCG11 acts as a molecular sponge of miR-144-3p in OC. **A,** The binding sites between HCG11 and miR-144-3p. **B,** The relative luciferase activity of HCG11 was detected by luciferase reporter assay. **C,** The expression level of miR-144-3p when si-HCG11 or HCG vector transfected into SKOV3 cells. **D,** HCG11 expression regulated by miR-144-3p mimic or miR-144-3p inhibitor. **E,** HCG11 had a negative correlation with miR-144-3p in OC tissues. **p<0.01.

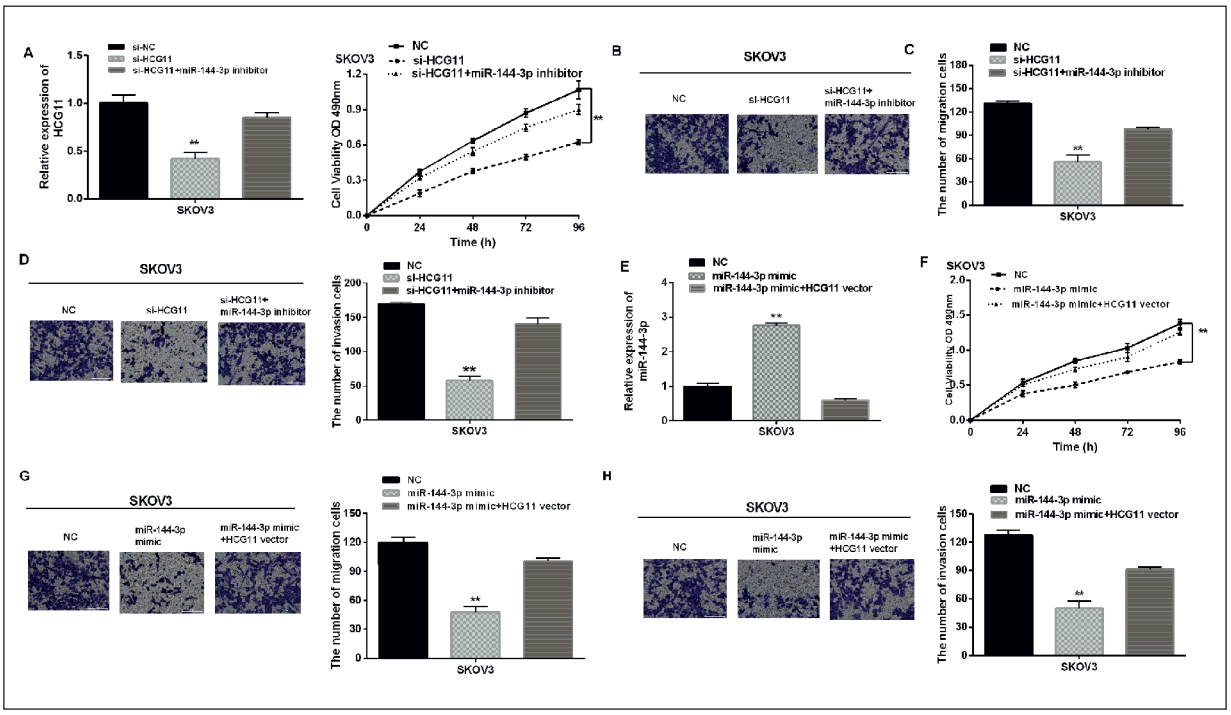


Figure 4. HCG11/miR-144-3p axis regulates the progression of OC. **A,** The expression of HCG11 with si-HCG11 or si-HCG11+miR-144-3p inhibitor in SKOV3 cells. **B,** The cell proliferation with miR-144-3p inhibitor transfection in the presence of si-HCG11. **C, D,** Cell migration and invasion with miR-144-3p inhibitor transfection in the presence of si-HCG11. **E,** The expression of miR-144-3p with miR-144-3p mimic or miR-144-3p mimic+HCG11 vector. **F, G, H,** The cell proliferation, migration and invasion of SKOV3 cells with HCG11 vector transfection in the presence of miR-144-3p mimic. $^{**}p<0.01$.

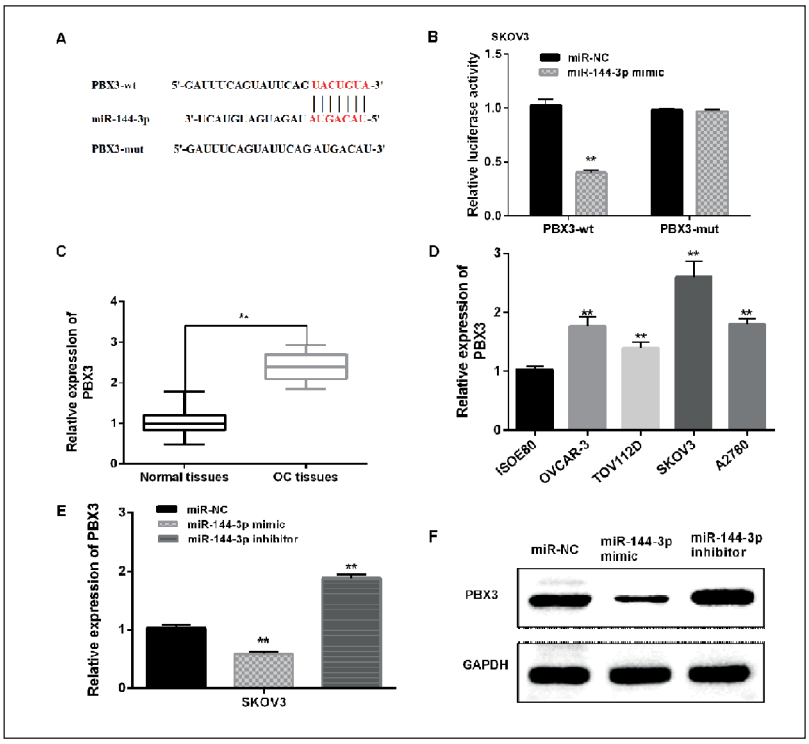
the increased expression of miR-144-3p stimulated by miR-144-3p mimic ($p<0.01$; Figure 4E). Furthermore, miR-144-3p overexpression was demonstrated to inhibit SKOV-3 cell proliferation, but HCG11 vector attenuated the inhibition effect induced by miR-144-3p mimic ($p<0.01$; Figure 4F). HCG11 vector also impaired the suppressing effect on SKOV-3 cell migration and invasion stimulated by miR-144-3p mimic ($p<0.01$; Figure 4G, H). Accordingly, we manifest that HCG11/miR-144-3p axis acts as an important role in the progression of OC.

PBX3 is a Direct Target Gene of MiR-144-3p

TargetScan was performed to predict the target genes of miR-144-3p. As shown in Figure 5A, miR-144-3p had binding sites with PBX3's 3-UTR. Then, the Luciferase reporter assay clarified what we predicted. The results displayed that miR-144-3p mimic reduced the Luciferase activity of PBX3-wt, but not PBX3-mut ($p<0.01$; Figure 5B). Furthermore, the expression of PBX3 was detected in OC tissues and OC cell lines. Our results discovered that PBX3 was highly expressed in OC tissues and cells than normal groups ($p<0.01$; Figure 5C, D). Furthermore, we found that miR-144-3p mimic descended the mRNA expression of PBX3, whereas miR-144-3p inhibitor escalated the expression ($p<0.01$; Figure 5E). In addition, miR-144-3p had the same effect on the protein expression of PBX3 ($p<0.01$; Figure 5F). Based on these data, we disclose that PBX3 is a target gene of miR-144-3p.

HCG11/MiR-144-3p Axis Regulates OC Progression by Mediating PBX3

To explore the role of HCG11/miR-144-3p/PBX3 in the progression of OC, HCG11 vector or miR-144-3p inhibitor was transfected into SKOV-3 cells with si-PBX3. As evident from Figure 6A, si-PBX3 descended the mRNA expression level of PBX3, but the inhibitory effect was impaired when HCG11 vector or miR-144-3p inhibitor transfected into SKOV-3 cells with si-PBX3 ($p<0.01$; Figure 6A). Moreover, HCG11 vector and miR-144-3p inhibitor also weakened the inhibition of PBX3 protein expression stimu-



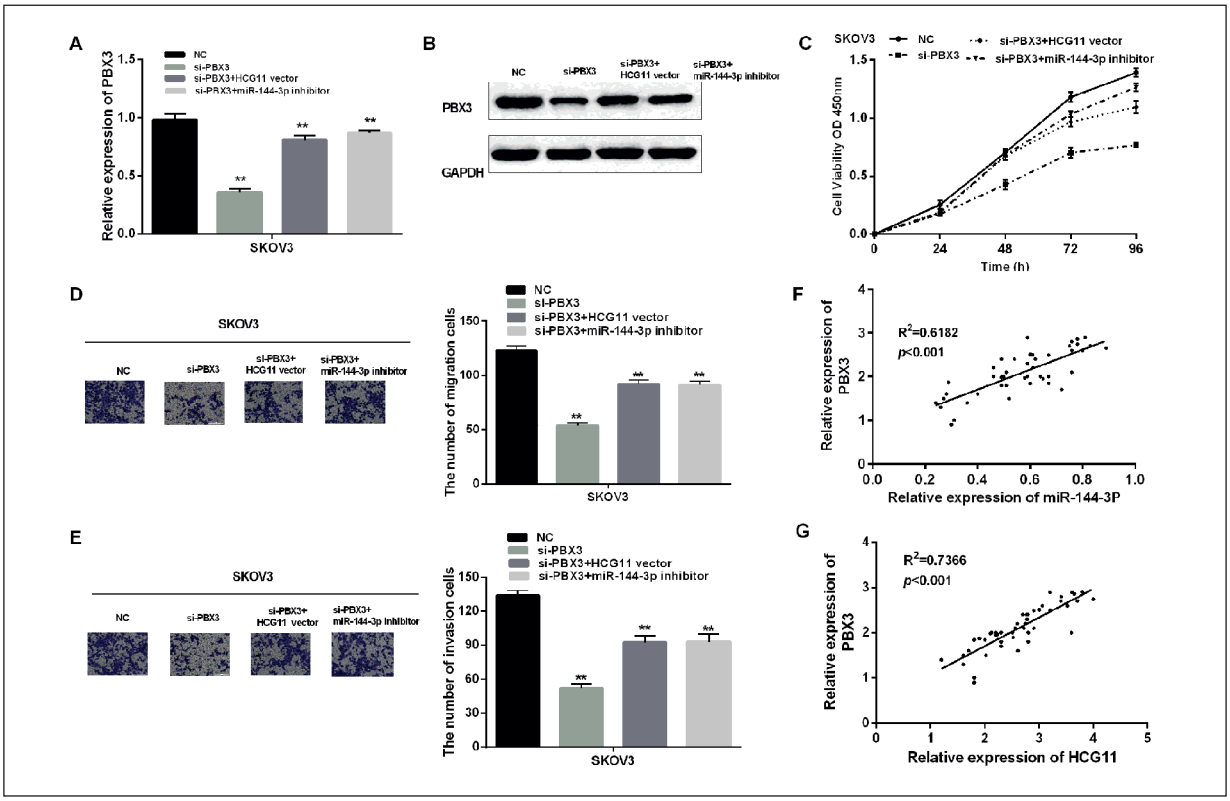


Figure 5. PBX3 is a direct target of miR-144-3p. **A,** The binding sites between miR-144-3p and PBX3. **B,** The relative Luciferase activity of PBX3 was detected. **C,** PBX3 was highly expressed in OC tissues. **D,** The expression level of PBX3 was increased in four OC cell lines. **E, F,** The mRNA expression and protein expression level of PBX3 induced by miR-144-3p. **$p<0.01$.

Figure 6. HCG11/miR-144-3p axis regulates OC progression by mediating PBX3. **A, B,** The relative mRNA and protein expression of PBX3 stimulated by HCG11 vector or miR-144-3p inhibitor. **C, D, E,** The cell proliferation, migration and invasion of SKOV3 cells when transfected with HCG11 vector or miR-144-3p inhibitor in presence of si-PBX3 (scale bar=100 μm). F, PBX3 was negatively correlated with miR-133-3p in OC tissues. **G,** There was a positive correlation between HCG11 and PBX3 in OC tissues. **$p<0.01$.

lated by si-PBX3 (p<0.01; Figure 6B). Functionally, si-PBX3 suppressed SKOV-3 cell proliferation. However, HCG11 vector and miR-144-3p inhibitor enhanced the cell proliferation ability (p<0.01; Figure 6C). Furthermore, HCG11 vector and miR-144-3p inhibitor impaired the suppression of SKOV3 cell migration and invasion stimulated by si-PBX3 (p<0.01; Figure 6D). Besides that, there was an inverse correlation between PBX3 and miR-144-3p (p<0.01; Figure 6E). Inversely, we found a positive correlation between HCG11 and PBX3 (p<0.01; Figure 6F). In sum, HCG11/miR-144-3p enhances the progression by upregulating PBX3 expression in OC.

Discussion

In recent years, emerging evidence suggested that many lncRNAs were participated in the tumorigenesis and development of OC, such as MEG3[12], MALAT1[13], SOX4[14], and H19[15]. LncRNA HCG11 has been reported to be abnormally expressed in tumorigenesis and progression of several human cancers. We discovered that HCG11 was dramatically high expressed in OC tissues and cell lines. Moreover, functional experiments indicated that HCG11 silencing prevented SKOV3 cell viability. Xu et al[16] verified that the depletion of HCG11 inhibited cell proliferation and enhanced cell apoptosis by modulating IGF2BP1 in hepatocellular carcinoma, which was parallel to our results. Interestingly, HCG11 acted as a tumor inhibitor in glioma[17], prostate cancer[18], and hepatocellular carcinoma[16]. All results indicated that HCG11 might be a target biomarker for the treatment of OC.

MiR-144-3p played a role in multiple human diseases. Gong et al[19] found that miR-144-3p suppressed MALAT1-induced cardiomyocyte apoptosis. In addition, miR-144-3p prevented cell proliferation and metastasis in endometrial cancer[20] and osteosarcoma[21]. Consistent with above findings, we noticed that miR-144-3p expression was declined in OC tissues and cells. In our study, HCG11 was confirmed to be a sponge of miR-144-3p. Moreover, miR-144-3p was found to restrict cell viability of SKOV3 cells. Besides that, miR-144-3p inhibitor impaired the inhibitory effects of HCG11 silencing on cell viability of SKOV3 cells. Our results displayed that miR-144-3p acted as tumor inhibitor in the development of OC.

To explore the mechanism of miR-144-3p in the development of OC, we predicted that PBX3 was the binding target to miR-144-3p. In our study, we discovered that PBX3 was up expressed in OC tissues and cell lines. Furthermore, PBX3 silencing prevented cell power of SKOV3 cells. Consistent with our study, PBX3 was also modulated by miR-144-3p and restrained cell progression in gastric cancer[22]. Additionally, PBX3 was verified to serve as an oncogene in pancreatic cancer[23], cervical cancer[24], and prostate cancer[25]. In addition, HCG11 overexpression or miR-144-3p down expression can both impair the inhibitory effect of PBX3 silencing on cell viability. PBX3 was negatively modulated by miR-144-3p and positively regulated by HCG11. All data displayed that HCG11/miR-144-3p regulated the OC cell progression by suppressing PBX3 expression. However, there are still limitations. For instance, the EMT and the *in vivo* study shoukd be explored in the further experiments.

Conclusions

Taken together, we identified that HCG11 was involved in the development of OC. For the first time, HCG11 knockdown was indicated to prevent the cell progression of OC by sponging miR-144-3p and downregulating PBX3 expression. Therefore, we suggested that HCG11 might be a therapeutic target for OC treatment.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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