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The Long Non-Coding RNA MALAT1 Enhances Ovarian Cancer Cell Stemness by Inhibiting YAP Translocation from Nucleus to Cytoplasm

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The purpose of this work was to unearth the effects and underlying mechanism of long non-coding RNA (lncRNA) MALAT1 in ovarian cancer cell stemness.

Material/Methods: Western blot, quantitative polymerase chain reaction (qPCR) and sphere forming analysis were performed to evaluate the stem-like traits of cells and MALAT1-induced effects on ovarian cancer cell stemness. Cell viability was performed to evaluate MALAT1 role in the chemoresistance of ovarian cancer cells. RNA immunoprecipitation (RIP) and luciferase reporter analysis were constructed to investigate the underlying mechanisms.

Results: Here, qPCR assay showed that MALAT1 level was remarkably higher in non-adherent spheres formed by adherent ovarian cancer cells, as well as cisplatin-resistant ovarian cancer cells. Additionally, MALAT1 knockdown reduced ovarian cancer cell stemness, characterized as the decrease of sphere forming ability, expression of stemness regulatory masters, and attenuation of cisplatin resistance. Moreover, MALAT1 interacted with yes-associated protein (YAP), inhibited its nuclear-cytoplasm translocation, promoted YAP protein stability and expression and thus increased its activity. Notably, rescuing expression of YAP attenuated the inhibition of MALAT1 knockdown on ovarian cancer cell stemness.

Conclusions: In conclusion, these results demonstrate a MALAT1/YAP axis responsible for ovarian cancer cell stemness.

MeSH Keywords: Neoplastic Stem Cells • Ovarian Neoplasms • RNA, Long Noncoding

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Background

Ovarian cancer (OC) is a common malignant tumor of women and its incidence is very high, second only to cervical cancer and uterine body cancer [1]. It is difficult to diagnose early in clinic and 70% of patients are in the advanced stage of cancer when diagnosed. This greatly increases the mortality rate of women, making OC the highest mortality rate of female malignant tumors [2]. Therefore, there is an urgent need to elucidate the mechanism contributing to OC progression and find novel targets for OC diagnosis and treatment.

Genomic studies have found that 97% of the human genome is composed of introns, regulatory sequences and non-coding RNA (ncRNA), which are non-coding genes [3]. Long non-coding RNA (lncRNA) belongs to one of ncRNAs with a length greater than 200 nucleotides [4]. LncRNAs were initially regarded as "transcriptional garbage" because they do not have the function of coding proteins [4]. However, more and more studies have shown that lncRNAs are closely related to the cancer progression, invasion and drug resistance of tumors [5]. They are engaged in protein bridges, localization of chromatin modifying enzyme, RNA bait, and RNA complementation [6].

MALAT1 has been shown to be highly expressed in various tumors. For example, MALAT1 is highly expressed in breast cancer and associated with the poor prognosis of breast cancer patients [7,8]. MALAT1 is engaged in hepatocellular carcinoma metastasis and poor prognosis [9]. Notably, MALAT1 predicts poor prognosis in epithelial OC and promotes OC cell proliferation, migration, and chemosensitivity [10]. Additionally, exosomal MALAT1 promotes angiogenesis of OC cells [11]. However, its roles and the related mechanism in regulating OC cell stemness are still confusing.

Yes-associated protein (YAP) is a proline-rich phosphoprotein encoded by YAP1 gene, and it is also called YAP65 because of its molecular weight of 65 kDa [12]. YAP, a key downstream executor of Hippo pathway, is involved in regulating the expression of genes related to proliferation and apoptosis [13]. Abnormal expression or mutation of YAP may lead to abnormal regulation of Hippo-YAP pathway. Apart from being regulated by Hippo signaling, YAP is modulated by other pathways, such as, mechanical pressure [14] and Rho-GTPase [15,16]. Recent works showed that lncRNAs are associated with YAP activity, such as lncRNA B4GALT1-AS1 [17,18], lncRNA TUG1 [19], and lncRNA THOR [20], in which YAP transcriptional activity is responsible for lncRNA-mediated regulation on cell stemness; these effects supporting the promoting role of YAP in tumor cell stemness [21,22]. Moreover, it is indicated that MALAT1 induces YAP activity contributing to the stemness-related traits of esophageal squamous cell carcinoma [23]. We wondered whether YAP is essential for MALAT1-induced effects on OC cell stemness.

In the present study, it was found that lncRNA MALAT1 level was highly expressed in the non-adherent spheres and cisplatin-resistant cells formed by parental OC cells compared to parental cells. Functional experiments indicated that knockdown (kd) of MALAT1 reduced the stemness of OC cells through interacting with YAP and regulating YAP protein stability and activity. This work identified a novel MALAT1/YAP signaling responsible for OC cell stemness.

Material and Methods

Cell culture and reagents

OC cell line SKOV3 was purchased from Biobw (Beijing, China) and stored in our laboratory. SKOV3-CR cells with cisplatin resistance were constructed by culturing with 1 μM cisplatin (Apexbio) for 14 days, followed by culturing with 1 nM cisplatin for at least 3 months. The resistance index was confirmed by using these cells as cisplatin-resistant cells. Cells were cultured in RPIM 1640 medium (Thermo Fisher Scientific, Waltham, MA, USA) with 15% fetal bovine serum (FBS, Thermo Fisher Scientific) under 5% CO_2 with humidified atmosphere at 37°C. Cell lines were authenticated through short tandem repeat (STR) DNA profiling every 6 months.

Quantitative real-time PCR (RT-qCR)

RNA extraction was performed using RNA isolator Total RNA Extraction Reagent (Vazyme, Nanjing, China). Then cDNA was reversely synthesized, and RT-qPCR was performed using Hifair™ III One Step RT-qPCR Probe Kit (YEASEN). RT-qPCR was constructed using the StepOne Plus PCR system. The probe sequences were listed as follows:
ALDH1-forward, 5'-CACGCCAGACTTACCTGTCCTACT-3';
ALDH1-reverse, 5'-TGTCAACATCCTCCTTATCTCCTT-3';
Nanog-forward, 5'-AGCACCTACCTACCCCAGCCTTTA-3';
Nanog-reverse, 5'-GCAGCTTCCAARGCAGCCTCCAAG-3';
MALAT1-forward, 5'GCAAAACAAAAACCCCTAAAAAAG-3';
MALAT1-reverse, 5'-CTGAAAGTGCTCACAAGGCAAATC-3';
YAP-forward, 5'-TACACCCACAGCTCAGCATCTTCG-3';
YAP-reverse, 5'-GTCATGGCTTGTTCCCATCCATCA-3';
β-actin-forward, 5'-TCACCACCACTGCCGAAAGAGAAA-3';
β-actin-reverse, 5'-AGAGGGAAGCCAGGATGGAACCAC-3'.

The RT-qPCR procedure was 95°C 15 minutes, 94°C 15 seconds, 60°C 30 seconds, 72°C 60 seconds, 40 cycles, 95°C 15 seconds, 60°C 15 seconds and 95°C 15 seconds to verify the characteristics of the PCR products. $2^{-\Delta\Delta ct}$ method was performed to calculate the relative expression levels of transcripts.

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Western blot

Cells were lysed and whole protein was extracted using RNA immunoprecipitation assay (RIPA) lysis buffer (Beyotime, Beijing, China). BCA Protein Quantification Kit (Tiangen, Beijing, China) was used to measure the protein concentration. Then detailed procedure was performed following the protocols mentioned in the previous work [23].

Construction of lentivirus vectors

The MALAT1 kd shRNA-encoding and YAP overexpression (oe) lentivirus vectors were constructed by GenePharma (Shanghai, China), denoted as MALAT1-kd and YAP-oe, respectively.

Sphere forming analysis

The detailed procedure was mentioned in the previous work [15]. Briefly, SKOV3, SKOV3-CR and SKOV3 spheroid cells with MALAT1 knockdown or not were digested into single cells. After counting, 2000/mL cells were inoculated into 24-well plates with stem cell culture medium (Thermo Fisher Scientific). The cells were cultured in 37°C, after 10 days, spheres were observed under laser-confocal microscope, and the spheres with diameter >50 μm were counted. The quantitative experiments have been repeated more than 3 times, and the results of random selection are shown.

RNA immunoprecipitation (RIP)

RIP analysis was carried out using EZ-Magna RIP™ RNA-Binding Protein Immunoprecipitation Kit (Merck Millipore, Billerica, MA, USA) to detect the RNA abundance pulled down by anti-YAP.

Luciferase reporter assay

The activity of 8xGTIIC-luciferase (8G-Luc) plasmid (Plasmid #34615, Addgene), driven by YAP-responsive synthetic promoter, was detected to evaluate the YAP transcriptional activity in SKOV3-CR cells with MALAT1 kd, this process was referred to the previous work [20].

Cell viability detection

Cells with different transfection or treatment were maintained in 96-well plates and treated with cisplatin (10 μM) 12 hours later [24]. Then at 24, 48, and 72 hours later, cell viability was evaluated via Cell Counting Kit-8 (CCK-8) assay (YEASEN, Shanghai, China).

RNA-Fluorescence *in situ* hybridization (RNA-FISH)

Fluorescence *in situ* hybridization for MALAT1 was performed in SKOV3 and SKOV3-CR cells following the manufacturer's protocols. The 5'CY3-labeled Locked Nucleic Acid (LNA) probes directed against MALAT1 was synthesized by GenePharma (Shanghai, China).

Statistical analysis

All data were expressed as the mean±standard error of the mean (SEM), where mean represents number of independent experiments ($n \geq 3$). Statistical analysis was performed using Prism7 (GraphPad software). The differences between the groups were analyzed using one-way ANOVA with the Tukey-Kramer post-test, only 2 groups were analyzed using the Student's *t*-test. *P* value less than 0.05 was considered significant.

Results

Cisplatin-resistant OC cells exhibited a stronger stemness than the parental cells

CSCs are considered as the root of chemoresistance [25], we wonder whether cisplatin-resistance OC cells hold similar traits as CSCs. We constructed cisplatin-resistant OC cells (SKOV3-CR) and found that SKOV3-CR cells exhibited a stronger stemness than the parental SKOV3 cells, characterized by the upregulation of sphere number and size (Figure 1A, 1B) and expression of stemness regulatory masters (Nanog and ALDH1) (Figure 1C, 1D).

MALAT1 expression was increased in cisplatin-resistant OC cells and non-adherent spheres

Furthermore, as the non-adherent spheres are regarded as stemness-like cells, we collected non-adherent spheres. Then MALAT1 expression was examined in non-adherent spheres and cisplatin-resistant OC cells, and it was found that MALAT1 level was significantly upregulated in SKOV3-CR and non-adherent spheres compared with the parental cells (Figure 2A, 2B). Additionally, RNA-FISH experiments were performed, and the results showed that MALAT1 was located in both the nucleus and cytoplasm in SKOV3 as well as in SKOV3-CR cells (Figure 2C). Thus, we speculate that MALAT1 may promote OC cell stemness.

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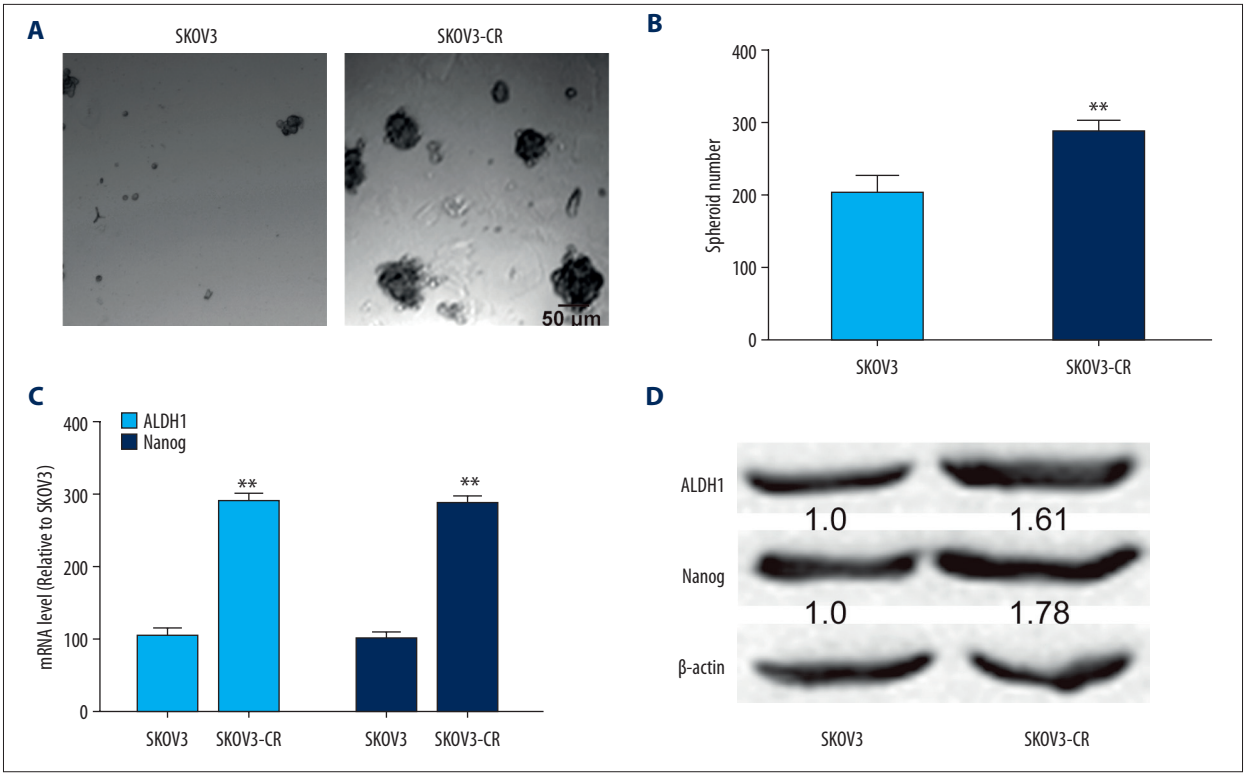

Figure 1. Cisplatin-resistant ovarian cancer cells exhibit a stronger stemness than the parental cells. (**A, B**) The sphere forming ability was evaluated in SKOV3 and SKOV3-CR cells. (**C, D**) The expression of stemness regulatory masters was measured in SKOV3 and SKOV3-CR cells. The difference was assayed using one-way ANOVA with the Tukey-Kramer post-test. Data are presented as the mean±standard deviation, n≥3, ** *P*<0.01 versus SKOV3.

MALAT1 kd reduced the stemness of cisplatin-resistant OC cells and non-adherent spheres

Then MALAT1 was knocked down in SKOV3-CR cells and non-adherent spheres by lentivirus infection. RT-qPCR was performed to evaluate the kd efficiency (Figure 3A). As expected, MALAT1 kd reduced the expression of stemness regulatory masters (Figure 3B–3D). Furthermore, the sphere forming capacity was decreased by MALAT1 kd in SKOV3-CR cells and non-adherent spheres, which was evident by the decrease of sphere number and size (Figure 3E, 3F). Moreover, MALAT1 kd attenuated the cisplatin resistance of SKOV3-CR cells (Figure 3G, 3H). Thus, our results demonstrate that MALAT1 regulates OC cell stemness positively.

MALAT1 interacted with YAP, inhibited YAP nucleus-cytoplasm translocation and promoted its activity

We further investigated the underlying mechanism contributing to MALAT1-mediated regulation on OC cell stemness. As the previous study has shown that MALAT1 could interact with YAP, we wondered whether this MALAT1-YAP interaction exists in OC cells. RIP assay showed that MALAT1 could interact with YAP in SKOV3-CR cells and non-adherent spheres (Figure 4A). Additionally, MALAT1 kd promoted the nucleus-cytoplasm translocation of YAP (Figure 4B, 4C), and reduced YAP protein expression but had little effects on YAP mRNA expression (Figure 4D, 4E). Moreover, luciferase reporter assay indicated that MALAT1 kd decreased the activity of 8G-Luc plasmid, a luciferase expression plasmid driven by YAP-responsive synthetic promoter (Figure 4F). Moreover, the activity of 8G-Luc plasmid displayed a higher level in SKOV3-CR cells and non-adherent spheres relative to that in SKOV3 cells (Figure 4G).

MALAT1 regulated the stemness of OC cells dependent on YAP

Finally, we investigated whether YAP expression was essential for MALAT1-mediated effects on OC cell stemness. As shown in Figure 5A–5C, YAP oe attenuated MALAT1 kd-induced inhibition on the expression of stemness regulatory masters. YAP oe efficiency was confirmed too (Figure 5C). Additionally, the decreased sphere forming ability led by MALAT1 kd was rescued by YAP oe (Figure 5D, 5E). Consistently, YAP oe partially reversed the attenuation of MALAT1 kd on cisplatin resistance (Figure 5F, 5G), and the enhancement of MALAT1 kd on cisplatin sensitivity (Figure 5H). Collectively, these results indicated that MALAT1 positively regulated OC cell stemness dependent on YAP activity.

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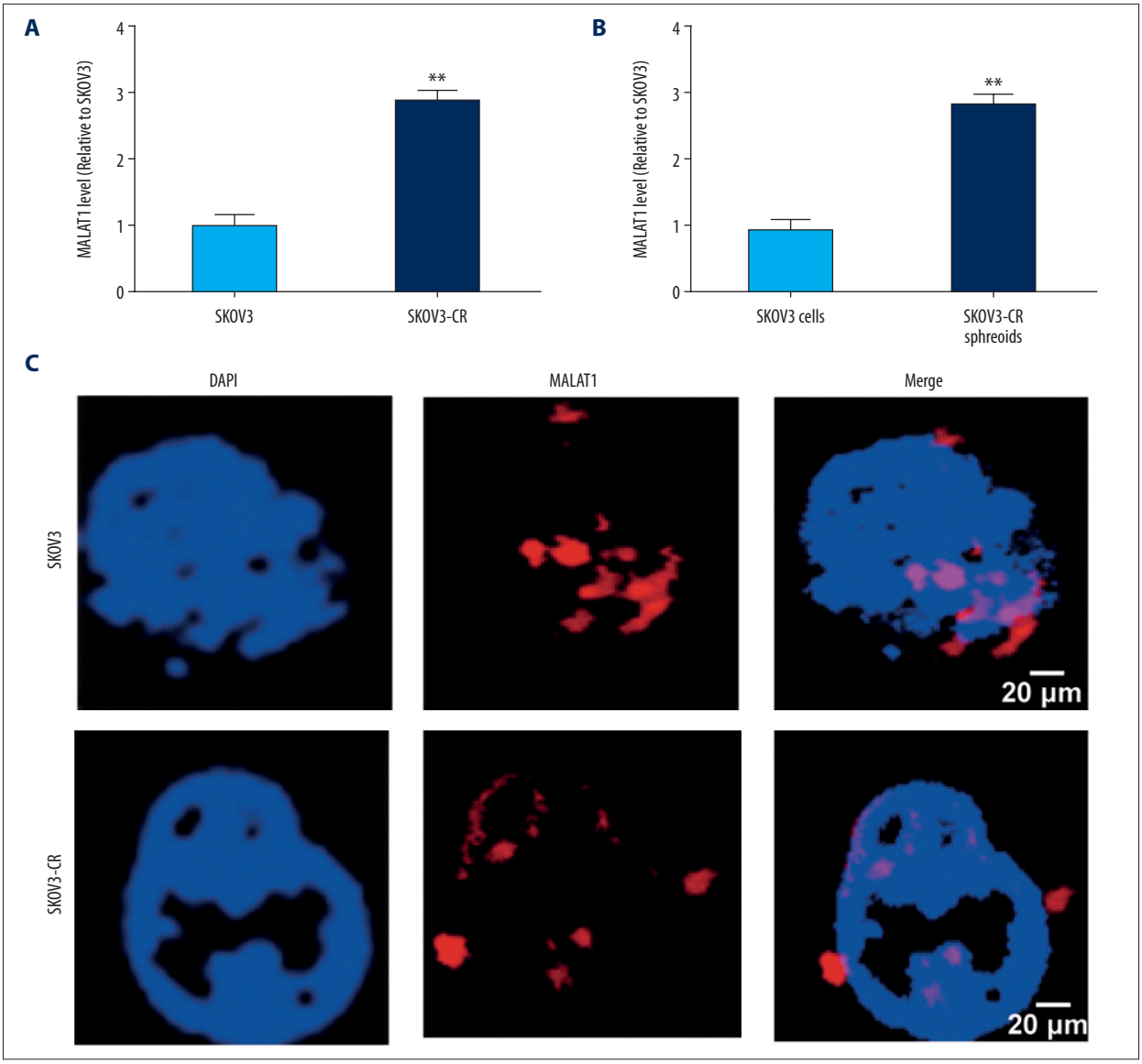

Figure 2. MALAT1 expression is increased in cisplatin-resistant ovarian cancer cells and non-adherent spheres. (**A**) The expression of MALAT1 was detected in SKOV3 and SKOV3-CR cells. (**B**) MALAT1 expression was examined in SKOV3 and SKOV3-CR cells. (**C**) RNA-FISH experiments were performed to determine the localization of MALAT1 in SKOV3 and SKOV3-CR cells. The difference was assayed using one-way ANOVA with the Tukey-Kramer post-test. Scale bar, 20 μm. Data are presented as the mean±standard deviation, n≥3, ** P<0.01 versus SKOV3.

Discussion

Here, cisplatin-resistant OC cells and OC spheres were used as the stem-like OC cells. MALAT1 expression was found to be significantly increased in the stem-like OC cells compared to parental OC cells. Further functional experiments showed that MALAT1 kd reduced the stemness of OC stem-like cells. The mechanistic study revealed that MALAT1 regulated the stemness of OC stem-like cells through interacting to YAP and thus enhancing YAP transcriptional activity. Notably, the MALAT1/YAP axis promoted chemoresistance of OC cells.

LncRNAs are closely related to tumor occurrence and development [26]. The abnormal expression of lncRNAs in tumor cells is expected to be used as a tumor marker in the diagnosis of tumors, especially in the early stage of some tumors, the diagnostic value of lncRNAs may be greater. MALAT1 level is significantly higher in lung cancer, bladder cancer, cervical cancer, and other metastatic tissues than that in normal tissues, and it is also used to predict the recurrence of patients after liver transplantation [27–29]; these effects indicate that MALAT1 holds the promoting roles in various tumors although some works indicate its inhibitory roles in breast cancer [30]. In this

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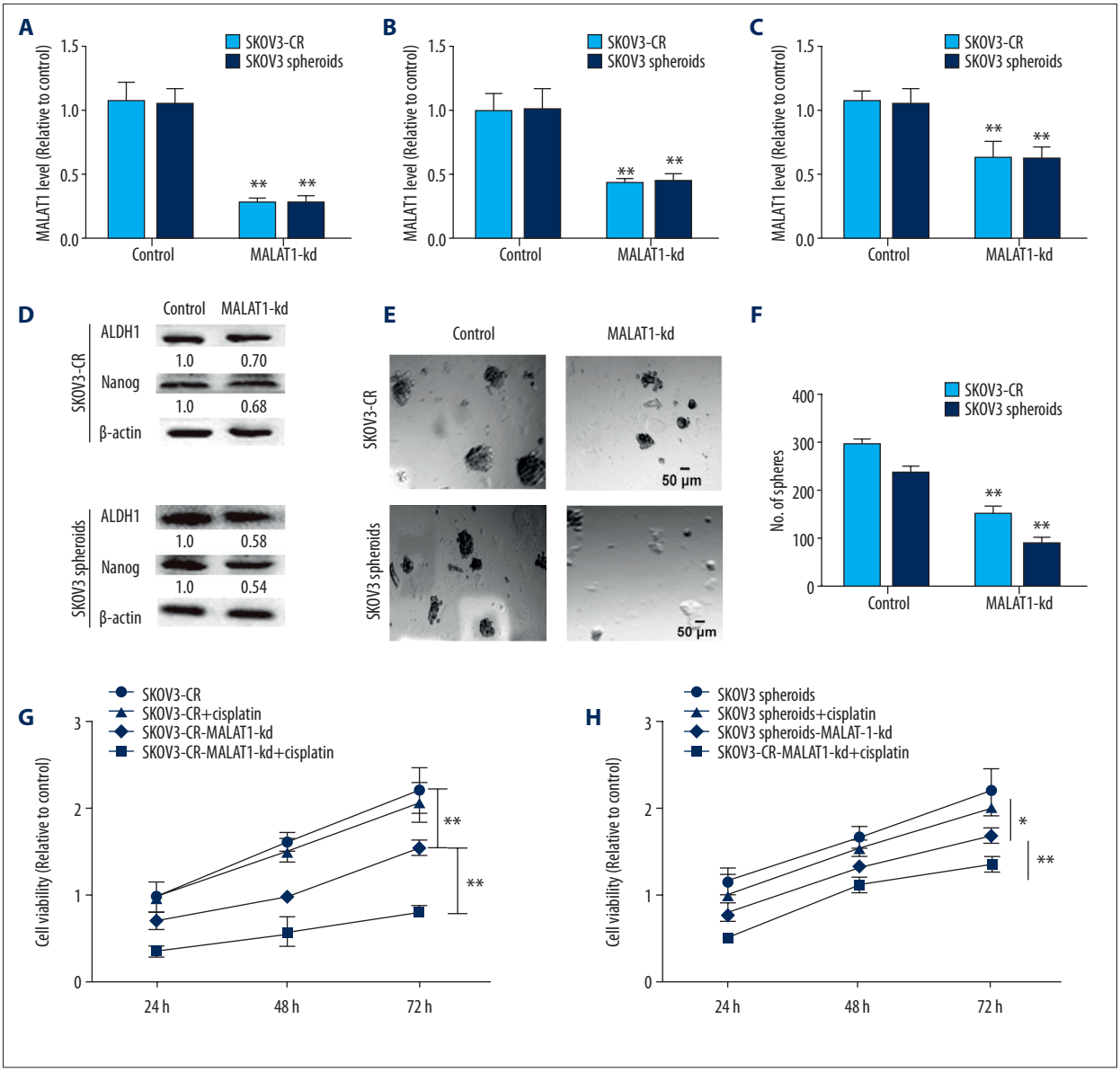

Figure 3. MALAT1 knockdown (kd) reduces the stemness of cisplatin-resistant ovarian cancer cells and non-adherent spheres. (**A**) MALAT1 level was measured in SKOV3 spheres and SKOV3-CR cells with or without MALAT1 kd. (**B–D**) The expression of stemness regulatory masters was detected in SKOV3 spheres and SKOV3-CR cells with or without MALAT1 kd. (**E, F**) Sphere forming capacity was assessed in SKOV3 spheres and SKOV3-CR cells with or without MALAT1 kd. (**G**) Cell viability assay was performed in SKOV3-CR cells with MALAT1 kd after cisplatin treatment or not. (**H**) Cell viability assay was performed in SKOV3 spheres with MALAT1 kd after cisplatin treatment or not. The difference was assayed using one-way ANOVA with the Tukey-Kramer post-test. Scale bar, 50 μm. Data are presented as the mean±standard deviation, n≥3, ** P<0.01 versus control.

study, it was indicated that MALAT1 promotes the stemness-related traits of OC cells, which is in accordance with the previous studies indicating that MALAT1 promotes the EMT (epithelial-mesenchymal transition) process [23,31]. Since EMT process holds a mutually reinforcing relationship with cell stemness and combined with our results in this work, we strongly believe that MALAT1 holds critical roles in OC cell stemness.

Recent studies have shown that lncRNAs have similar mechanisms in regulating gene expression, including acting as RNA baits, protein bridges, RNA complementation, competitive endogenous RNA (ceRNA), and chromatin modifiers [32,33]. Here, we found that MALAT1 acts as a YAP co-activator to inhibit its nucleus-cytoplasm translocation and thus enhancing its activity, this process is responsible for MALAT1-mediated effects on OC cell stemness and chemoresistance. The nucleus-cytoplasm

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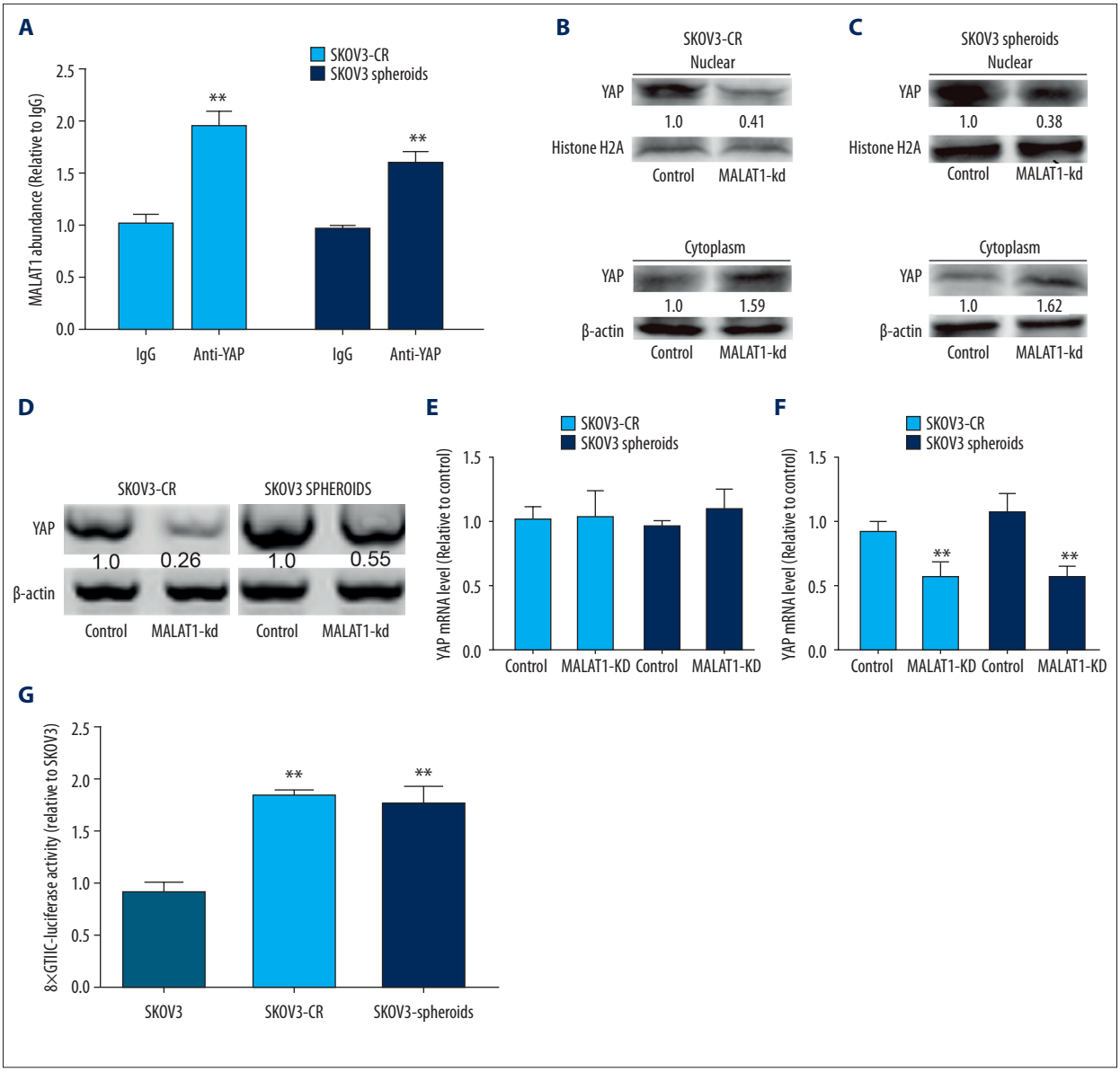

Figure 4. MALAT1 interacts with yes-associated protein (YAP), inhibits YAP nucleus-cytoplasm translocation and promotes its activity. (**A**) RNA immunoprecipitation (RIP) analysis was performed to examine MALAT1 level in RNA pulled down by anti-YAP or control antibody. (**B, C**) The expression of YAP in nucleus and cytoplasm was detected in SKOV3-CR cells and SKOV3 spheres with or without MALAT1 knockdown (kd). (**D**) Total YAP protein level was measured in SKOV3-CR cells and SKOV3 spheres with or without MALAT1 kd. (**E**) YAP mRNA level was detected in SKOV3-CR cells and SKOV3 spheres with or without MALAT1 kd. (**F**) 8G-Luc activity was detected in SKOV3-CR cells and SKOV3 spheres with or without MALAT1 kd. (**G**) 8G-Luc activity was measured in SKOV3, SKOV3-CR and SKOV3 spheres. The difference was assayed using one-way ANOVA with the Tukey-Kramer post-test. Data are presented as the mean±standard deviation, n≥3, ** $P<0.01$ versus control or SKOV3.

translocation of YAP has been shown to play critical roles in stem cell progression, such as in breast cancer [15] and skeletal stem cells [34]. We assume that MALAT1 could act as a co-activator for other proteins as MALAT1 localizes in the nucleus. Although the MALAT1/YAP axis has been confirmed in esophageal squamous cell carcinoma [23], further studies should be performed to elucidate whether this axis is a common phenomenon in other tumors, which may facilitate the predictive role of MALAT1 expression. Notably, MALAT1 was previously demonstrated to interact with Notch1 and thus activating Notch signaling in OC cells [35], which plays an important role in tumor cell stemness. Thus, we cannot exclude that MALAT1 may regulate the stemness of OC cells through other mechanisms, which should be further explored.

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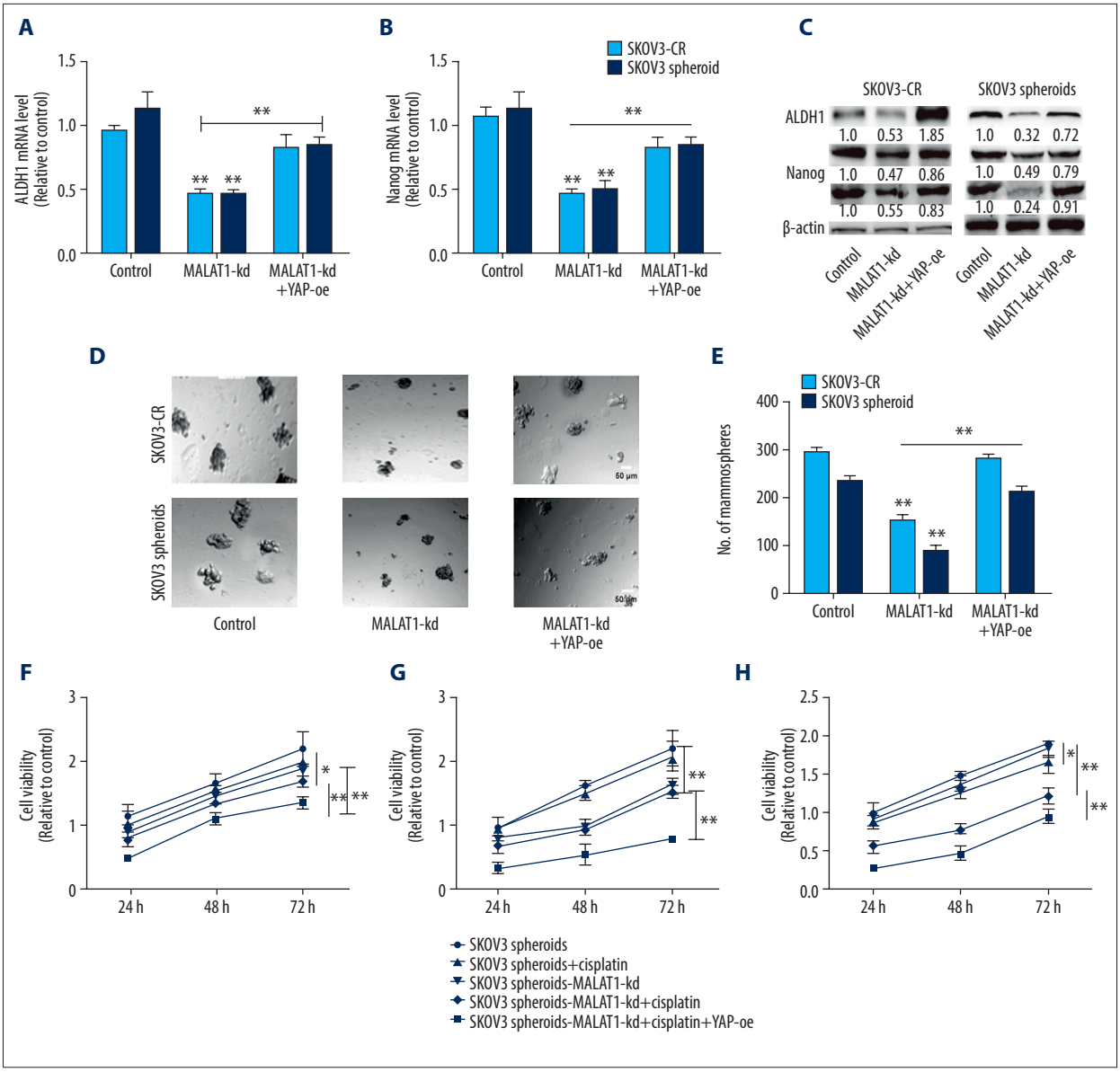

Figure 5. MALAT1 regulates the stemness of ovarian cancer cells dependent on yes-associated protein (YAP). (**A–C**) The expression of stemness regulatory masters was examined in SKOV3-CR and SKOV3 spheres with MALAT1 knockdown (kd) as well as YAP overexpression (oe) or not. (**D, E**) The capacity of sphere forming was evaluated in SKOV3-CR and SKOV3 spheres with MALAT1 kd as well as YAP oe or not. (**F, G**) SKOV3-CR and SKOV3 spheres with MALAT1 kd as well as YAP oe or not were treated with cisplatin or not and further subjected to cell viability analysis. (**H**) SKOV3 cells MALAT1 kd as well as YAP oe or not were treated with cisplatin or not and further subjected to cell viability analysis. Scale bar, 50 μm. The difference was assayed using one-way ANOVA with the Tukey-Kramer post-test. Data are presented as the mean±standard deviation, n≥3, ** P<0.01 versus control or SKOV3.

Conclusion

In conclusion, this work demonstrated that MALAT1 level was significantly higher in OC cells with a stronger stemness. Further functional and mechanistic experiments revealed that MALAT1 facilitates OC cell stemness through enhancing YAP transcriptional activity. Thus, MALAT1 might be a potential target to overcome OC progression or OC chemoresistance.

Conflict of interest

None.

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