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RNA Binding Protein RNPC1 Suppresses the Stemness of Human Endometrial Cancer Cells via Stabilizing MST1/2 mRNA

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Background: RNA binding protein RNPC1 has a tumor-suppressive role in various tumors, nevertheless, the role of RNPC1 in human endometrial cancer (EC) are never been reported.

Material/Methods: Western blot, quantitative polymerase chain reaction and sphere forming analysis were performed to evaluate the stem-like traits of cells and RNPC1-induced effects on EC cell stemness. RNA immunoprecipitation (RIP) was constructed to investigate the underlying mechanisms.

Results: The spheres formed by EC cells, named EC spheres, exhibited a remarkably higher stemness than the parental cells, which is characterized as the increase of sphere forming ability, ALDH1 activity, stemness marker expression and migration ability. Notably, RNPC1 expression was decreased in poorly differentiated EC cells than that in EC cells with moderately differentiated. Additionally, RNPC1 expression was significantly decreased in EC spheres and RNPC1 overexpression attenuated the stemness of EC spheres. Moreover, RNPC1 overexpression decreased the migration ability of EC spheres. Mechanistic studies showed that RNPC1 overexpression activated the Hippo pathway through directly binding to MST1/2. Inhibition of MST1/2 rescued RNPC1-mediated effects on EC sphere stemness.

Conclusions: Therefore, our results indicate a novel RNPC1/MST1/2 signaling responsible for EC cell stemness.

MeSH Keywords: Endometrial Neoplasms • Neoplastic Stem Cells • RNA-Binding Proteins

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Background

Human endometrial cancer (EC) is one of the malignant tumors of the female reproductive tract [1]. With the increase of aging populations, obesity, and other metabolic diseases, as well as the delay of marriage and the increasing number of infertile patients, the incidence of EC is increasing and shows a younger trend [1]. Early diagnosis and treatment can improve the prognosis of patients with EC and reduce their clinical mortality [2]. However, for some early asymptomatic people, the diagnosis is in the late stage of EC and the etiology of EC has not been fully clarified. Therefore, it is still an urgent issue to elucidate the mechanisms contributing to EC occurrence.

Cancer stem cells (CSCs) are a small number of cells with the capacity for self-renewal, infinite proliferation, and multi-directional differentiation in tumor tissue [3]. Their anti-apoptotic, tumorigenic, and migratory ability differs significantly from those of highly differentiated cancer cells [3]. CSCs are considered to be the source of swelling of tumor cells with different differentiation degrees, and thus the origin of infinite proliferation and metastasis of tumors. A large number of clinical and experimental studies have confirmed that the occurrence, development, metastasis and recurrence of EC is closely related to CSCs, for example, treatment with 1 mM metformin reduced the proportion and activity of EC stem cells without affecting cell viability [4]. A recent study indicated that SPARC-related modular calcium binding 2 (SMOC-2) could be used as a new EC stem cell marker, and that targeting SMOC-2 overcomes the chemoresistance of EC stem cells [5]. Notably, EC spheres formed by EC cells displayed CSCs-related phenotypes and preference for oxidative metabolism [6]. RNA binding protein RNPC1 has been shown to play suppressive roles in various tumors, such as RNPC1 as a suppresser of metastasis and epithelial-mesenchymal transition (EMT) of breast cancer via directly binding to HOXD10 and CDH5 mRNAs and thus resulting in the activation of STARD13-correlated competitive endogenous RNA (ceRNA) relationship [7] and inducing the sensitivity of HER-2-positive breast cancer cells to trastuzumab through upregulating HER2 [8]. Additionally, RNPC1 attenuates non-small cell lung cancer (NSCLC) progression by enhancing CASC mRNA through suppressing miR-181a binding to CASC mRNA [9]. However, its roles in EC progression have never been demonstrated.

The Hippo pathway, a tumor-suppressive signaling, was first found in the screening of genes inhibiting tissue growth in Drosophila melanogaster. It was subsequently found to be dysfunctional in various tumors and substantially engaged in tumor progression. The Hippo signaling pathway has been confirmed to regulate organ growth, stem cell homeostasis, tumorigenesis, and development in mammals. In mammals, the main members of this pathway are MST1/2 kinase, LATS1/2 kinase, and their junction proteins Sav and MOBI1. The main function of the Hippo signaling pathway is to regulate the activity of transcriptional co-activators YAP and TAZ. When the Hippo signaling pathway is activated, MST1/2 kinase binds to and activates its ligand protein Sav. Then phosphorylated LATS1/2 kinase and MOB1 protein increase the formation of LATS/MOB1 complex and activate LATS1/2 kinase. Activated LATS1/2 kinase inactivates YAP and its byproduct TAZ. Hippo pathway has also been proven to be involved in EC progression, for example, Hippo pathway is essential for FAT tumor suppressor homologue 4 (FAT4)-USP51 complex-mediated regulation on EC cell proliferation and invasion [10]. MiR-31 promotes EC cell progression by suppressing the Hippo pathway [11]. TAZ, a critical transducer of the Hippo pathway, has been indicated as a facilitator of EC progression [12]. In the current work, it was found that RNPC1 directly bound to MST1/2 mRNA and enhanced its stability, thus RNPC1/MST1/2 axis suppressed EC cell stemness.

Material and Methods

Cell culture and reagents

EC cell lines AN3CA, KLE, HEC-1A, and HEC-1B cells were obtained from the Shanghai Suer Shengwu Technology Co., Ltd. (Shanghai, China). Cells were cultured in RPIM 1640 medium (Hyclone, South Logan, UT, USA) with 15% fetal bovine serum (FBS, Sigma-Aldrich, St. Louis, MO, USA) under 5% CO_2 with humidified atmosphere at 37°C. XMU-MP-1, an inhibitor of MST1/2, was purchased from MP Biomedicals (Irvine, CA, USA), and the concentration of 70 nM was used in this work.

Quantitative real-time PCR (qRT-PCR)

RNA extraction was performed using RNA isolater Total RNA Extraction Reagent (Vazyme, Nanjing, China). Then cDNA was reversely synthesized, and quantitative real-time polymerase chain reaction (qRT-PCR) was performed using Hifair™ III One Step RT-qPCR Probe Kit (YEASEN). The expression levels of mRNAs were calculated using $2^{-\Delta\Delta ct}$ method.

Construction of lentivirus vectors

The RNPC1 overexpression lentivirus, knockdown lentivirus, and empty vectors were constructed by Ubigene (Guangzhou, China), denoted as RNPC1-OE and RNPC1-kd, respectively.

mRNA stability assay

RNPC1 was overexpressed by infecting with RNPC1-OE for 48 hours. Then 5 μg/mL of ActD (Cayman Chemical, Ann Arbor, MI, USA) was used to suppress the *de novo* RNA synthesis.

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mRNA expression at the denoted time points was measured by qRT-PCR. The half-life of MST1/2 was assessed by comparing to the original level of mRNA before ActD treatment.

Western blot

Cells were lysed and whole protein was extracted using RIPA lysis buffer (Beyotime, Beijing, China). BCA Protein Quantification Kit (Tiangen, Beijing, China) was used to measure the protein concentration. Then the detailed procedure was performed following the protocols mentioned in the previous work [13]. The antibody information was listed as below: CD133 (cat # 66666-1-Ig, 1: 1000, Proteintech, Wuhan, China), CD44 (Cat # 15675-1-AP, 1: 1000, Proteintech), β-actin (Cat # 66009-1-Ig, 1: 1000, Proteintech), RNPC1 (Cat # ab200403, 1: 3000, Abcam, Cambridge, MA, USA), MST1 (Cat # ab232551, 1: 3000, Abcam), MST2 (Cat # ab23232, 1: 2000, Abcam), LATS1 (Cat # ab70561, 1: 3000, Abcam), LATS2 (Cat # ab110780, 1: 3000, Abcam), p-LATS1 (Cat # 9157S, 1: 1500, Cell Signaling Technology, Danvers, MA, USA) and p-LATS2 (Cat # RY-K4082, 1: 500, Shanghai Runyu, Shanghai, China).

Sphere forming analysis

The detailed procedure was followed in the protocol mentioned in the previous work [14]. Briefly, cells were digested and centrifuged, the serum medium was removed and washed twice with phosphate-buffered saline (PBS), and then suspended with stem cell culture medium (DMEM/F12 medium, 1 x B27, 20 ng/mL bFGF, 20 ng/mL EGF). Select ultra-low 6-well plates, add 4 mL stem cell culture medium for 3000 cells/well and culture for 8 days, then count the spheres with size more than 50 μm and take photos. For manipulation on spheres, collect the spheres formed by cells, and make a centrifugation to remove the supernatant and trypsin digestion. Then cells from the spheres were processed according to the protocols of different experiments.

ALDH1 activity analysis

ALDH1 activity was examined using ALDH Activity Assay Kit (Colorimetric) (Abnova, Taipei, China) according to the manufacturer protocol.

RNA immunoprecipitation (RIP)

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

Transwell migration assay

Cells were suspended in medium without fetal bovine serum (FBS) and adjusted to the density of 8×10^5 cells/mL, followed by seeding into 24-well Transwell chambers with the volume of 200 μL. The medium contained 20% FBS was added into the lower chamber. After 24 hours, cotton swabs were used to remove the immigrated cells in upper-chamber, which was stained with 0.3% crystal violet, and then followed by 30% acetic acid-mediated elution. The migrated cells were photographed and counted in 5 random fields under microscope. Finally, the absorbance value was measured at 570 nm, which could indicate the migrated cell number.

Statistical analysis

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

Results

EC spheres exhibited a stronger stemness than the parental EC cells

Since EC spheres formed by EC cells show CSCs-related phenotypes [6], we first collected EC spheres formed by EC cell AN3CA. It was found that EC spheres exhibited a higher ALDH1 activity than the parental EC cells (Figure 1A). Additionally, EC spheres displayed a stronger stemness than the parental EC cells, characterized as the increased sphere size and number (Figure 1B, 1C). Moreover, the expression of EC stem cell markers (CD133 and CD33) was increased in EC spheres compared to the parental EC cells (Figure 1D, 1E). CSCs contributed to tumor metastasis, and we further detected the migration ability of EC spheres. As expected, EC spheres showed a stronger metastatic ability than the parental EC cells (Figure 1F, 1G). Therefore, these results indicated that the spheres formed by EC cells exhibited CSCs-related characteristics.

RNPC1 expression was significantly increased in EC spheres and in cells with poorly differentiated characteristics

To explore the potential roles of RNPC1 in EC cell stemness, its expression was first examined in EC spheres and cells. It was found that RNPC1 expression exhibited a remarkably lower level in EC spheres than that in EC cells (Figure 2A, 2B). Notably, RNPC1 expression was significantly decreased in EC cells with poorly differentiated (AN3CA and KLE) compared with that in EC cells with moderately differentiated (HEC-1A

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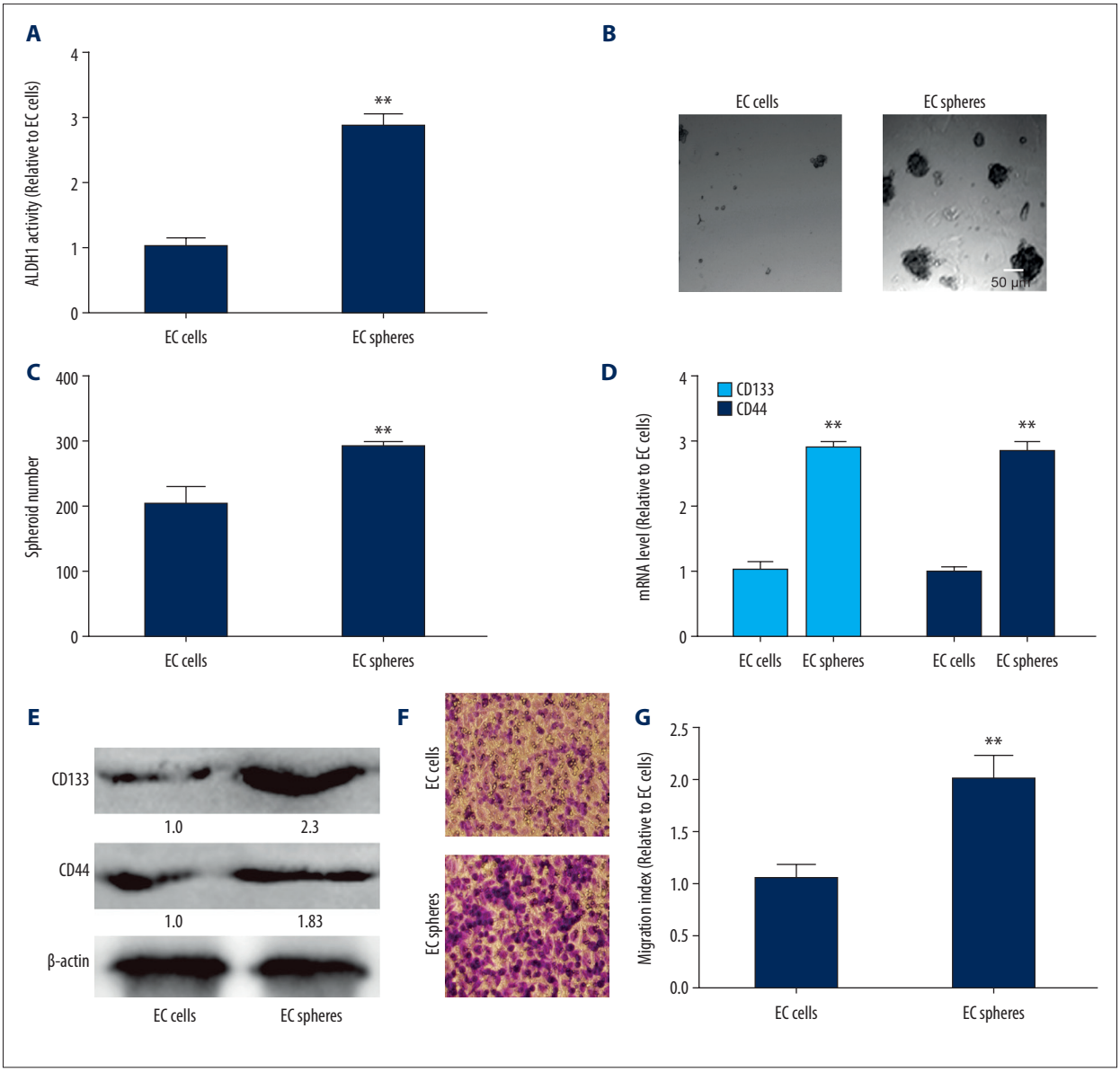

Figure 1. Endometrial cancer (EC) spheres exhibit a stronger stemness than the parental EC cells. (**A**) ALDH1 activity was measured in EC cells and spheres. (**B**) Sphere size was evaluated in EC cells and spheres. (**C**) Sphere number was measured in EC cells and spheres. (**D**) The mRNA levels of EC stem cell markers (C133 and CD44) were determined in EC cells and spheres. (**E**) The protein levels of EC stem cell markers (C133 and CD44) were determined in EC cells and spheres. (**F, G**) The migration ability was examined in EC cells and spheres. ** *P*<0.01 versus EC cells.

and HEC-1B) [15], (Figure 2C, 2D). Thus, we assume that RNPC1 might suppress EC cell stemness.

RNPC1 overexpression attenuates the stemness of EC spheres

Since RNPC1 expression was remarkably decreased in EC spheres, it was overexpressed in EC spheres by lentivirus infection. The infection efficiency of RNPC1-OE was confirmed by qRT-PCR and western blot (Figure 3A, 3B). As shown in Figure 3C, RNPC1 overexpression significantly reduced ALDH1 activity in EC spheres. Additionally, the sphere-forming ability was attenuated by RNPC1 overexpression, which is evident by the decreased sphere size and number (Figure 3D, 3E). Furthermore, RNPC1 overexpression reduced the expression of stemness markers (CD133 and CD44) of EC spheres (Figure 3F, 3G). In contrast, knockdown of RNPC1 increased the stemness of EC cells (Figures 3A–3G).

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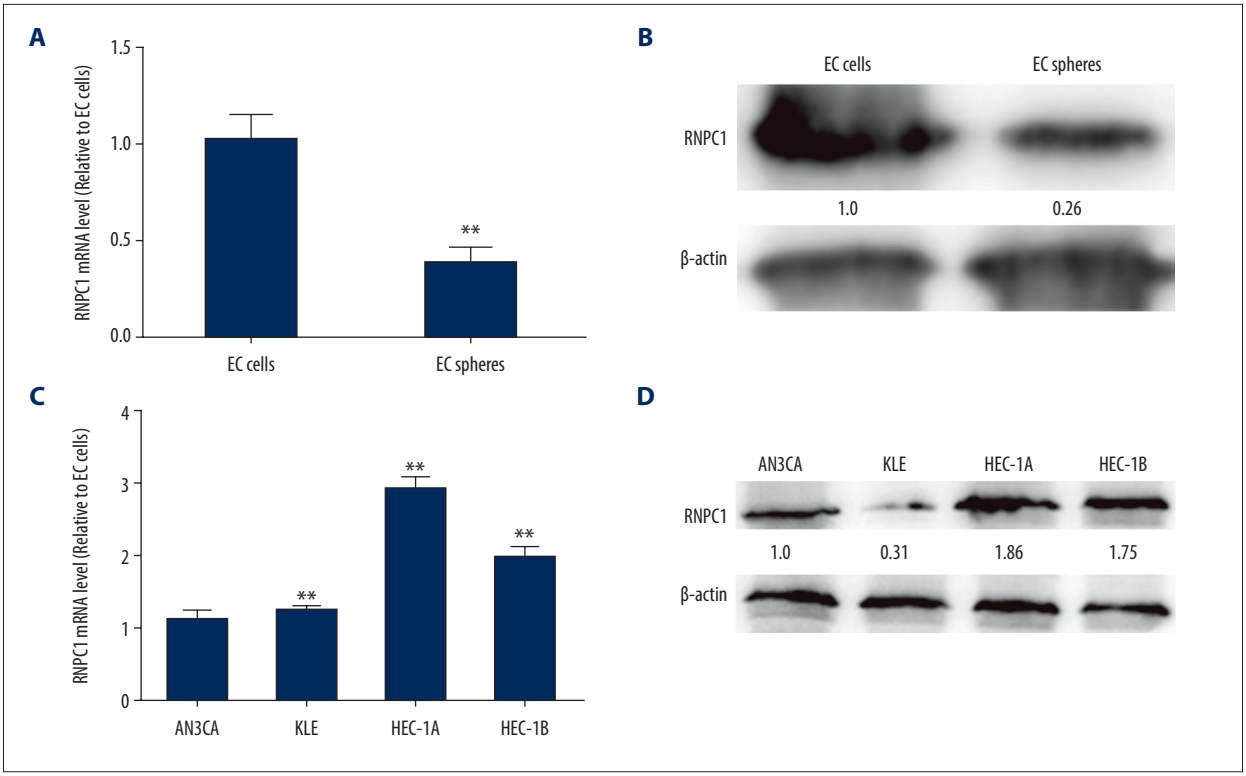

Figure 2. RNPC1 expression is significantly increased in endometrial cancer (EC) spheres and cells with poorly differentiated. (**A**) RNPC1 mRNA level was detected in EC cells and spheres. ** $P<0.01$ versus EC cells. (**B**) RNPC1 protein level was examined in EC cells and spheres. (**C**) RNPC1 mRNA level was determined in different EC cells. ** $P<0.01$ versus AN3CA cells. (**D**) RNPC1 protein level was measured in different EC cells.

RNPC1 directly bound to MST1/2 and enhanced their mRNA stability

Then we investigated the underlying mechanisms contributing to RNPC1-mediated effects on EC cell stemness. As the Hippo pathway is a tumor-suppressive signaling and RNPC1 always binds to mRNAs and enhances their stability, we wondered whether RNPC1 could activate the Hippo pathway. We found that the expression of MST1/2 and LATS1/2 was decreased in EC spheres compared with EC cells (Figure 4A, 4B). However, RNPC1 overexpression increased MST1/2 but not LAST1/2 mRNA levels in EC spheres (Figure 4C). Thus, we speculated that RNPC1 could directly bind to MST1/2 mRNA and thus activate the Hippo pathway. As expected, RIP analysis showed that MST1/2 was enriched in RNA pulled down by anti-RNPC1 but not the control IgG in EC spheres, but LATS1/2 was not enriched (Figure 4D). Additionally, MST1/2 mRNA stability was enhanced by RNPC1 overexpression in EC spheres (Figure 4E, 4F).

Inhibition of MST1/2 rescued the inhibition of RNPC1 overexpression on the stemness of EC spheres

Finally, we explored whether RNPC1 attenuated the stemness of EC spheres dependent on MST1/2. XMU-MP-1, an inhibitor of MST1/2, was added to EC spheres with RNPC1 overexpression. The expression of the downstream effectors of MST1/2, phosphorylated LATS1/2 (p-LATS1/2), was determined to evaluate the inhibitory efficiency of XMU-MP-1 (Figure 5A). As shown in Figure 5B, XMU-MP-1 rescued the decreased ALDH1 activity, which was mediated by RNPC1 overexpression. Additionally, the reduced sphere forming ability led by RNPC1 overexpression was partially reversed by XMU-MP-1 treatment (Figure 5C, 5D). Furthermore, XMU-MP-1 partially resumed RNPC1 overexpression-induced reduction of stemness marker expression (Figure 5E, 5F). Therefore, these results suggest that RNPC1 attenuates the stemness of EC spheres through binding to MST1/2 and thus activating the Hippo pathway.

Discussion

The mechanisms contributing to EC progression are still unclear. Since CSCs are related to the origin of tumor occurrence, here, we focused on investigating the mechanisms involved in EC cell stemness by collecting EC spheres which displayed the stem-like traits. We found that the expression of RNA binding protein RNPC1 was decreased in EC spheres and EC cells with poorly differentiated. Further functional experiments indicated that RNPC1

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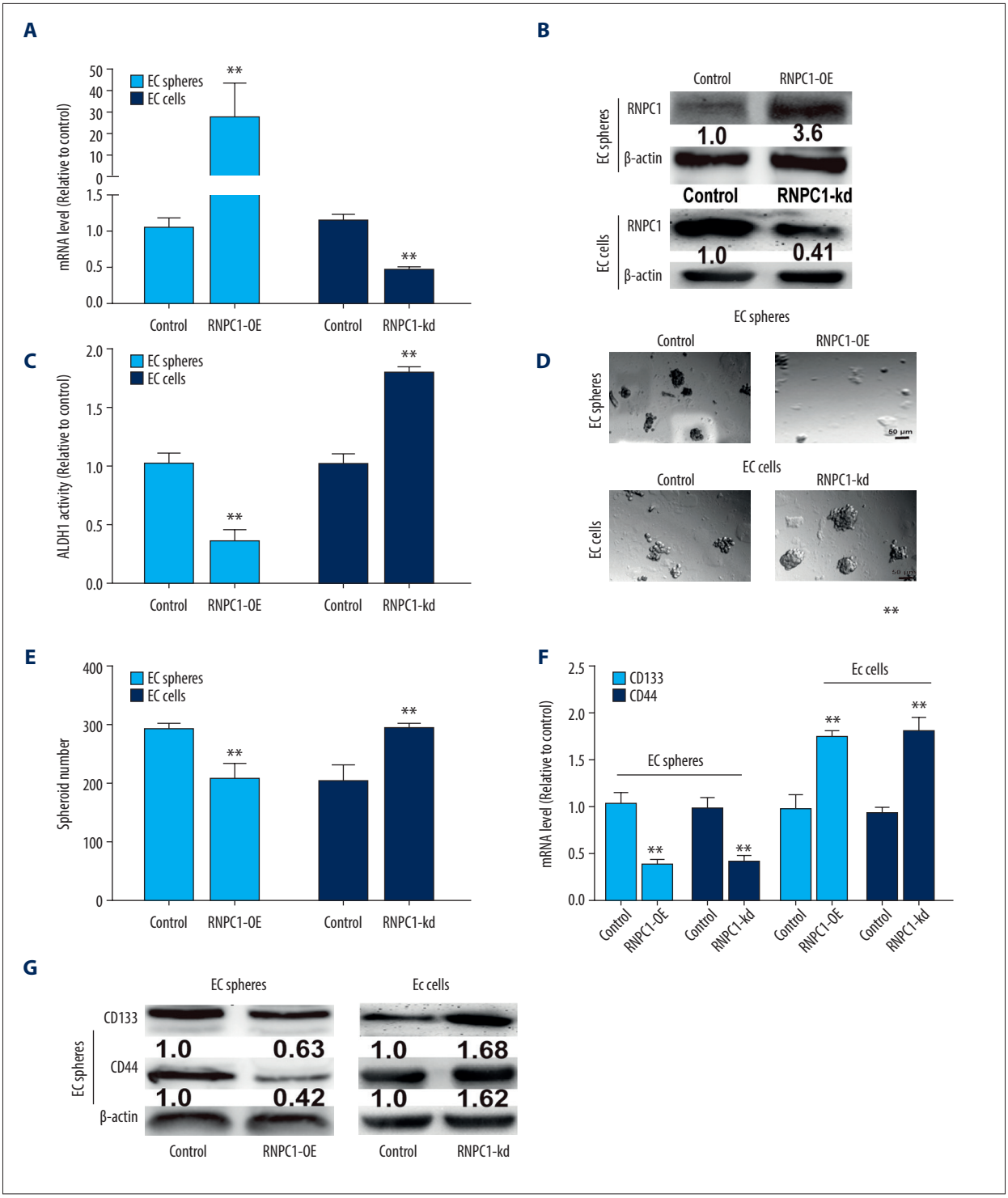

Figure 3. RNPC1 overexpression attenuates the stemness of EC spheres. (**A, B**) The expression of RNPC1 was detected in EC spheres with or without RNPC1 overexpression, and EC cells with or without RNPC1 knockdown. (**C**) ALDH1 activity was determined in EC spheres with or without RNPC1 overexpression, and EC cells with or without RNPC1 knockdown. (**D, E**) The sphere forming ability was evaluated in EC spheres with or without RNPC1 overexpression, and EC cells with or without RNPC1 knockdown. (**F, G**) The expression of stemness markers was determined in EC spheres with or without RNPC1 overexpression, and EC cells with or without RNPC1 knockdown. ** *P*<0.01 versus control.

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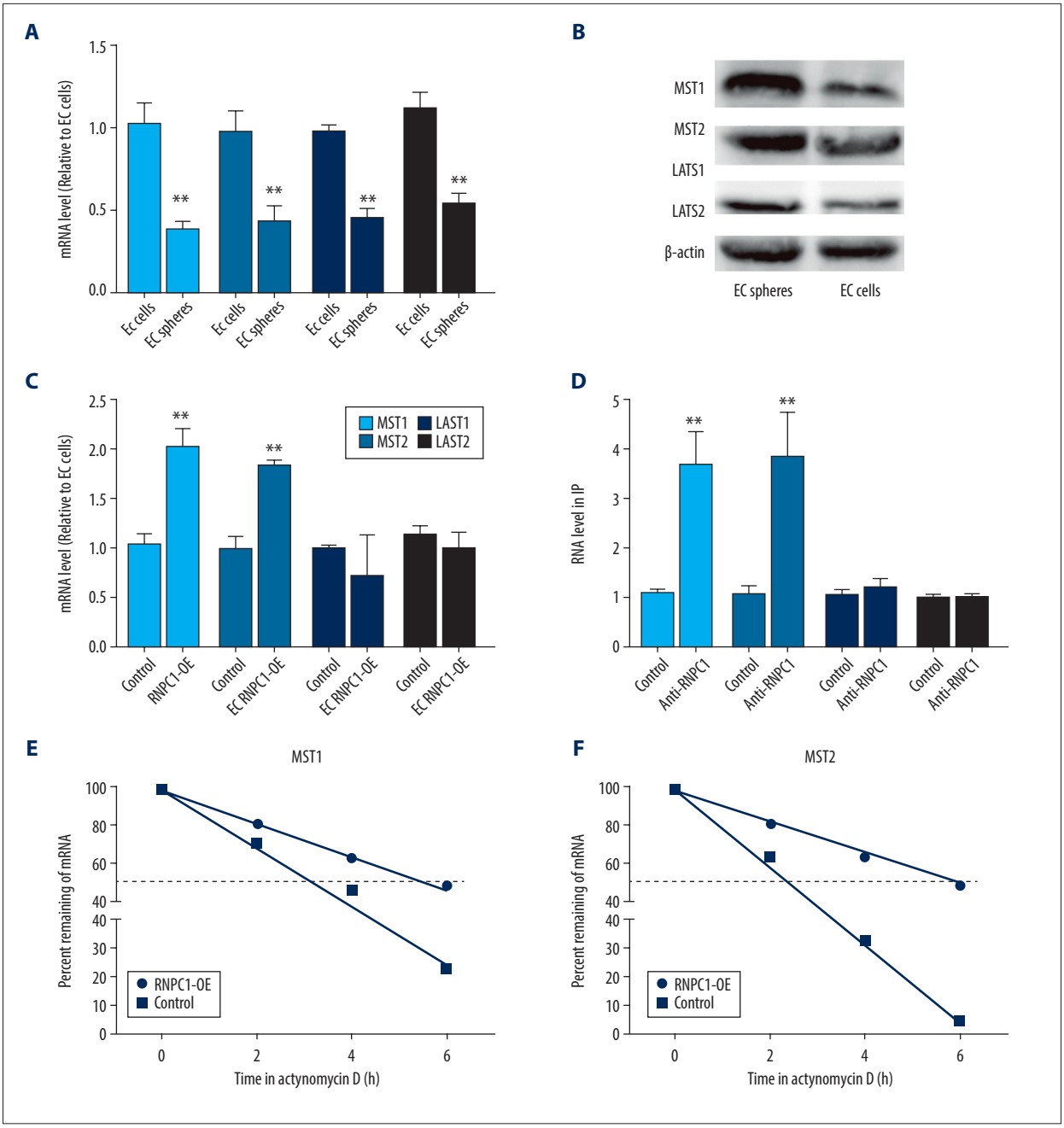

Figure 4. RNPC1 directly binds to MST1/2 and enhances their mRNA stability. (**A, B**) The expression of MST1/2 and LATS1/2 was detected in EC cells and spheres. ***P* < 0.01 versus EC cells. (**C**) The expression of MST1/2 and LATS1/2 was examined in EC spheres with or without RNPC1 overexpression. (**D**) The mRNA levels of MST1/2 and LATS1/2 were measured in RNA pulled down by anti-RNPC1 or IgG (control). (**E, F**) The mRNA stability of MST1/2 was evaluated in EC spheres with or without RNPC1 overexpression. ** *P*<0.01 versus control.

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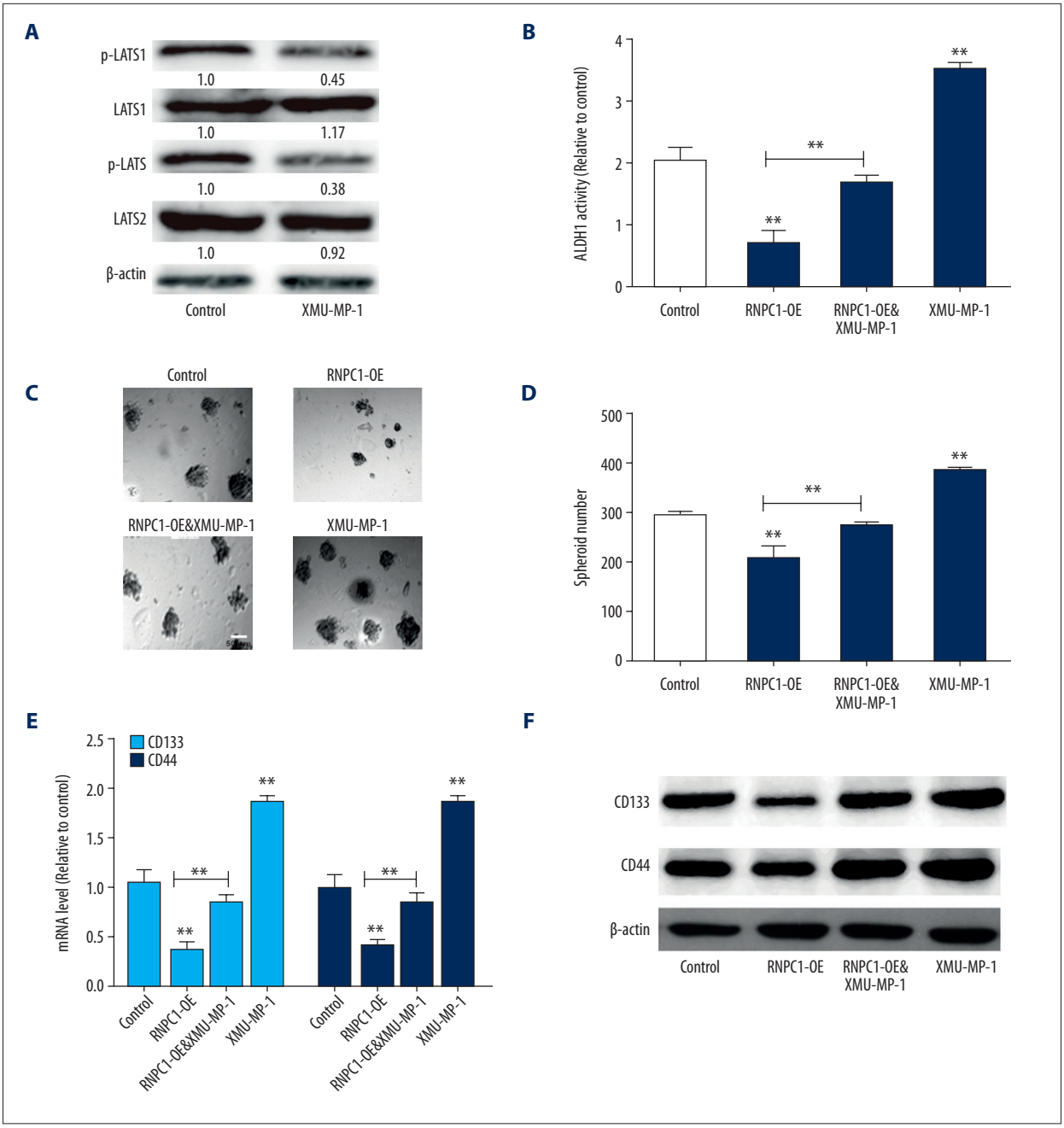

Figure 5. Inhibition of MST1/2 rescues the inhibition of RNPC1 overexpression on the stemness of EC spheres. (**A**) The expression of p-LATS1/2 and LATS1/2 was examined in EC spheres with or without XMU-MP-1 treatment. (**B**) ALDH1 activity was determined in EC spheres with RNPC1 overexpression plus XMU-MP-1 treatment or not. (**C, D**) The sphere-forming ability was evaluated in the spheres described in (**B**). (**E, F**) The expression of stemness markers was examined in the spheres depicted in (**B**). ** *P*<0.01 versus control.

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overexpression suppressed the stemness of EC spheres via directly binding to MST1/2 and thus activating the Hippo pathway.

RNA-binding proteins are a class of proteins that bind to RNAs and participate in the process of cutting, transporting, editing, intracellular localization, and translation regulation of RNAs. RNPC1 is a newly discovered RNA binding protein and has been shown to play anti-cancer roles in colorectal [16] and esophageal adenocarcinoma [17]. Notably, recent studies have shown that RNPC1 suppresses breast cancer progression via directly binding to HOXD10- and CDH5-3'UTR (un-translation region) and thus activating the STARD13-mediated ceRNA network [7], or binding to progesterone receptor and enhancing its mRNA stability [18]. Additionally, RNPC1 could bind to CASC2 3'UTR and hinder the miR-181a binding to CASC2, which is responsible for RNPC1-induced suppressive roles in non-small cell lung cancer [9]. These studies indicate that RNPC1 holds different targets in different tumors. However, in EC, RNPC1 targets have not been revealed. In the current work, it was found that MST1/2, the key components of tumor-suppressive Hippo pathway, is first identified as the targets of RNPC1 in EC cells via RIP analysis. Future works could be performed to examine whether MST1/2 is the targets of RNPC1 in other tumors.

Although the Hippo pathway has been shown to suppress EC progression [11,12], targeting this signaling pathway could not achieve good effects, which could be due to the unclear mechanisms by which the Hippo signaling was regulated in EC progression. A previous study showed that miR-31 promoted anchorage-independent growth and the tumor-forming potential of EC by targeting LAST2 3'UTR [11]. Additionally, FAT4-USP51 complex has been identified in EC, and it could decrease phosphorylation of LATS1/2, which is associated with promotion of EC cell proliferation and invasion [10]. Notably, previous studies showed that activating STARD13 ceRNA network could increase LAST1/2 expression, but RNPC1 overexpression could not increase LATS1/2 expression [14], this might be due the fact that RNPC1 could not activate STARD13 ceRNA network in EC cells.

Conclusions

In this study, RNPC1 was identified as the upstream regulator of MST1/2. However, the detailed binding regions or sites were not elucidated in this study, and therefore should be investigated in future work. Although the main conclusion should be confirmed by further *in vivo* experiments, targeting RNPC1 might be a good strategy to activating the Hippo pathway during EC progression.

Conflicting interests

None.

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