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EDITORIAL

- 4037 Improving clinical outcomes of patients with hepatocellular carcinoma: Role of antiviral therapy, conversion therapy, and palliative therapy
Shelat VG
- 4042 Unresectable hepatocellular carcinoma: Transarterial chemoembolization combined with lenvatinib in combination with programmed death-1 inhibition is a possible approach
Zhao FY, Wang DY, Qian NS
- 4045 Advances in endoscopic diagnosis and management of colorectal cancer
Li SW, Liu X, Sun SY
- 4052 Multidisciplinary approaches in the management of advanced hepatocellular carcinoma: Exploring future directions
Liu XJ, Lin YX, Chen LX, Yang WJ, Hu B
- 4055 Clinical implications of the latest advances in gastrointestinal tumor research
Dai W, Li YQ, Zhou Y
- 4060 Targeting methyltransferase-like 5-mediated sphingomyelin metabolism: A novel therapeutic approach in gastric cancer
Zhang JJ, Yuan C, Dang SC

REVIEW

- 4064 Research progress of tumor-associated macrophages in immune checkpoint inhibitor tolerance in colorectal cancer
Fan Q, Fu ZW, Xu M, Lv F, Shi JS, Zeng QQ, Xiong DH

MINIREVIEWS

- 4080 Update understanding on diagnosis and histopathological examination of atrophic gastritis: A review
Ma XZ, Zhou N, Luo X, Guo SQ, Mai P

ORIGINAL ARTICLE

Retrospective Cohort Study

- 4092 Establishing prognostic models for intrahepatic cholangiocarcinoma based on immune cells
Wang ZR, Zhang CZ, Ding Z, Li YZ, Yin JH, Li N

Retrospective Study

- 4104** Constructing a nomogram to predict overall survival of colon cancer based on computed tomography characteristics and clinicopathological factors
Hu ZX, Li Y, Yang X, Li YX, He YY, Niu XH, Nie TT, Guo XF, Yuan ZL
- 4115** Computed tomography-based radiomic model for the prediction of neoadjuvant immunochemotherapy response in patients with advanced gastric cancer
Zhang J, Wang Q, Guo TH, Gao W, Yu YM, Wang RF, Yu HL, Chen JJ, Sun LL, Zhang BY, Wang HJ
- 4129** Characteristics and risk factor analyses of high-grade intraepithelial neoplasia in older patients with colorectal polyps
Zhang X, Wang Y, Zhu T, Ge J, Yuan JH
- 4138** Clinicopathological analysis of small intestinal metastasis from extra-abdominal/extra-pelvic malignancy
Zhang Z, Liu J, Yu PF, Yang HR, Li JY, Dong ZW, Shi W, Gu GL
- 4146** Uninvolved liver dose prediction in stereotactic body radiation therapy for liver cancer based on the neural network method
Zhang HW, Wang YH, Hu B, Pang HW

Observational Study

- 4157** Small particle drug-eluting beads-transarterial chemoembolization combined with targeted therapy in the clinical treatment of unresectable liver cancer
Qi JS, Zhao P, Zhao XB, Zhao YL, Guo YC
- 4166** Nationwide questionnaire survey on pediatric pancreatic tumors in Japan
Makita S, Uchida H, Kano M, Kawakubo N, Miyake H, Yoneda A, Tajiri T, Fukumoto K

Clinical and Translational Research

- 4177** Burden landscape of hepatobiliary and pancreatic cancers in Chinese young adults: 30 years' overview and forecasted trends
Chen DS, Chen ZP, Zhu DZ, Guan LX, Zhu Q, Lou YC, He ZP, Chen HN, Sun HC

Basic Study

- 4194** Long noncoding RNA steroid receptor RNA activator 1 inhibits proliferation and glycolysis of esophageal squamous cell carcinoma
He M, Qi Y, Zheng ZM, Sha M, Zhao X, Chen YR, Chen ZH, Qian RY, Yao J, Yang ZD
- 4209** Jianpi-Huatan-Huoxue-Anshen formula ameliorates gastrointestinal inflammation and microecological imbalance in chemotherapy-treated mice transplanted with H22 hepatocellular carcinoma
Wang YN, Zhai XY, Wang Z, Gao CL, Mi SC, Tang WL, Fu XM, Li HB, Yue LF, Li PF, Xi SY
- 4232** Intratumoural microorganism can affect the progression of hepatocellular carcinoma
Liu BQ, Bai Y, Chen DP, Zhang YM, Wang TZ, Chen JR, Liu XY, Zheng B, Cui ZL

- 4244 Clinical significance of upregulated Rho GTPase activating protein 12 causing resistance to tyrosine kinase inhibitors in hepatocellular carcinoma

Wang XW, Tang YX, Li FX, Wang JL, Yao GP, Zeng DT, Tang YL, Chi BT, Su QY, Huang LQ, Qin DY, Chen G, Feng ZB, He RQ

CASE REPORT

- 4264 Rare and lacking typical clinical symptoms of liver tumors: Four case reports
Zhao Y, Bie YK, Zhang GY, Feng YB, Wang F
- 4274 Conversion therapy in advanced perihilar cholangiocarcinoma based on patient-derived organoids: A case report
He YG, Zhang LY, Li J, Wang Z, Zhao CY, Zheng L, Huang XB
- 4281 Transformed gastric mucosa-associated lymphoid tissue lymphoma originating in the colon and developing metachronously after *Helicobacter pylori* eradication: A case report
Saito M, Tanei ZI, Tsuda M, Suzuki T, Yokoyama E, Kanaya M, Izumiyama K, Mori A, Morioka M, Kondo T

LETTER TO THE EDITOR

- 4289 Conversion therapy for unresectable hepatocellular carcinoma: Advances and challenges
He YF

CORRECTION

- 4298 Correction to "Research progress of ferroptosis regulating lipid peroxidation and metabolism in occurrence of primary liver cancer"
Shu YJ, Lao B, Qiu YY

ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (WJGO, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc.*

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Basic Study

Long noncoding RNA steroid receptor RNA activator 1 inhibits proliferation and glycolysis of esophageal squamous cell carcinoma

Ming He, Ye Qi, Ze-Mao Zheng, Min Sha, Xiang Zhao, Yu-Rao Chen, Zheng-Hai Chen, Rong-Yu Qian, Juan Yao, Zheng-Dong Yang

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Abstract

BACKGROUND

The clinical effects and detailed roles of long non-coding RNA (LncRNA) steroid receptor RNA activator 1 (SRA1) in esophageal squamous cell carcinoma (ESCC) remain ambiguous. In the present study, the complementary sites between LncRNA SRA1, miRNA-363-5p, and phospholysine phosphohistidine inorganic pyrophosphate phosphatase (LHPP) predicted *via* bioinformatics analysis stimulated us to hypothesize that miRNA-363-5p/LHPP axis might be required for SRA1-mediated ESCC progression.

AIM

To investigate the molecular events of SRA1 in the malignant behavior in ESCC.

METHODS

Thirty-eight ESCC tissues and paired adjacent normal tissues were acquired. SRA1 expression was detected in ESCC tissues and cell lines using quantitative reverse transcription-polymerase chain reaction. Cell counting Kit-8 assay,

transwell invasion assay, glycolysis assay, and xenograft tumor model were performed to address the malignant biological behaviors of ESCC cells after the introduction of SRA1. The *t*-test and the χ^2 test were used for comparison between groups. Survival curve analysis was performed using the Kaplan-Meier method.

RESULTS

SRA1 downregulation was identified in ESCC. ESCC patients exhibiting a low SRA1 expression faced shorter overall survival than those with a high SRA1 expression. The introduction of SRA1 inhibited cell proliferation, glucose uptake, and lactate production in ESCC. *In vivo*, the growth of ESCC was hindered by SRA1 overexpression. Then, SRA1 overexpresses the LHPP by inhibiting miRNA-363-5p. Lastly, the introduction of small interfering RNA si-LHPP or miRNA-363-5p mimic could abrogate the inhibition roles triggered by SRA1.

CONCLUSION

SRA1 inhibits the oncogenicity of ESCC *via* miRNA-363-5p/LHPP axis. The SRA1/miRNA-363-5p/LHPP pathway may be a therapeutic target for ESCC.

Key Words: Steroid receptor RNA activator 1; Esophageal squamous cell carcinoma; Phospholysine phosphohistidine inorganic pyrophosphate phosphatase; Cancer therapy; MicroRNA; Long non-coding RNA

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Core Tip: In this study, we identified abnormal expression of steroid receptor RNA activator 1 (SRA1) in esophageal squamous cell carcinoma (ESCC). SRA1 was significantly downregulated in ESCC tissues and cell lines, and its low expression was strongly associated with advanced tumor stage, metastasis, larger tumor size, and poor survival. Functional and rescue assays demonstrated that SRA1 could impede ESCC cell proliferation and glycolysis *via* miRNA-363-5p and phospholysine phosphohistidine inorganic pyrophosphate phosphatase (LHPP). Mechanistically, SRA1 elevated LHPP expression by sponging miRNA-363-5p, thereby inhibiting ESCC cell proliferation and glycolysis.

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INTRODUCTION

There were 604100 new cases and 544076 deaths from esophageal squamous cell carcinoma (ESCC) estimated by 2020[1, 2]. Because of the lack of obvious clinical symptoms and effective screening methods in the early stage, most patients with esophageal cancer are already in the middle and advanced stages when they are diagnosed[3,4].

Long non-coding RNAs (lncRNAs) are a class of biological macromolecules with a length greater than 200 nucleotides [5,6]. Tumor cells often use glycolysis to metabolize glucose[7]. Generally, increased glycolysis can meet the energy requirements of tumor cells and provide a favorable microenvironment for tumor occurrence and development[7]. Studies found that many lncRNAs are involved in the glycolysis process of tumors[8-11]. MiRNAs, in the form of oncogenes or tumor suppressor genes, play a role in promoting or suppressing tumors in ESCC[12]. Tumor suppressor protein, phospholysine phosphohistidine inorganic pyrophosphate phosphatase (LHPP), has the opposite effect of histidine kinase[13]. Studies found that low expression of LHPP can lead to up-regulation of histidine phosphorylation [14-16]. In the present study, the complementary sites between lncRNA steroid receptor RNA activator 1 (SRA1), miRNA-363-5p, and LHPP predicted *via* bioinformatics analysis stimulated us to hypothesize that miRNA-363-5p/LHPP axis might be required for SRA1-mediated ESCC progression.

In this study, the expression of SRA1 was verified in ESCC tissues. Then, we characterized the clinical implication as well as the biological function of SRA1 in ESCC. We found that SRA1 functions as a tumor suppressor gene in ESCC. In terms of mechanism, SRA1 inhibits the glycolysis and malignant biological behaviors of ESCC cells *via* functioning as a molecular sponge for miRNA-363-5p and upmodulating LHPP expression.

MATERIALS AND METHODS

Clinical tissues

ESCC and paired adjacent tissues (the area of tumor margin > 5 cm) were acquired from 38 ESCC patients in the Huai'an Hospital of Huai'an City from January to December 2016. The age of the patients ranged from 54 to 77 years (median age

was 65 years). There were 26 males and 12 females. The inclusion criteria for ESCC patients in this study were as follows: The patient was diagnosed as ESCC by two pathologists; The patient's personal information and pathological data were complete; The patient did not receive therapy before radical ESCC surgery; The patient completed the follow-up (36 months), and obtain complete follow-up data. The exclusion criteria for patients were as follows: The patient was re-diagnosed as non-squamous cell carcinoma; The patient's personal information and pathological data were missing; Patients sign an informed consent form for participation. Study was performed under the Ethics Committee of the Huai'an Hospital of Huai'an City (No. 2016.0112).

RNA extraction

RNA extraction and purification were carried out following the manufacturer's guidelines using TRIzol reagent (Invitrogen, Carlsbad, CA, United States). The concentration and purity of RNA in each sample were assessed using a NanoDrop ND-1000. Additionally, the integrity of the RNA was evaluated using an Agilent 2100 system (Agilent, Santa Clara, CA, United States). After eliminating ribosomal RNAs, the remaining RNA molecules were subjected to high-temperature fragmentation, resulting in the generation of smaller fragments. Subsequently, the fragmented RNA pieces underwent reverse transcription to produce cDNA.

Identification of lncRNAs

Candidate lncRNAs were selected using two criteria: (1) Transcripts with a length less than 200 nucleotides and reads coverage below 3 were excluded to eliminate interference from other noncoding RNAs (such as ribosomal RNA, transfer RNA, small nucleolar RNA, and small nuclear RNA); and (2) The coding ability of the transcripts was assessed using the coding-noncoding index and coding potential calculator, and transcripts with coding potential were excluded. The remaining transcripts were then categorized as lncRNAs.

Cell culture and transfection

Normal esophageal epithelial cells Het-1A and ESCC cells (TE1, Eca109, KYSE30, EC9706, KYSE180) were used. Cells were kept in DMEM under the condition of 5% CO₂ and 37 °C. SRA1 was cloned into pcDNA3.1 vector to construct SRA1 overexpressing plasmid (pcDNA3.1-SRA1). The pcDNA3.1 vector was used as a negative control (NC).

Quantitative reverse transcription-polymerase chain reaction

Quantitative reverse transcription-polymerase chain reaction (QRT-PCR) was performed using the SYBR Green qPCR Kit (Thermo Fisher Scientific, Waltham, MA, United States) with a StepOne™ Real-Time PCR System (Applied Biosystems, Carlsbad, CA, United States). The glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and U6 were used as control references for lncRNA/mRNA and miRNA. Their primers were purchased from Sangon Biotech (Shanghai, China), and the sequences as described previously are listed in Table 1. In this study, the amplification efficiencies of SRA1, miRNA-363-5p, LHPP, GAPDH and U6 were 97.8%, 96.9%, 99.8%, 98.4% and 99.2%, respectively.

CCK-8 assay

After transfection, ESCC cells (2×10^3 cells/well) were plated onto 96-wells plates and cultivated for 0, 24, 48, and 72 hours, followed by addition into 10 μ L CCK-8 solution (Abcam, Cambridge, MA, United States).

Analysis of glycolysis

Glycolysis assay was performed as described previously[17-19]. After transfection, 2×10^5 ESCC cells were plated onto 6-wells plates, and the levels of glycolysis were measured (BioVision, Milpitas, CA, United States).

Western blot

The membranes were incubated with LHPP (ab116175; 1:1000 dilution; Abcam, United States), glucose transport protein type 1 (GLUT1; 1:1000 dilution; ab115730, Abcam, United States), lactate dehydrogenase (LDHA; 1:1000 dilution; ab101562, Abcam, United States), GAPDH (1:3000 dilution; ab128915; Abcam, United States) antibodies.

Immunohistochemistry

Immunohistochemistry was performed in paraffin-embedded sections using an Immunohistochemistry kit (SV0002, BOSTER, China). Tissue samples were incubated with primary antibodies against Ki-67 (ab254123, Abcam, United States), followed by incubation with the secondary antibody.

Xenograft tumor model analysis

Twelve Balb/c nude mice (3-4 weeks, male) were randomly divided into pcDNA3.1-NC group and pcDNA3.1-SRA1 group. And 1×10^6 EC9706 or TE1 cells were subcutaneously injected into nude mice. After 28 days, the mice were sacrificed. All animal experiments were conducted by the guideline of the Ethical Committees of Huai'an Hospital of Huai'an City (No. 2016.A023).

Statistical analysis

The *t*-test and the χ^2 test were used for comparison between groups. Survival curve analysis was performed using the Kaplan-Meier method. *P* < 0.05 indicated statistical significance.

Table 1 Quantitative reverse transcription-polymerase chain reaction primer sequences

Name	Primer sequence
lncRNA SRA1	F: 5'-GCTGGGCACTGGGAATGTAA-3' R: 5'-CACGACCCTACAACCCTCTG-3'
miRNA-363-5p	F: 5'-GGCGAGTTTAAATTCTATT-3' R: 5'-ATCAACTGCTCTCGTGA-3'
LHPP	F: 5'-GACGCAGCACTCACCCATCT-3' R: 5'-CCAGGCATTCGGTGATGTG-3'
GAPDH	F: 5'-AGAAGGCTGGGCTCATTTG-3' R: 5'-GCAGGAGGCATTGCTGATGAT-3'
U6	F: 5'-GCTTCGGCAGCACATATACTAAAAT-3' R: 5'-CGCTTCACGAATTGCGTGTCTAT-3'

lncRNA: Long non-coding RNA; SRA1: Steroid receptor RNA activator 1; LHPP: Phospholysine phosphohistidine inorganic pyrophosphate phosphatase.

RESULTS

SRA1 Level was decreased in ESCC

The lncRNA expression patterns were performed through hierarchical clustering between ESCC and adjacent normal tissues (Figure 1A). Changes in the lncRNA level were displayed in the volcano (Figure 1B) plot. As was observed, SRA1 had the highest fold of differential expression (Figure 1C). In clinical samples, we indicated that SRA1 expression was downregulated in ESCC tissues (Figure 1D) and cell lines (Figure 1E). Furthermore, ESCC patients with low SRA1 had shorter overall survival than patients with high SRA1 ($\chi^2 = 6.162$, $P = 0.013$; Figure 1F). In addition, the low SRA1 expression was correlated with lymph node metastasis, depth of tumor invasion, and TNM stage, but not with age, sex, or body mass index (Table 2).

SRA1 upregulation suppresses ESCC cell proliferation and glycolysis in vitro

The relatively lower SRA1 was detected in the EC9706 and TE1 cells. To ascertain whether SRA1 is involved in the tumor resistance of ESCC, pcDNA3.1-SRA1 or NC was transfected into EC9706 and TE1 cells to overexpress endogenous SRA1 expression. The pcDNA3.1-SRA1#2 presented higher overexpressing efficiency; thus, the pcDNA3.1 was used (Figure 2A). Transfection with pcDNA3.1-SRA1 caused an obvious decrease in proliferation rate (Figure 2B) in EC9706 and TE1 cells. For glycolysis assay, when compared with NC group, a significant decrease in glucose consumption and lactate secretion was displayed in EC9706 and TE1 cells after pcDNA3.1-SRA1 transfection (Supplementary Figure 1). Additionally, upregulation of SRA1 triggered a decrease of GLUT1 and LDHA in EC9706 and TE1 cells than NC group (Figure 2C).

MiRNA-363-5p is sponged by SRA1 in ESCC

Next, SRA1 was observed in the cytoplasm (Figure 3A), which offered a theoretical basis for the ceRNA. Using lncRNABase, starBase, and RegRNA2.0, three miRNAs (miRNA-363-5p, miRNA-127-3p, and miRNA-326) were predicted to contain putative binding sites within SRA1 (Figure 3B). MiRNA-363-5p expression was inhibited in cells transfected with pcDNA3.1-SRA1 (Figure 3C). Furthermore, upregulated miRNA-363-5p was found in ESCC tissues (Figure 3D), which exhibited an inverse expression relation with SRA1 ($r = -0.519$, $P < 0.001$; Figure 3E). The Luciferase assay (Figure 3F and G) and RIP assay (Figure 3H) confirmed these findings.

MiRNA-363-5p directly targets LHPP in ESCC cells

We next tried to ascertain the roles of miRNA-363-5p in ESCC cells. si-miRNA-363-5p was transfected into EC9706 and TE1 cells. MiRNA-363-5p remarkably decreased after si-miRNA-363-5p transfection (Figure 4A). Inhibition of miRNA-363-5p expression significantly attenuated proliferation (Figure 4B) and glycolysis (Figure 4C, Supplementary Figure 2) in EC9706 and TE1 cells.

To clarify the mechanism of miRNA-363-5p on ESCC, bioinformatics analysis was performed to explore the target of miRNA-363-5p. LHPP was predicted to have binding sequences for miRNA-363-5p (Figure 4D). Then, luciferase reporter turned out that miRNA-363-5p mimic weakened the luciferase activity of WT-LHPP (Figure 4E). Furthermore, downregulating miRNA-363-5p enhanced the LHPP protein (Figure 4F) levels in EC9706 and TE1 cells. Besides, LHPP expression was low in ESCC tissues compared to adjacent normal tissues (Figure 4G). An inverse correlation between miRNA-363-5p and LHPP was found in ESCC ($r = -0.565$, $P < 0.001$; Figure 4H). Collectively, miRNA-363-5p directly targets LHPP in ESCC cells.

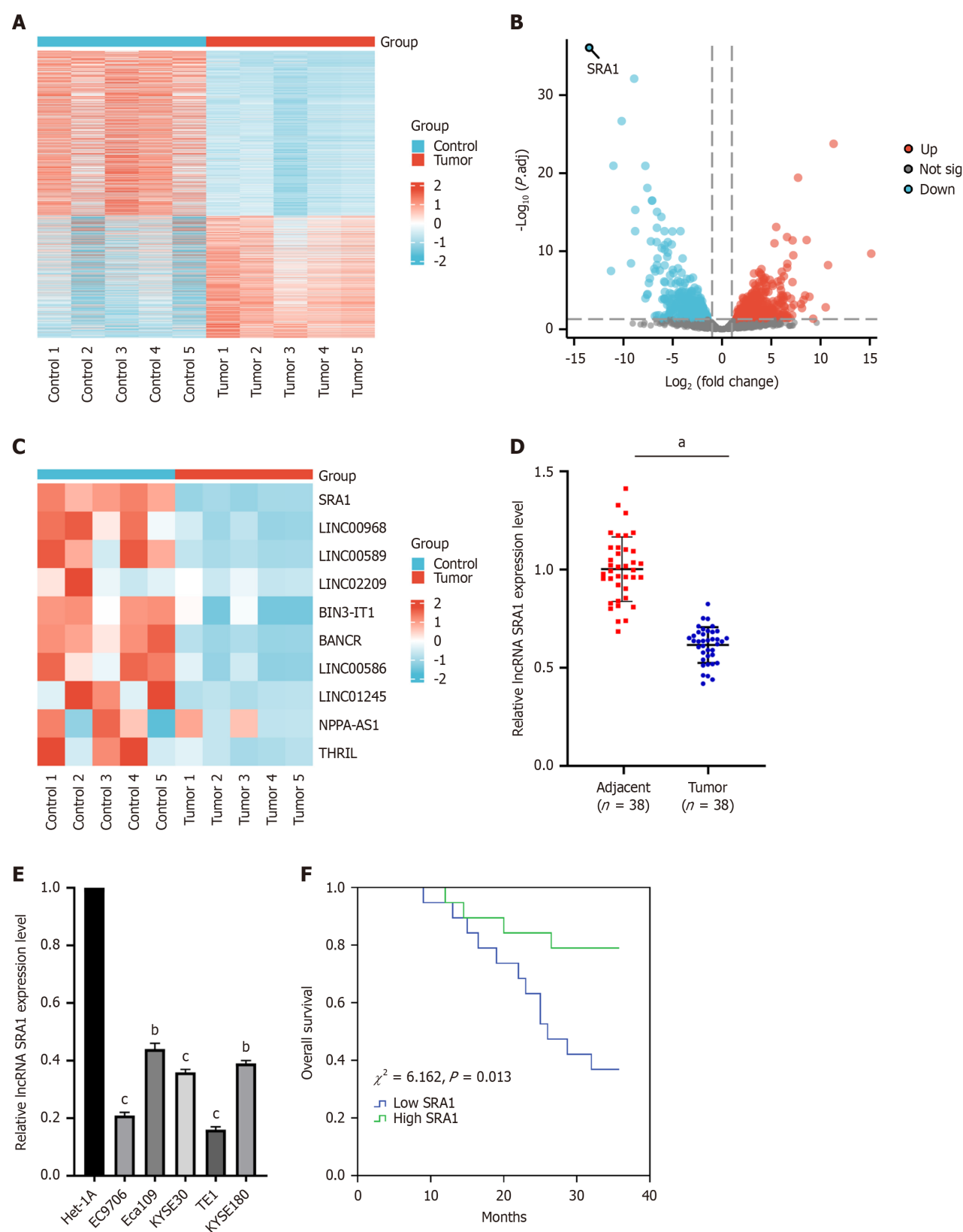


Figure 1 Steroid receptor RNA activator 1 expression level was decreased in human esophageal squamous cell carcinoma tissues and cell lines. A: The five pairs of esophageal squamous cell carcinoma (ESCC) and adjacent normal tissues were carried out long non-coding RNA (lncRNA) microarray analysis, and the lncRNA expression patterns were performed through hierarchical clustering; B: Changes in the lncRNA level were displayed in the volcano plot; C: lncRNA SRA1 had the highest fold of differential expression; D: Steroid receptor RNA activator 1 (SRA1) expression was apparently downregulated in ESCC tissues; E: SRA1 expression was apparently downregulated in ESCC cell line; F: ESCC patients with low SRA1 expression had shorter overall survival than patients with high SRA1 expression. ^a $P < 0.01$; ^b $P < 0.05$ vs Het-1A; ^c $P < 0.01$ vs Het-1A; lncRNA: Long non-coding RNA; SRA1: Steroid receptor RNA activator 1.

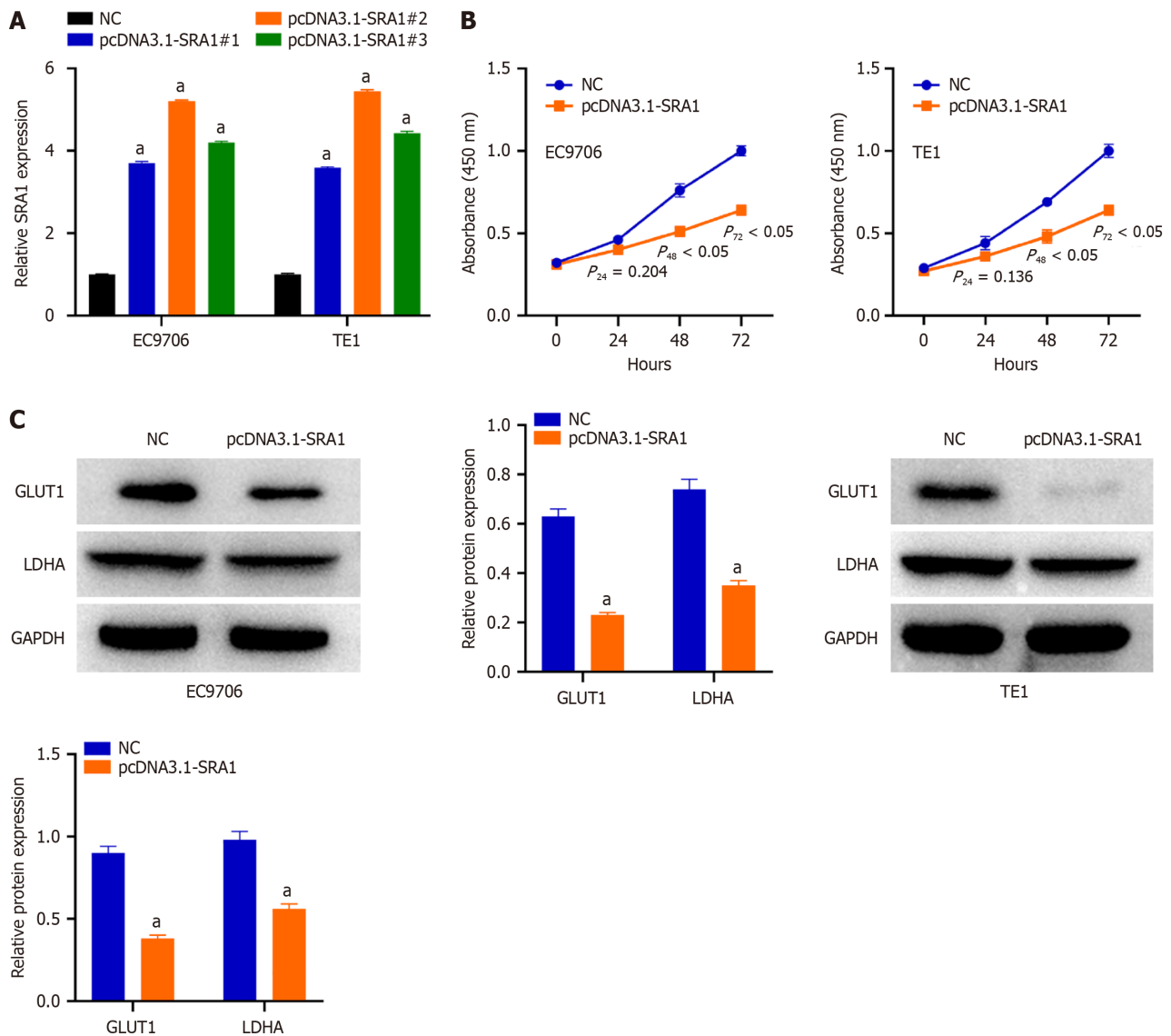


Figure 2 Overexpression of steroid receptor RNA activator 1 suppresses esophageal squamous cell carcinoma cell proliferation and glycolysis *in vitro*. **A**: Steroid receptor RNA activator 1 (SRA1) overexpression was verified by quantitative reverse transcription-polymerase chain reaction; **B**: Overexpression of SRA1 caused an obvious decrease in proliferation rate in EC9706 and TE1 cells; **C**: Upregulation of SRA1 triggered a decrease of GLUT1 and LDHA in EC9706 and TE1 cells. ^a $P < 0.01$ vs negative control; NC: Negative control; SRA1: Steroid receptor RNA activator 1.

SRA1 overexpression promotes LHPP level in ESCC by sponging miRNA-363-5p

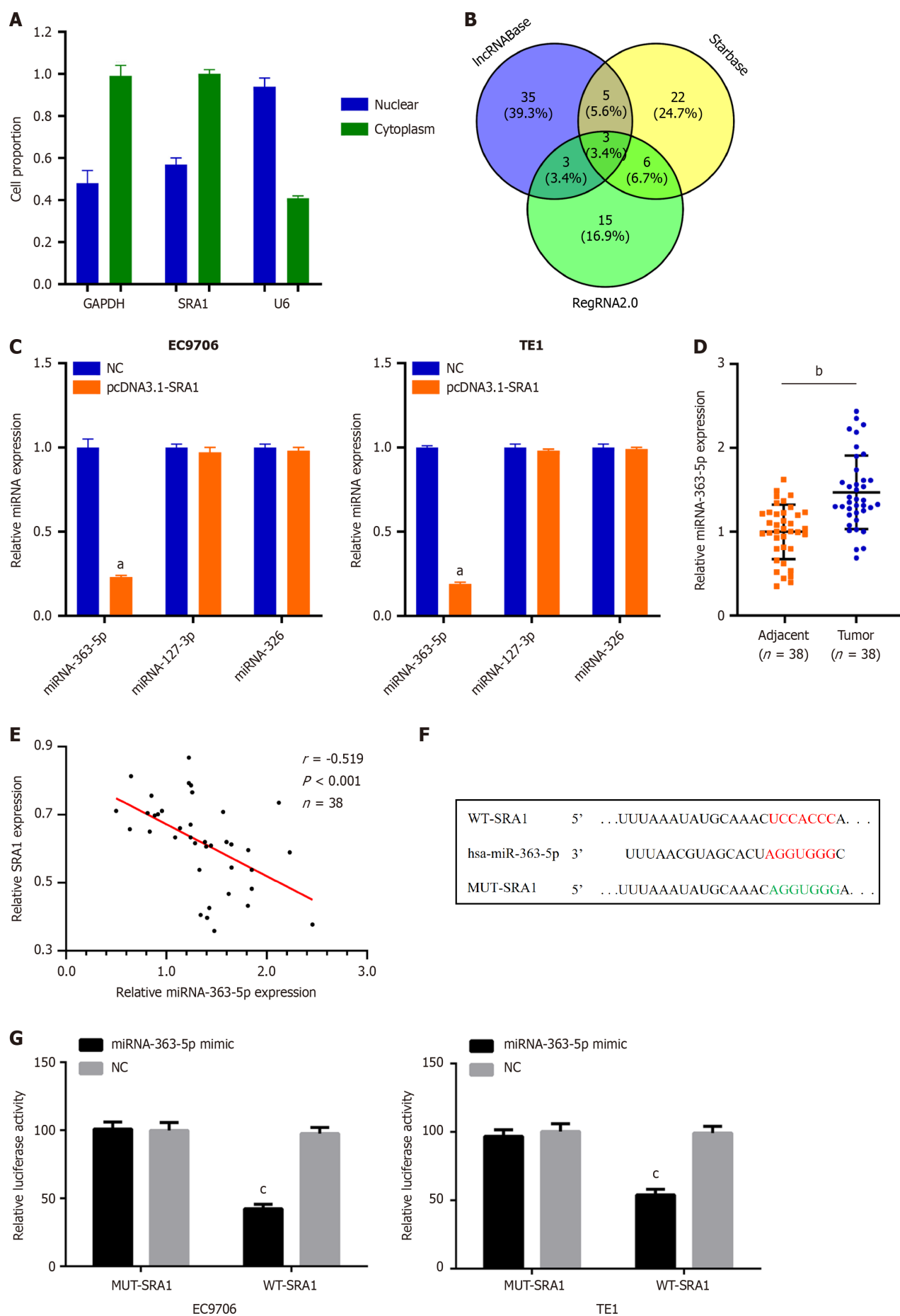
Then, EC9706 and TE1 cells were transfected with pcDNA3.1-SRA1 and miRNA-363-5p mimic either alone or in combination. The overexpression efficiency of miRNA-363-5p mimic in ESCC cells was tested by qRT-PCR. The delivery of miRNA-363-5p mimic caused a prominent miRNA-363-5p upregulation in EC9706 and TE1 cells (Figure 5A). SRA1 upregulation triggered an obvious overexpressed effect on the endogenous LHPP mRNA (Figure 5B) and protein (Figure 5C) levels in EC9706 and TE1 cells, whereas the delivery of miRNA-363-5p mimic counteracted such effect (Figure 5D). Furthermore, LHPP expression was positively correlated with SRA1 expression in ESCC tissues ($r = 0.583$, $P < 0.001$; Figure 5E). Besides, compared with the anti-IgG NC group, SRA1, miRNA-363-5p, and LHPP were preferentially concentrated in the anti-Ago2 precipitate (Figure 5F).

SRA1 overexpression inhibits ESCC tumor growth *in vivo*

We implanted EC9706 and TE1 ESCC cells infected with pcDNA3.1-SRA1 into the nude mouse. Overexpressing SRA1 exhibited weaker tumorigenic ability (Figure 6A-C). The immunohistochemical staining found a low level of Ki-67 in the tumors with overexpressing SRA1 (Figure 6D).

DISCUSSION

In this study, we found the abnormally expressed SRA1 in ESCC. Here, SRA1 was clearly downmodulated in ESCC



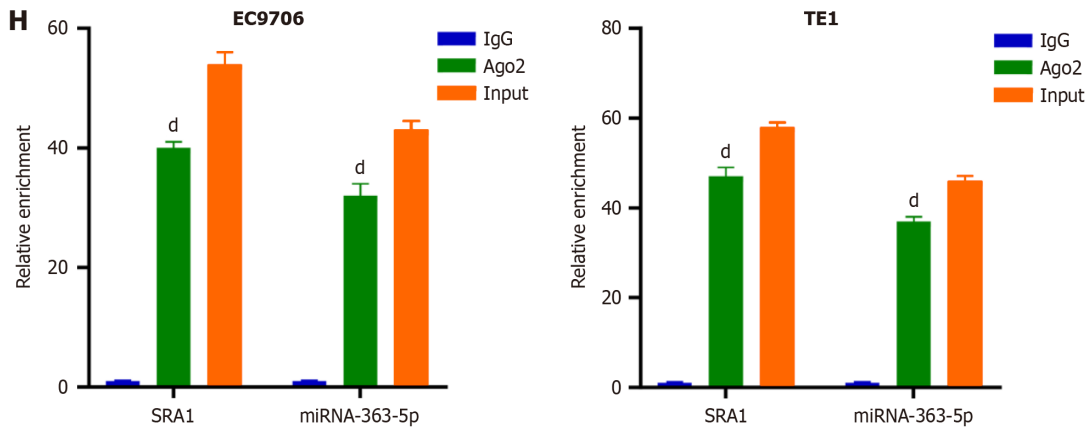
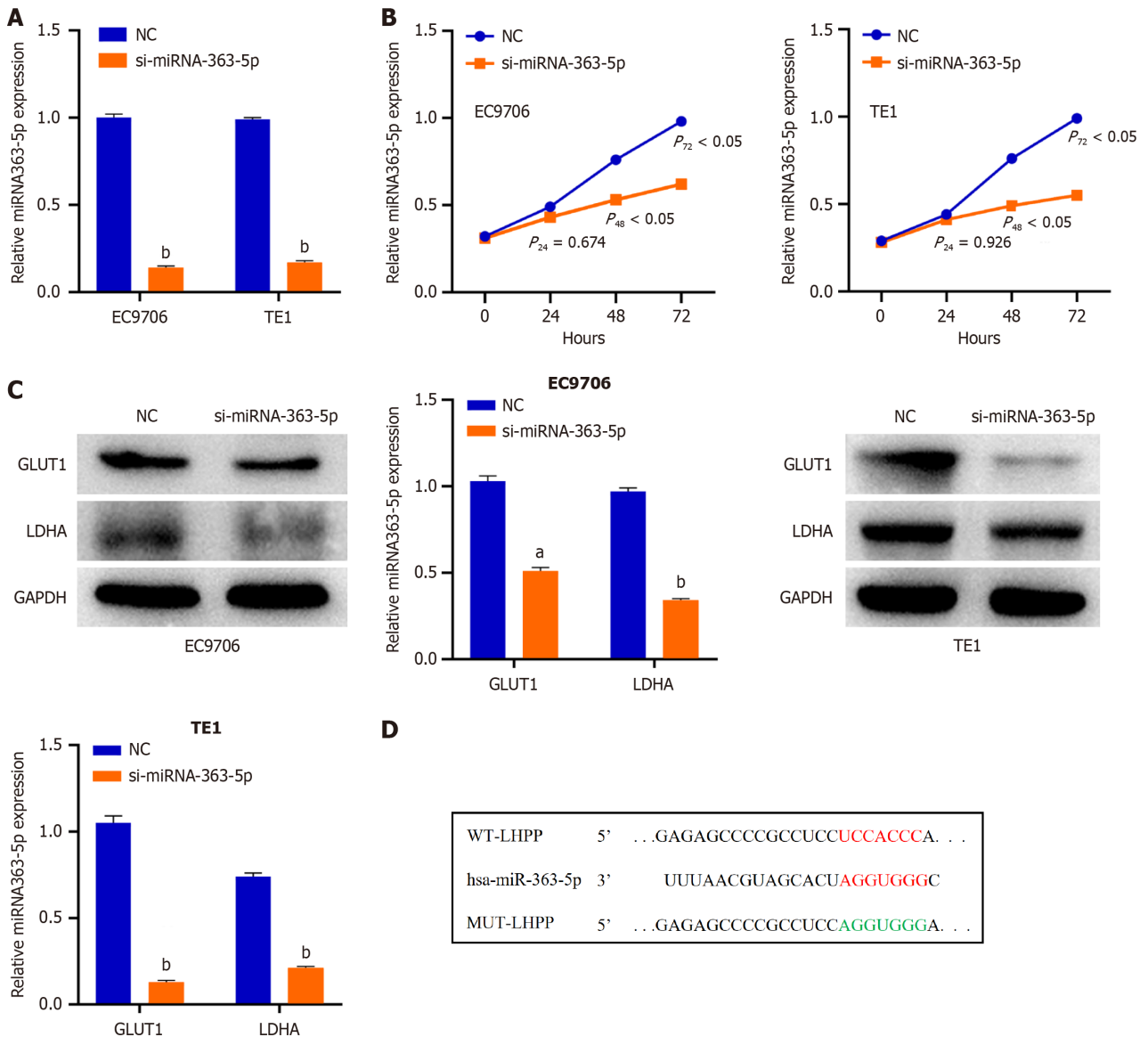


Figure 3 MiRNA-363-5p is sponged by steroid receptor RNA activator 1 in esophageal squamous cell carcinoma. A: Steroid receptor RNA activator 1 (SRA1) was observed to be enriched in the cytoplasm of esophageal squamous cell carcinoma (ESCC) cells; B: Using lncRNABase, starBase, and RegRNA2.0, a total of 3 miRNAs were predicted to contain putative binding sites within SRA1; C: MiRNA-363-5p expression was inhibited in EC9706 and TE1 cells transfected with pcDNA3.1-SRA1; D: Upregulated miRNA-363-5p was found in ESCC tissues; E: MiRNA-363-5p is negatively correlated with SRA1; F and G: Luciferase activity of WT-SRA1 instead of MUT-SRA1 was evidently decreased by miRNA-363-5p upregulation in EC9706 and TE1 cells; H: RIP assay defined that both SRA1 and miRNA-363-5p could be remarkably enriched by anti-Ago2 in EC9706 and TE1 cells. ^a $P < 0.01$ vs negative control (NC); ^b $P < 0.01$ vs Adjacent; ^c $P < 0.05$ vs NC; ^d $P < 0.01$ vs IgG; NC: Negative control; LncRNA: Long non-coding RNA; SRA1: Steroid receptor RNA activator 1.



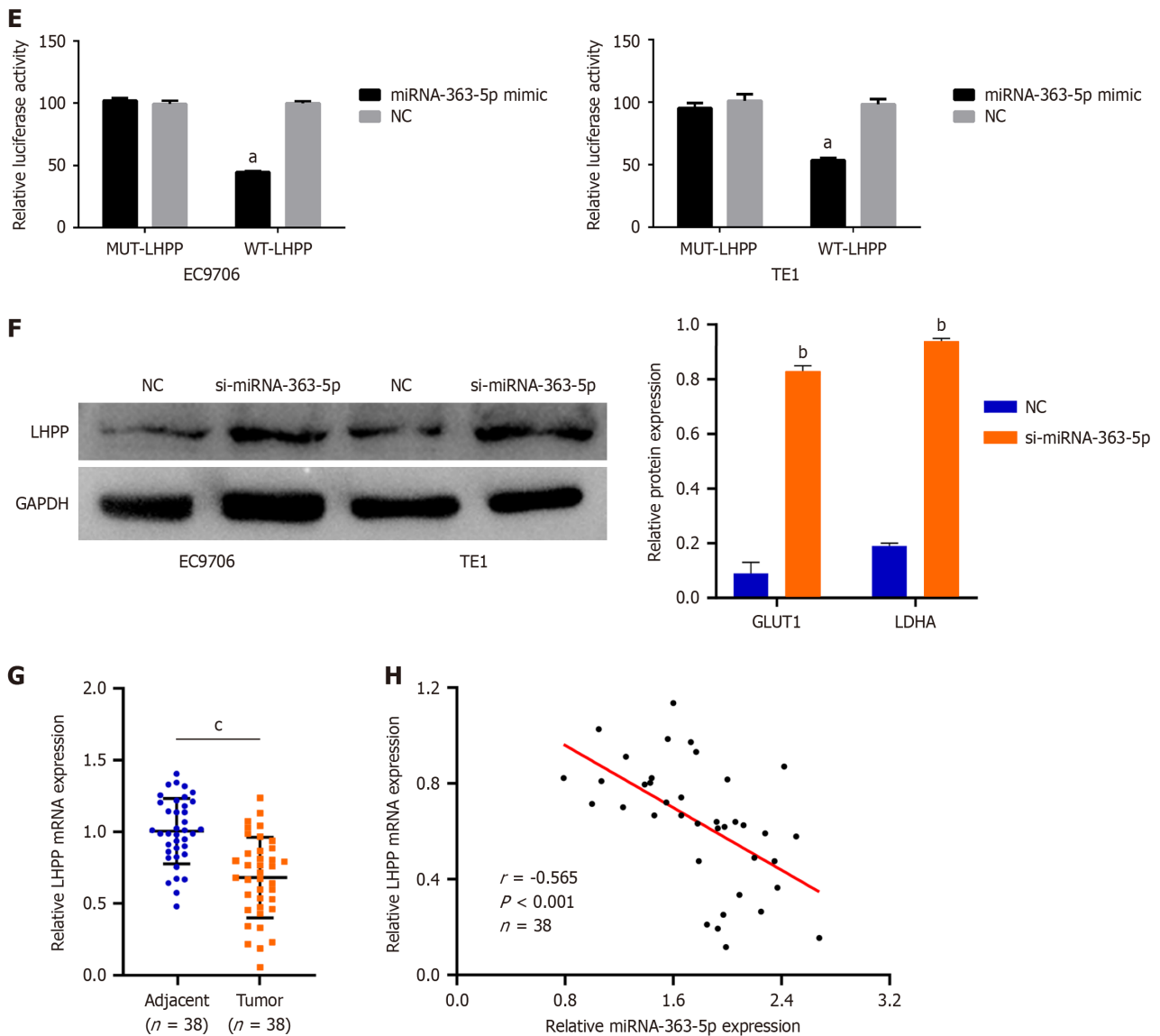


Figure 4 MiRNA-363-5p directly targets phospholysine phosphohistidine inorganic pyrophosphate phosphatase in esophageal squamous cell carcinoma cells. A: Quantitative reverse transcription-polymerase chain reaction analysis indicated that miRNA-363-5p expression remarkably decreased after si-miRNA-363-5p transfection; B: Inhibition of miRNA-363-5p expression significantly attenuated proliferation in EC9706 and TE1 cells; C: Inhibition of miRNA-363-5p expression significantly attenuated glycolysis in EC9706 and TE1 cells; D: Phospholysine phosphohistidine inorganic pyrophosphate phosphatase (LHPP) was predicted to have binding sequences for miRNA-363-5p; E: Luciferase reporter turned out that miRNA-363-5p mimic clearly weakened the luciferase activity of WT-LHPP; F: Downregulating miRNA-363-5p enhanced the LHPP protein levels in EC9706 and TE1 cells; G: LHPP expression was low in esophageal squamous cell carcinoma tissues compared to adjacent normal tissues; H: MiRNA-363-5p is negatively correlated with LHPP. ^a $P < 0.05$ vs NC; ^b $P < 0.01$ vs NC; ^c $P < 0.01$ vs Adjacent. NC: Negative control; LHPP: Phospholysine phosphohistidine inorganic pyrophosphate phosphatase.

tissues and cell lines, and low expression of SRA1 was significantly associated with advanced tumor stage, metastasis, larger tumor size, and poor survival. Function and rescue assays demonstrated that SRA1 could impede cell proliferation and glycolysis of ESCC cells *via* miRNA-363-5p and LHPP. Regarding the mechanism, SRA1 elevated LHPP expression by sponging miRNA-363-5p, leading to inhibition of ESCC cell proliferation and glycolysis (Figure 7).

Increasing studies have demonstrated that non-coding RNAs, including miRNAs, lncRNAs and circRNAs, play a pivotal role in ESCC formation, and may be used as therapeutic targets or diagnostic and prognostic biomarkers for ESCC patients[20-26]. At present, there are many reports on SRA1 and tumor progression, but its role in different tumors reflects tumor heterogeneity. There have been many reports on the research of SRA1 in some gynecological solid tumors. These studies have found that SRA1 plays an oncogene role, such as cervical cancer[27], endometrial cancer[28], breast cancer[29]. However, a number of studies in several tumors have pointed out that SRA1 acts as a tumor suppressor gene, such as hepatocellular carcinoma[30] and prostate cancer[31]. Moreover, using online bioinformatics software and qRT-PCR analysis, we screened a few miRNAs sharing binding sites with SRA1. In the present study, our bioinformatics analyses showed that miR-363-5p has binding sites for SRA1, and further experiments showed SRA1 knockdown strongly accelerated miR-363-5p expression in ESCC cells. And miR-363-5p was found to be upmodulated, and was inversely correlated with SRA1 Levels in ESCC tissues. Importantly, using luciferase reporter and RIP assays, SRA1 still has a targeting relationship with miR-363-5p. Further, we conducted the loss-of-function and rescue experiments, and found

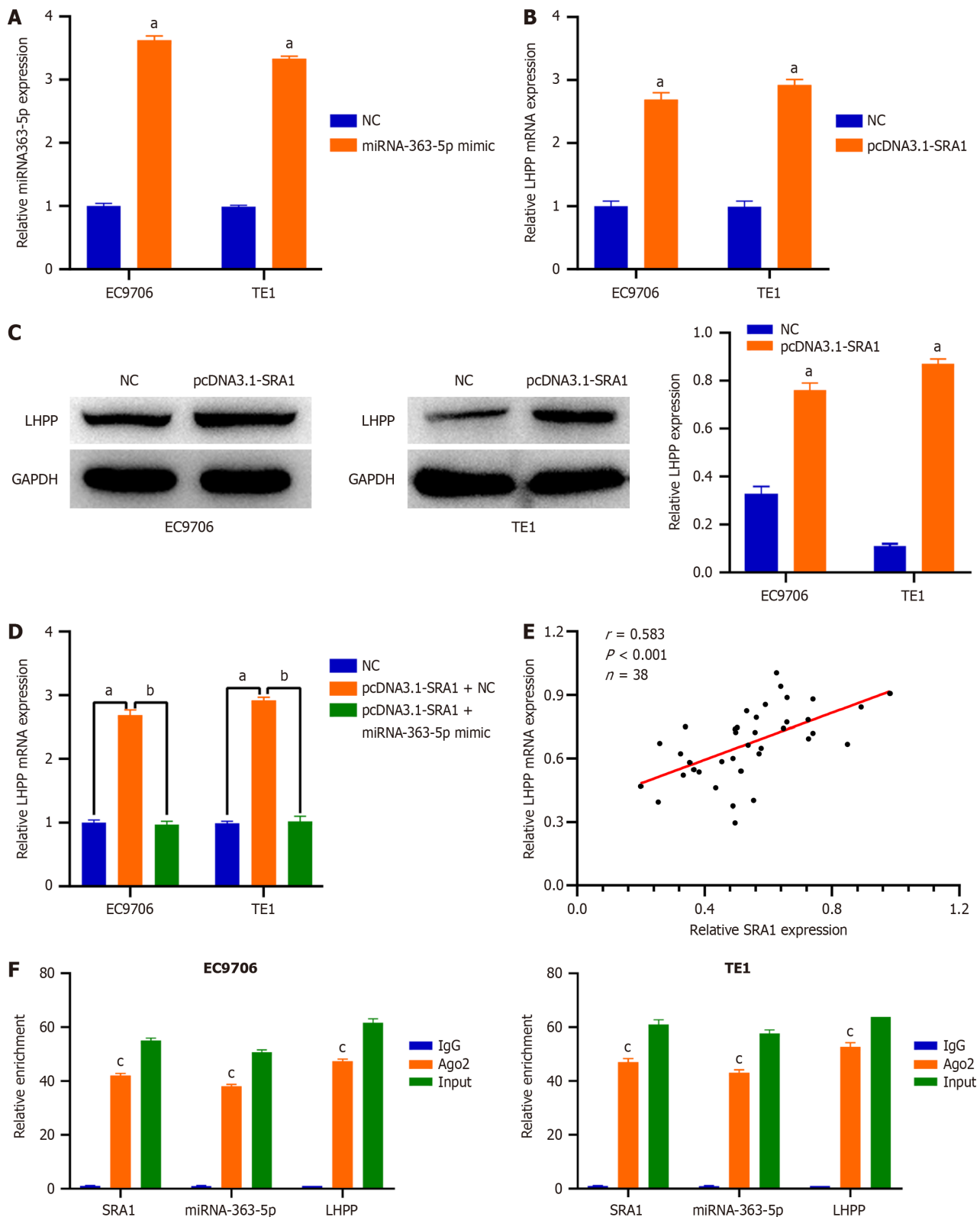


Figure 5 Steroid receptor RNA activator 1 overexpression promotes phospholysine phosphohistidine inorganic pyrophosphate phosphatase expression in esophageal squamous cell carcinoma cells by sponging miRNA-363-5p. A: The delivery of miRNA-363-5p mimic caused a prominent miRNA-363-5p upregulation in EC9706 and TE1 cells; B-D: Steroid receptor RNA activator 1 (SRA1) upregulation triggered an obvious overexpressed effect on the endogenous phospholysine phosphohistidine inorganic pyrophosphate phosphatase (LHPP) mRNA and protein levels in EC9706 and TE1 cells, whereas the delivery of miRNA-363-5p mimic counteracted such effect; E: LHPP expression was positively correlated with SRA1 expression in ESCC tissues; F: SRA1, miRNA-363-5p, and LHPP were preferentially concentrated in the anti-Ago2 precipitate. ^a $P < 0.01$ vs NC; ^b $P < 0.01$ vs pcDNA3.1-SRA1 + miRNA-363-5p mimic; ^c $P < 0.01$ vs IgG; NC: Negative control; SRA1: Steroid receptor RNA activator 1; LHPP: Phospholysine phosphohistidine inorganic pyrophosphate phosphatase.

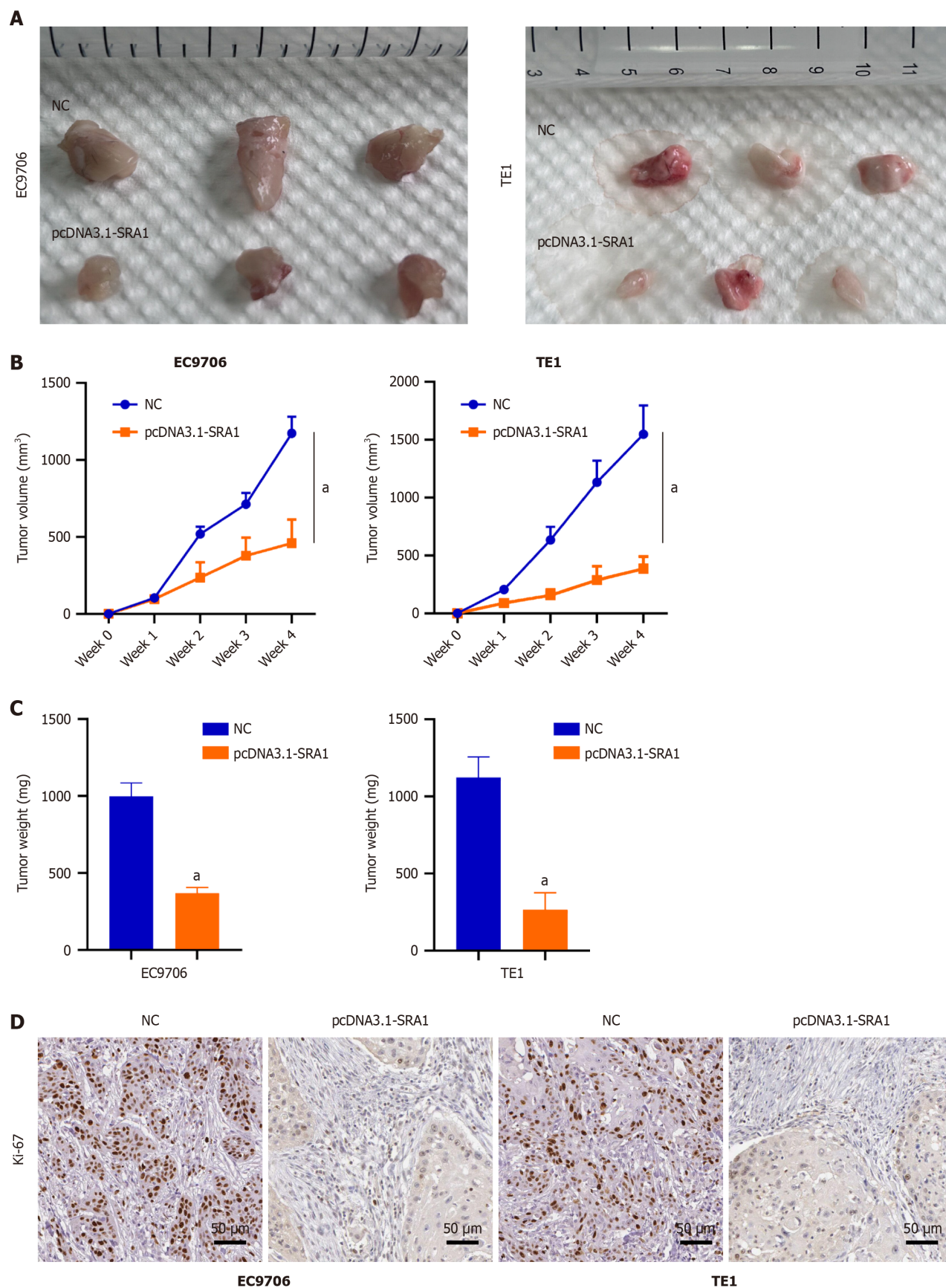


Figure 6 Steroid receptor RNA activator 1 overexpression inhibits esophageal squamous cell carcinoma tumor growth *in vivo*. A-C: Overexpressing steroid receptor RNA activator 1 (SRA1) exhibited weaker tumorigenic ability; D: Immunohistochemical staining confirmed the relatively low level of proliferation marker Ki-67 in the tumors with overexpressing SRA1. Scale bar = 50μm. ^a*P* < 0.01 vs negative control; NC: Negative control.

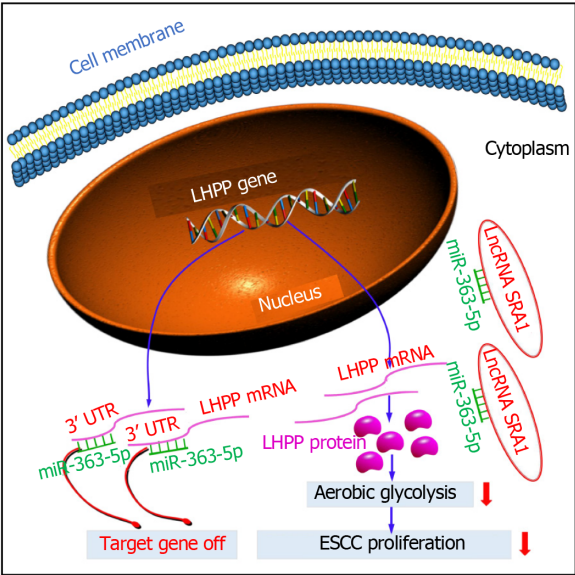


Figure 7 Schematic diagram showing the regulatory mechanism of steroid receptor RNA activator 1 in esophageal squamous cell carcinoma. LncRNA: Long non-coding RNA; SRA1: Steroid receptor RNA activator 1; ESCC: Esophageal squamous cell carcinoma; LHPP: Phospholysine phosphohistidine inorganic pyrophosphate phosphatase.

that the suppressive effects of SRA1 overexpression on cell proliferation, glucose uptake, and lactate production of ESCC cells were rescued by miR-363-5p mimic. The partial reversal effect of miR-363-5p mimic on pcDNA3.1-SRA1 function proved that miR-363-5p was one of the downstream miRNAs of SRA1.

However, this study has some limitations. (1) Our research explored and found for the first time that SRA1 inhibits the carcinogenicity of ESCC cells by targeting the miRNA-363-5p/LHPP axis. However, the downstream regulatory molecules of LHPP need to be further studied; and (2) Finally, it is worthy of our attention that we only detected the expression of SRA1/miRNA-363-5p/LHPP in ESCC tissues. Then, by expanding the number of ESCC patients, whether the detection of serum SRA1/miRNA-363-5p/LHPP in ESCC patients can discover early noninvasive markers of ESCC patients remains to be explored.

CONCLUSION

In conclusion, we found that SRA1 inhibits the oncogenicity of ESCC *via* miRNA-363-5p/LHPP axis. The SRA1/miRNA-363-5p/LHPP pathway may be a therapeutic target for ESCC.

Table 2 Correlations between steroid receptor RNA activator 1 expression and clinical characteristics in esophageal squamous cell carcinoma patients

Characteristics	Case (n = 38)	SRA1 expression		χ^2	P value
		High	Low		
Sex					
Male	26	12	14	0.487	0.485
Female	12	7	5		
Age (years)				1.310	0.252
≤ 60	9	3	6		
> 60	29	16	13		
Pathological differentiation grade				0.186	0.911
Well	7	4	3		
Moderately	23	11	12		
Poorly	8	4	4		

T Stage				5.265	0.022 ^a
T1-T2	20	13	7		
T3-T4	18	5	13		
TNM Stage				8.622	0.003 ^b
I-II	17	13	4		
III-IV	21	6	15		
Lymph node metastasis				8.526	0.004 ^b
Negative	19	14	5		
Positive	19	5	14		

^a*P* < 0.05.

^b*P* < 0.01.

The χ^2 test was used for comparison between groups. SRA1: Steroid receptor RNA activator 1.

FOOTNOTES

Author contributions: He M, Qi Y, Zheng ZM, Yao J and Yang ZD conceptualized and designed the research; He M, Qi Y, Sha M and Yao J screened patients and acquired clinical data; He M, Qi Y, Zheng ZM, Qian RY and Yao J collected tissue specimen and performed the research; He M, Zhao X, Chen YR and Chen ZH performed data analysis; He M, Qi Y, Zheng ZM and Yao J wrote the paper. All the authors have read and approved the final manuscript. He M proposed, designed and conducted tissue specimen collection, performed data analysis and prepared the first draft of the manuscript. Qi Y was responsible for patient screening, enrollment, collection of clinical data and tissue specimens. Both authors have made crucial and indispensable contributions towards the completion of the project and thus qualified as the co-first authors of the paper. Both Yao J and Yang ZD have played important and indispensable roles in the experimental design, data interpretation and manuscript preparation as the co-corresponding authors. Yao J applied for and obtained the funds for this research project. Yao J conceptualized, designed, and supervised the whole process of the project. She searched the literature, revised and submitted the early version of the manuscript. Yang ZD was instrumental and responsible for data re-analysis and re-interpretation, figure plotting, comprehensive literature search, preparation and submission of the current version of the manuscript. This collaboration between Yao J and Yang ZD is crucial for the publication of this manuscript.

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