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ORIGINAL RESEARCH

Regulatory Role and Mechanism of lncRNA RNF217-AS1 in the Proliferation and Migration of Esophageal Cancer Cells

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Objective: This study aims to explore the effect of the long non-coding RNA (lncRNA) RNF217-AS1 on the proliferation and migration of esophageal cancer cells, and to uncover the molecular mechanisms through which RNF217-AS1 regulates these processes.

Methods: The expression of RNF217-AS1 was measured in esophageal cancer cell lines (EC9706, Ecal09, KYSE-510, and TE-13) and immortalized esophageal epithelial HET-1 A cells using RT-qPCR. KYSE-510 cells were transfected with si-NC or si-RNF217-AS1 plasmids. Colony formation assays were used to assess cell proliferation, while migration ability was evaluated using scratch assays. A dual-luciferase reporter system was employed to verify the interaction between RNF217-AS1 and miR-377-3p. The expression of miR-377-3p and key proteins related to cell migration and epithelial-to-mesenchymal transition (EMT) were detected by RT-qPCR and Western blot.

Results: RNF217-AS1 expression was significantly upregulated in esophageal cancer cells compared to HET-1 A cells ($P<0.01$). Downregulation of RNF217-AS1 in KYSE-510 and Eca109 cells led to a reduction in cell proliferation and migration ($P<0.01$). The dual-luciferase assay confirmed the interaction between RNF217-AS1 and miR-377-3p ($P<0.01$). miR-377-3p expression was elevated in the si-RNF217-AS1 group compared to the si-NC group ($P<0.01$). Furthermore, the protein levels of HOXA1, fibronectin, and FOXC2 were downregulated, while GRHL2 and E-cadherin expressions were increased in the si-RNF217-AS1 group ($P<0.01$).

Conclusion: RNF217-AS1 is upregulated in esophageal cancer cells, and its downregulation inhibits the proliferation, migration and EMT of esophageal cancer cells by regulating the miR-377-3p/HOXA1 axis.

Keywords: esophageal cancer, long non-coding RNA RNF217-AS1, miR-377-3p, cell proliferation, cell migration

Introduction

Esophageal cancer (EC) is one of the most common and aggressive malignancies of the digestive system, with a high mortality rate and poor prognosis. It arises primarily from the epithelial cells of the esophagus and is often diagnosed at an advanced stage, which severely limits treatment options and survival rates. The five-year survival rate for esophageal cancer patients remains alarmingly low, despite improvements in therapeutic strategies, including surgery, chemotherapy, and radiotherapy.[1] Given the complexity of the disease and the poor response to conventional therapies, novel molecular targets are urgently needed to improve diagnosis, prognosis, and treatment.

Recent advances in cancer genomics and transcriptomics have highlighted the important roles of long non-coding RNAs (lncRNAs) in cancer biology. lncRNAs are a class of non-coding RNAs that do not encode proteins but regulate critical cellular processes such as gene expression, chromatin remodeling, cell differentiation, and metabolism. These molecules have emerged as key regulators in the pathogenesis of various cancers, including esophageal cancer.[2,3] Although many lncRNAs have been implicated in tumorigenesis, the exact mechanisms by which they influence tumor progression remain poorly understood.

One such lncRNA is RNF217-AS1, which has recently garnered attention for its potential role in cancer biology. RNF217-AS1 is a 432-nucleotide-long lncRNA, and studies suggest that it may act as an oncogene in various cancers.[4,5]

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A recent study showed that the peptide encoded by the RNF217-AS1 ORF inhibited the progression of stomach cancer (SC) both in vitro and in vivo, while also suppressing macrophage recruitment and pro-inflammatory responses in SC.[4] However, its role in esophageal cancer has not been explored in depth. Bioinformatics analysis, including data from the LncBook database, suggests that RNF217-AS1 is highly expressed in esophageal cancer tissues. Notably, patients with elevated RNF217-AS1 expression tend to have poorer overall survival, suggesting that it may serve as a prognostic marker.

In this study, we investigate the regulatory role of RNF217-AS1 in esophageal cancer cell proliferation and migration, particularly in relation to the microRNA miR-377-3p. miR-377-3p has been shown to play a crucial role in regulating various cancer-related processes, including cell proliferation and migration, by targeting several downstream effectors.[6–8] We hypothesize that RNF217-AS1 modulates the expression of miR-377-3p, thus affecting the key signaling pathways involved in esophageal cancer progression. By elucidating these molecular mechanisms, we aim to provide new insights into the therapeutic potential of targeting RNF217-AS1 in esophageal cancer.

Materials and Methods

Experimental Cells and Main Reagents

Esophageal cancer cell lines (EC9706, Eca109, KYSE-510, TE-13) and the immortalized esophageal epithelial cell line (HET-1A) were procured from the American Type Culture Collection (ATCC). The si-NC plasmid (batch number: YS0032) and si-RNF217-AS1 plasmid (batch number: YS0081) were obtained from Shanghai YaJi Biotechnology Co., Ltd. Fetal bovine serum (FBS; batch number: A5256801) was sourced from Invitrogen, USA. TRIzol reagent (batch number: YT7863) was purchased from Beijing Yita Biotechnology Co., Ltd. RPMI-1640 medium (batch number: GT-T061) was acquired from TAKARA Biotechnology Co., Ltd., Japan. For molecular assays, the dual-luciferase reporter gene assay kit (batch number: SML144) and cDNA synthesis kit (batch number: SML262) were obtained from Sigma, USA. The psi-CHECK2 reporter vector (batch number: C802) was purchased from GeneCopoeia, USA. MicroRNA (miR)-377-3p (batch number: ECS048) and miR-NC (batch number: ECS096) were sourced from Shanghai Yishan Biotechnology Co., Ltd. Primary antibodies against key proteins, including homeobox protein A1 (HOXA1; batch number: ab230513), fibronectin (batch number: ab2413), β-actin (batch number: ab8226), forkhead-associated transcription factor C2 (FOXC2; batch number: ab308055), grainyhead-like protein 2 homolog (GRHL2; batch number: ab271023), and E-cadherin (batch number: ab40772), were purchased from Abcam, UK.

Cell Culture, Transfection, and Grouping

EC9706, HET-1A, Eca109, KYSE-510, and TE-13 cells were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum under standard conditions. KYSE-510 cells were plated in 12-well plates at a density of 7×10^4 cells per well and cultured for 10 hours. KYSE-510 cells were divided into the si-RNF217-AS1 group and the si-NC group, transfected with 2 μg of si-RNF217-AS1 plasmid and si-NC plasmid, respectively, according to the manufacturer's instructions for Lipofectamine™ 3000. After 45 hours of standard culture, KYSE-510 cells were collected.

Real-Time Quantitative PCR (RT-qPCR) for Detection of RNF217-AS1 and miR-377-3p Expression

Total RNA was extracted from EC9706, Eca109, KYSE-510, TE-13, and HET-1A cells using TRIzol reagent. cDNA was synthesized following the instructions of the cDNA synthesis kit. The primer sequences were as follows: β-actin: Forward 5'-CTCGCCTTTGCCGATCC-3', Reverse 5'-TCTCCATGTCGTCCCAGTTG-3'; RNF217-AS1: Forward 5'-TCCTCTCCTCGCTACAAATGC-3', Reverse 5'-GCTGGAAGCTCTTGCAGTCA-3'; U6: Forward 5'-CGCTTCACGAATTTGCGTGTCAT-3', Reverse 5'-GCTTCGGCAGCACATATACTAAAAT-3'; miR-377-3p: Forward 5'-GCCGAGATCACACAAAGGCAAC-3', Reverse 5'-CTCAACTGGTGTCGTGGA-3'. U6 and β-actin were used as internal controls. cDNA was amplified using the SYBR Green kit with the following reaction parameters: 96 °C pre-denaturation for 4 minutes, 96 °C denaturation for 15 seconds, 56 °C annealing for 16 seconds, and 70 °C extension for 36 seconds, repeated for 36 cycles. The relative expression levels of RNF217-AS1 and miR-377-3p were calculated using the 2-ΔΔCt method.

Colony Formation Assay to Detect KYSE-510 Cell Proliferation

Logarithmic-phase KYSE-510 cells from the si-NC group and si-RNF217-AS1 group were plated in 12-well plates at a density of 1.5×10^3 cells per well in 1.5 mL of cell suspension, with five replicates per group. After 8 days of incubation in the culture chamber, visible colonies formed. Each well was treated with 1.5 mL of paraformaldehyde for 90 minutes, followed by 1.5 mL of crystal violet solution for 90 minutes. The plates were rinsed under running water for 2 minutes and dried at room temperature for 24 hours. Six random fields were selected, and the number of colonies in each group was counted and recorded.

Wound Healing Assay to Detect KYSE-510 Cell Migration Ability

Straight lines were drawn uniformly and perpendicularly on the back of 12-well plates using a marker pen. Logarithmic-phase KYSE-510 cells from the si-NC group and si-RNF217-AS1 group were seeded into 12-well plates at a density of 1.5 mL of cell suspension per well. When the cells reached 90% confluence, a sterile pipette tip was used to create a scratch perpendicular to the lines on the back of the plate. The wells were washed six times with PBS to remove floating cells. The scratch width was observed and photographed at 0 h and 24 h post-scratch, and the migration rate of KYSE-510 cells in each group was measured.

Dual-Luciferase Reporter Gene Assay to Detect the Targeting Relationship Between RNF217-AS1 and miR-377-3p

The wild-type (WT) and mutant (MUT) sequences of the miR-377-3p binding site in RNF217-AS1 were cloned into the psi-CHECK2 vector. KYSE-510 cells were co-transfected with either RNF217-AS1-WT or RNF217-AS1-MUT and either miR-NC or miR-377-3p, followed by incubation for 44 h. The luciferase activity of KYSE-510 cells in each group was analyzed using the dual-luciferase reporter system.

Western Blot to Detect the Expression of HOXA1, Fibronectin, FOXC2, GRHL2, and E-cadherin Proteins

Total protein was extracted from KYSE-510 cells of the si-RNF217-AS1 group and si-NC group using RIPA lysis buffer on ice. Proteins were separated by 15% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to a nitrocellulose membrane at low temperature. The membrane was blocked with 10% skim milk for 3 h, followed by incubation with primary antibodies against HOXA1, Fibronectin, FOXC2, β-actin, GRHL2, and E-cadherin (all diluted 1:2000) at low temperature for 6 h. The membrane was then incubated with goat anti-rabbit secondary antibody at room temperature for 1.5 h. Chemiluminescent reagent was added, and the membrane was visualized using an imaging system.

Statistical Analysis

Statistical analysis was performed using SPSS 26.0 software. Measurement data conforming to a normal distribution were expressed as (EQN). Comparisons between group means were conducted using the *t*-test, with $P < 0.05$ considered statistically significant.

Results

Expression Level of RNF217-AS1 in Esophageal Cancer Cell Lines

As shown in Figure 1, RT-qPCR results revealed that RNF217-AS1 was highly expressed in esophageal cancer cell lines EC9706, Eca109, KYSE-510, and TE-13 compared to normal esophageal epithelial HET1A cells (all $P<0.01$). Among them, the expression of RNF217-AS1 was the highest in KYSE510 cells and the lowest in Eca109 cells. Therefore, we selected these two cells for subsequent studies.

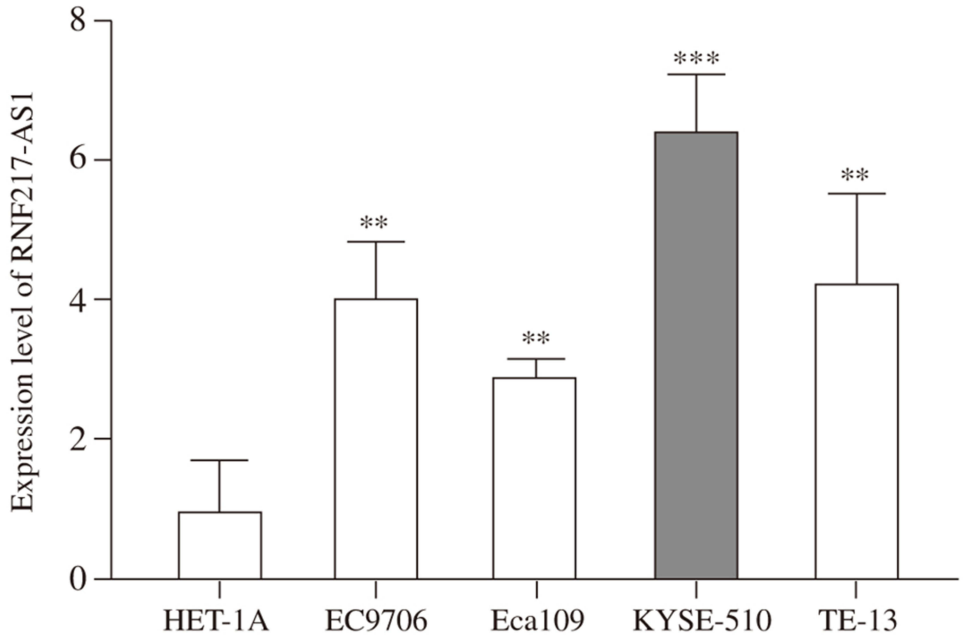

Figure 1 Comparison of RNF217-AS1 expression across various esophageal cancer cell lines.
Note: Compared to HET1A cells, **P<0.01, ***P<0.0001.

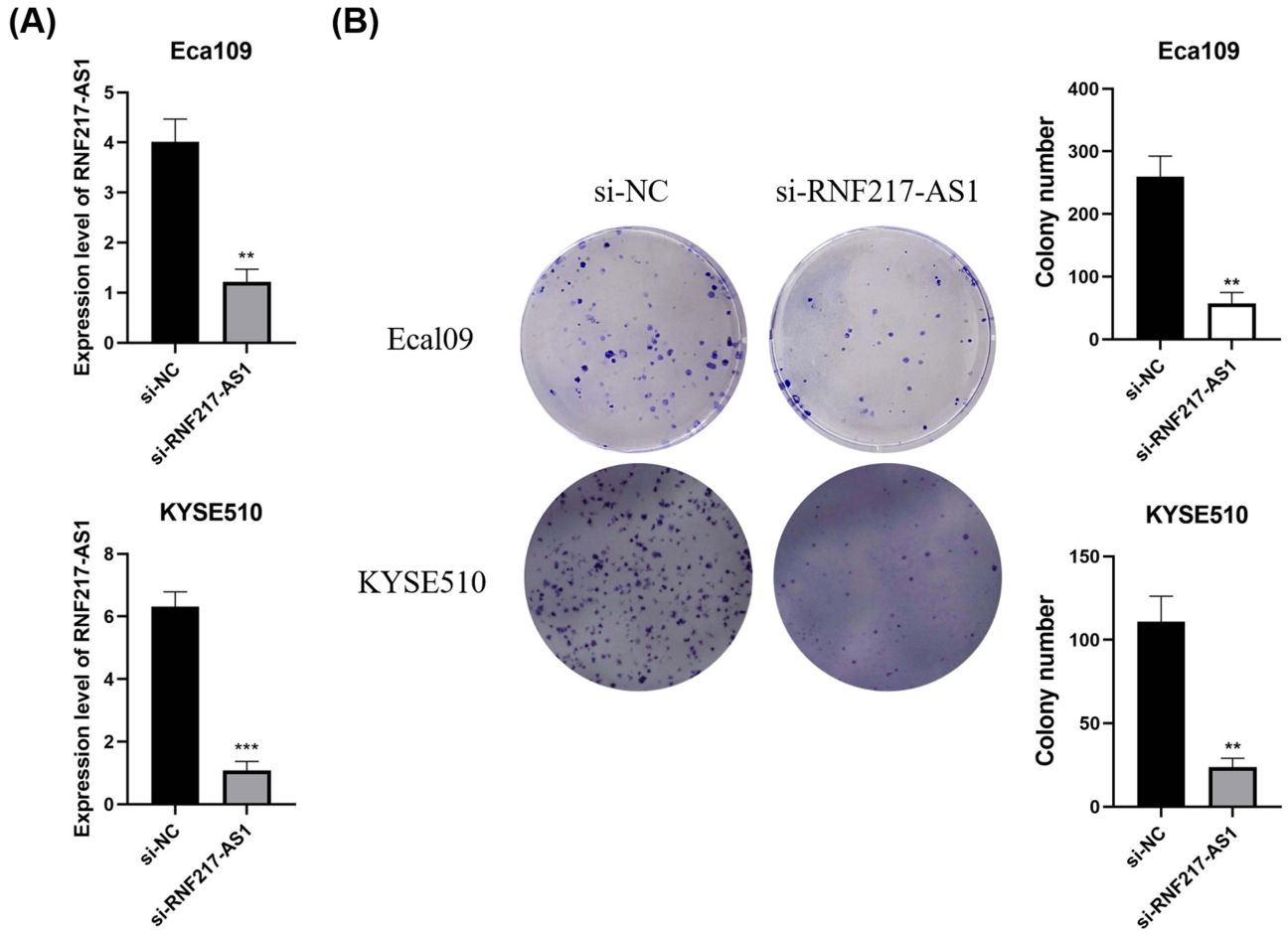

Figure 2 Effect of RNF217-AS1 knockdown on the proliferation activity of esophageal cancer l cells. (**A**) The knockdown of RNF217-AS1 expression by siRNA was verified by RT-qPCR in Eca109 and KYSE510 cells; (**B**) Colony formation assay demonstrated that knockdown of RNF217-AS1 inhibited proliferation activity of esophageal cancer cells (crystal violet staining).
Note: Compared to si-NC group, **P<0.01, ***P<0.001.

Effect of RNF217-AS1 Knockdown on Esophageal Cancer Cell Proliferation Activity

As illustrated in Figure 2A, transfection of siRNA effectively knocked down the expression levels of RNF217-AS1 in both Eca109 and KYSE510 cell lines (P<0.01). The colony formation assay showed that the number of colonies formed in the Eca109 and KYSE510 cells with knockdown of RNF217-AS1 was significantly reduced (Figure 2B, P<0.01), suggesting that knockdown of RNA inhibits the proliferation of esophageal cancer cells.

Effect of RNF217-AS1 Knockdown on Esophageal Cancer Cell Migration

As shown in Figure 3, wound healing assay results indicated that the migration rates of both Eca109 and KYSE510 cells were significantly reduced in the si-RNF217-AS1 group compared to the si-NC group, as evidenced by statistical analysis (P<0.01).

Validation of the Targeting Relationship Between RNF217-AS1 and miR-377-3p

As detailed in Figures 4A, the bioinformatics tool LncRNA2Target predicted a potential binding site between RNF217-AS1 and miR-377-3p. The expression level of miR-377-3p was significantly increased in the two esophageal cancer cells with knockdown of RNF217-AS1 (Figure 4B, P<0.01). Dual-luciferase reporter gene assay demonstrated that the luciferase activity of KYSE-510 cells co-transfected with RNF217-AS1-WT and miR-377-3p was significantly lower than that of cells co-transfected with RNF217-AS1-MUT and miR-NC (Figure 4C, P<0.01).

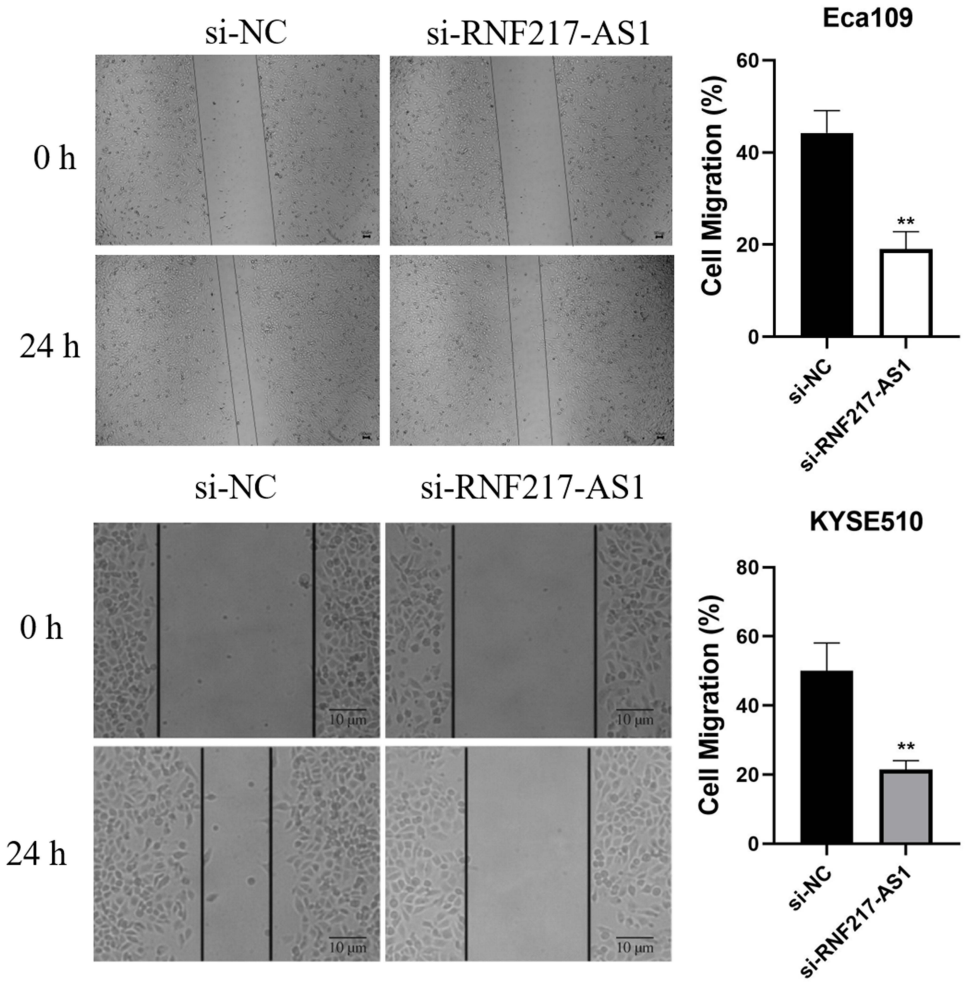

Figure 3 Effect of RNF217-AS1 knockdown on the migration of esophageal cancer cells (×200 magnification for KYSE510 cells, ×100 magnification for Eca109 cells).
Note: Compared to si-NC group, **P<0.01.

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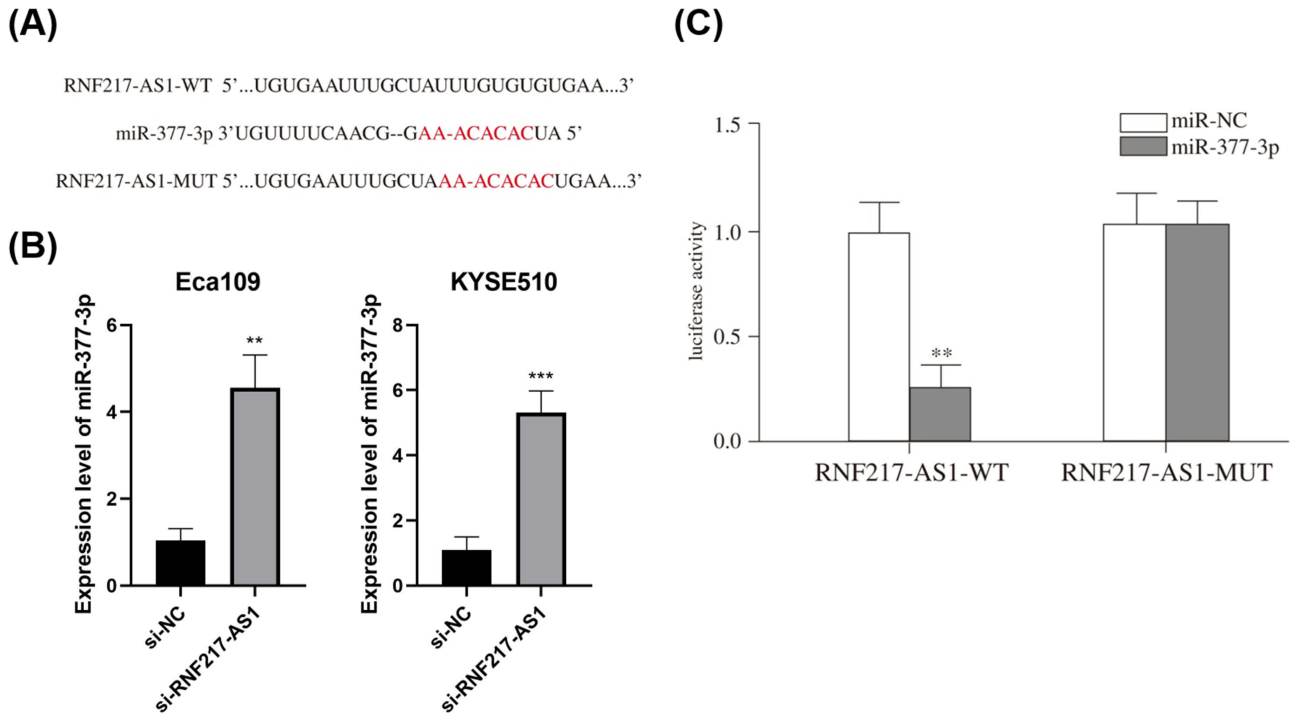

Figure 4 RNF217-AS1 targeted and negatively regulated the expression of miR-377-3p in esophageal cancer cells. (**A**) LncRNA2 Target analysis of the binding site between RNF217-AS1 and miR-377-3p; (**B**) Effect of RNF217-AS1 knockdown on miR-377-3p expression (Compared to si-NC group, **P<0.01, ***P<0.001); (**C**) Dual-luciferase reporter assay validating the targeting relationship between RNF217-AS1 and miR-377-3p (Compared to RNF217-AS1-WT, **P<0.01).

Effect of RNF217-AS1 Knockdown on the Expression of HOXA1, Fibronectin, FOXC2, GRHL2, and E-Cadherin Proteins

As presented in Figure 5, the si-RNF217-AS1 group exhibited a significant downregulation in the expression levels of HOXA1, fibronectin, and FOXC2 proteins, accompanied by a marked upregulation of GRHL2 and E-cadherin proteins in both two esophageal cancer cells, when compared to the si-NC group (all P<0.01).

Discussion

Long non-coding RNAs (lncRNAs) have emerged as key regulators in the pathogenesis of a wide range of diseases, from atherosclerosis and liver fibrosis to benign prostatic hyperplasia.[9] In the context of human malignancies, including glioma, thymic carcinoma, and retinoblastoma, lncRNAs exhibit dual roles – either promoting or suppressing tumorigenesis. This is achieved through their modulation of both intracellular and extracellular signaling pathways, as well as their active participation in shaping the tumor microenvironment.[10,11]

The involvement of lncRNAs in the initiation and progression of esophageal cancer has garnered significant attention. A growing body of evidence highlights the critical role of lncRNAs in regulating key cellular behaviors in esophageal cancer cells, such as adhesion, metabolic reprogramming, and differentiation.[12] One notable example is lncRNA PVT1, which is significantly upregulated in both esophageal cancer specimens and cell lines. Elevated expression of PVT1 correlates with poor survival outcomes in esophageal cancer patients. Mechanistically, silencing PVT1 enhances the chemosensitivity of esophageal cancer cells to cisplatin, with glutaminase identified as a direct downstream target of PVT1-mediated regulation.[13] Similarly, lncRNA HOXA10-AS has been found to be highly expressed in esophageal cancer cell lines. Experimental knockdown of HOXA10-AS not only attenuates the proliferative, invasive, and migratory capacities of esophageal cancer cells in vitro, but also suppresses tumorigenesis in vivo models.[14]

Ma et al reported that RNF217-AS1 were differentially expressed and associated with macrophage infiltration in SC.[4] And Guan et al[5] revealed RNF217-AS1 expression was significantly up-regulated in ESCC samples compared with healthy tissues. Bioinformatics analysis from the study of Lyn et al[15] identified RNF217-AS1 as feature genes for

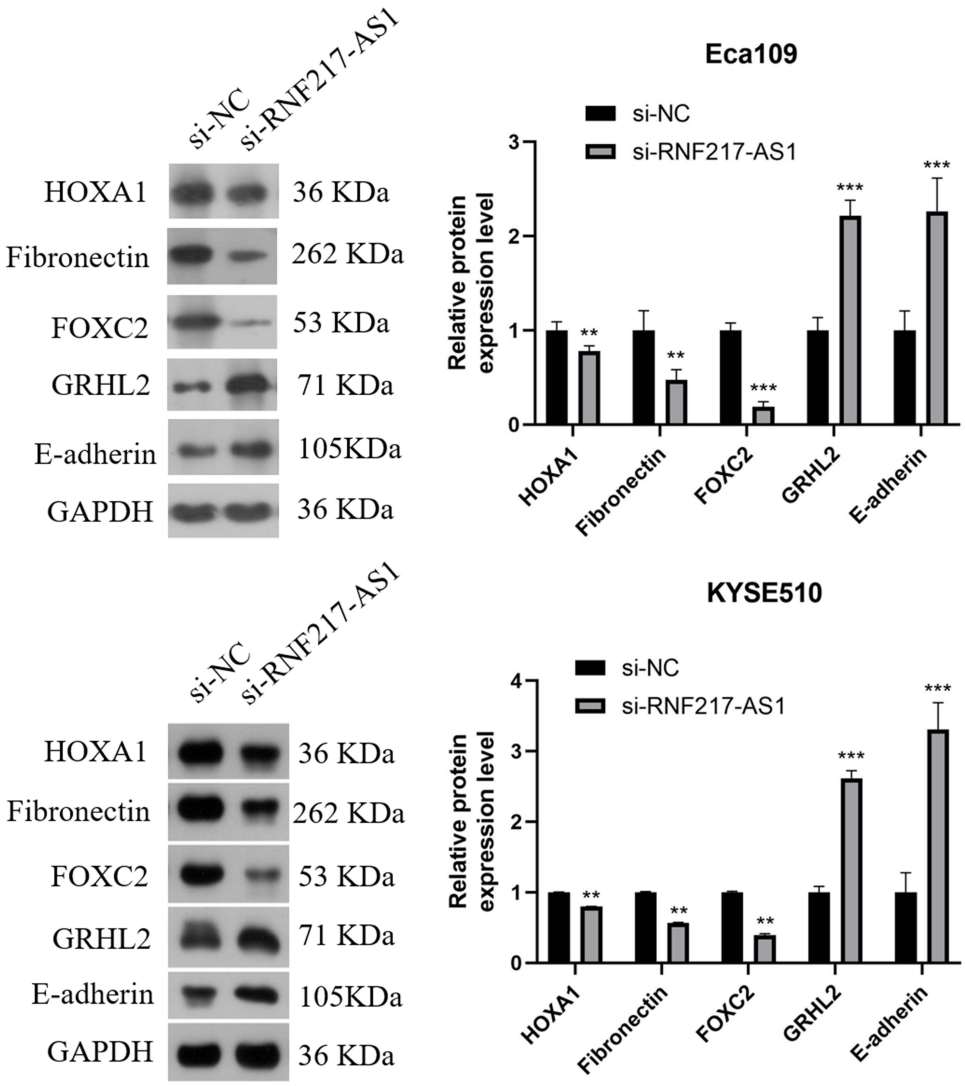

Figure 5 Effects of RNF217-AS1 knockdown on the expression of epithelial-mesenchymal transition (EMT) related proteins in esophageal cancer cells (Western Blots).
Note: Compared to si-NC, **P<0.01, ***P<0.001.

keratoconus. In this study, RNF217-AS1 knockdown plasmids were successfully transfected into KYSE-510 cells. Subsequent colony formation and wound healing assays demonstrated that knockdown of RNF217-AS1 effectively suppressed the proliferation and migration of esophageal cancer KYSE-510 cells.

Epithelial-mesenchymal transition (EMT) plays a crucial role in the adhesion and migration of esophageal cancer cells, characterized by the downregulation of epithelial markers such as GRHL2 and E-cadherin, and upregulation of mesenchymal markers such as Fibronectin and FOXC2.[16] Western blot analysis indicated that knockdown of RNF217-AS1 led to decreased expression of Fibronectin and FOXC2 proteins, and increased expression of GRHL2 and E-cadherin proteins in KYSE-510 cells, suggesting the inhibition of EMT in these cells.

Studies[17,18] have confirmed that lncRNAs function as competitive endogenous RNAs (ceRNAs) by targeting and binding to miRNAs, playing a critical role in various diseases such as renal fibrosis, cancer, and cardiac ischemia-reperfusion injury through the negative regulation of miRNAs. For example, lncRNA KTN1-AS1 promotes EMT in esophageal cancer cells by targeting and downregulating miR-885-5p, thereby enhancing the proliferation and invasion capabilities of these cells.[19] In our study, bioinformatics tools such as LncRNA2Target were used to predict that RNF217-AS1 has a potential binding site with miR-377-3p, and further experiments confirmed the direct binding ability between RNF217-AS1 and miR-377-3p. Research[20–23] has shown that miR-377-3p is downregulated in tumor tissues

such as colorectal cancer, endometrial cancer, triple-negative breast cancer, and cervical cancer. Its expression level is closely associated with favorable patient prognosis, and miR-377-3p can serve as an early diagnostic marker for cancer patients. Overexpression of miR-377-3p inhibits tumor cell proliferation, cell cycle progression, and migration. Chen et al[24] found that miR-377-3p was downregulated in esophageal cancer tissues and cell lines, and restoring miR-377-3p expression significantly reduced the proliferation and migration abilities of esophageal cancer cells. The results of this study demonstrated that silencing RNF217-AS1 led to a significant increase in miR-377-3p expression, confirming that miR-377-3p is a downstream target of RNF217-AS1. In esophageal cancer cells, miR-377-3p exerts its tumor-suppressive function by targeting and inhibiting HOXA1 gene expression.[24] This study found that silencing RNF217-AS1 resulted in reduced HOXA1 protein expression, further indicating that knockdown of RNF217-AS1 may function through the miR-377-3p/HOXA1 axis.

To summarize, RNF217-AS1 is upregulated in esophageal cancer cells, and its knockdown may inhibit the proliferation and migration of these cells by regulating the miR-377-3p/HOXA1 axis. Research on RNF217-AS1 contributes to elucidating the pathogenesis of esophageal cancer and provides a basis for targeted therapy in esophageal cancer.

Data Sharing Statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This research was approved by the Ethics Committee of Hebei University of Chinese Medicine. Consent to participate was not applicable because this study does not involve any human participants.

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Disclosure

The authors declare that they have no competing interests.

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