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Original Article

Small protein DDX11-AS1-ORF encoded by lncRNA DDX11-AS1 promotes colorectal cancer progression through VEGFA-activated p38-MAPK pathway

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Abstract: This study aims to investigate the expression, function, and mechanism of action of the small protein DDX11 antisense RNA 1 - open reading frame (DDX11-AS1-ORF), encoded by the long non-coding RNA (lncRNA) DDX11 antisense RNA 1 (DDX11-AS1), in the progression of colorectal cancer (CRC). The expression levels of DDX11-AS1 were assessed by quantitative reverse transcription polymerase chain reaction (qRT-PCR) analysis in 10 pairs of colorectal cancer tissues and corresponding non-tumor tissues. Functional evaluations of DDX11-AS1 and DDX11-AS1-ORF were conducted using cell counting kit-8 (CCK8) assays, colony formation assays, Transwell migration assays, and in vitro tube formation assays. The coding potential of DDX11-AS1 was validated by western blot and immunofluorescence. The activation of the p38 mitogen-activated protein kinase (p38-MAPK) pathway by DDX11-AS1-ORF through VEGFA was analyzed using western blot. The results showed that DDX11-AS1 was significantly upregulated in colorectal cancer tissues and cells, promoting cancer cell proliferation, migration, and angiogenesis. DDX11-AS1 translated into a functional small protein, DDX11-AS1-ORF, which independently enhanced the malignant behaviors of tumor cells. DDX11-AS1-ORF promoted colorectal cancer progression by activating the p38-MAPK signaling pathway through Vascular Endothelial Growth Factor A (VEGFA). The critical role of the p38-MAPK pathway in DDX11-AS1-ORF mediated tumor promotion was confirmed using the p38-MAPK pathway inhibitor SB203580. In conclusion, the small protein DDX11-AS1-ORF, encoded by DDX11-AS1, plays a crucial role in the development of colorectal cancer by promoting tumor proliferation, migration, and angiogenesis through the activation of VEGFA and the p38-MAPK signaling pathway. These findings provide a novel potential target for molecular targeted therapy in colorectal cancer.

Keywords: Colorectal cancer, lncRNA, p38-MAPK pathway, VEGFA, small protein

Introduction

Colorectal cancer (CRC) is one of the most common malignancies, with global cancer statistics indicating that its incidence and mortality rates rank third worldwide [1]. Annually, CRC accounts for millions of new cases globally, with persistently high mortality rates. Despite advancements in surgery, chemotherapy, and targeted therapies over recent years, the overall prognosis for CRC remains suboptimal [2]. This is primarily due to challenges in early diagnosis, high tumor heterogeneity, drug resistance, and elevated recurrence rates [3, 4]. Consequently, there is an urgent need to identify more biomarkers and novel therapeutic targets to improve the diagnostic and therapeutic outcomes, as well as the survival rates of CRC patients.

In recent years, long non-coding RNAs (lncRNAs) have garnered significant attention due to their regulatory roles in various biological processes [5, 6]. Studies have demonstrated that lncRNAs play crucial roles in cell proliferation, apoptosis, migration, and invasion [7-9]. Moreover, some lncRNAs can translate into small peptides or small protein, which are also pivotal in tumori-

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genesis and cancer progression [10-12]. In CRC, micropeptides translated from lncRNAs may also significantly influence tumor progression and metastasis by regulating signaling pathways and affecting the tumor microenvironment [13]. Therefore, investigating the roles and mechanisms of lncRNA-encoded small peptides in CRC is a vital direction in current cancer research.

In our study, we found that the DDX11 antisense RNA 1 (DDX11-AS1) gene is significantly upregulated in CRC tissues and can translate into a small protein consisting of 89 amino acids, named DDX11-AS1-ORF. Functional studies indicate that this small protein plays a crucial role in CRC cell proliferation, migration, and invasion. In this paper, we systematically explore the biological functions and molecular mechanisms of the DDX11 antisense RNA 1 - open reading frame (DDX11-AS1-ORF) small protein in CRC. Through a series of experiments, we revealed that the DDX11-AS1-ORF small protein is expressed in colorectal cancer cells and promotes tumor proliferation, migration, and angiogenesis by activating the Vascular Endothelial Growth Factor A (VEGFA) and p38 mitogen-activated protein kinase (p38-MAPK) signaling pathways, providing new theoretical bases and research directions for the early diagnosis and targeted therapy of colorectal cancer.

Methods

Clinical specimens and cell lines

Human colorectal cancer tissues and paired normal colorectal mucosa tissues, totaling 10 pairs, were collected from the First Affiliated Hospital of Xinxiang Medical University. Written informed consent was obtained from all patients or their relatives. All human-related studies were approved by the Ethics Committee of Xinxiang Medical University. These tissue specimens were frozen in liquid nitrogen immediately after collection and subsequently stored at -80°C. The colorectal cancer cell lines used in this research were acquired from ATCC and cultured in RPMI 1640 (Hyclone) medium supplemented with 10% fetal bovine serum (FBS) (Gibco) and maintained at 37°C in a 5% CO_2 atmosphere.

Quantitative Real-Time PCR (qRT-PCR)

Total RNA was extracted from colorectal cancer cell lines and tissue samples using TRIzol reagent (Invitrogen) according to the manufacturer's instructions. RNA concentration and purity were determined using a NanoDrop 2000 spectrophotometer (Thermo Scientific). cDNA synthesis was performed using the RevertAid First Strand cDNA Synthesis Kit (Thermo Scientific). qRT-PCR was conducted on an ABI 7500 Fast Real-Time PCR System (Applied Biosystems) using SYBR Green PCR Master Mix (Thermo Scientific). Each sample was tested in triplicate, and data were analyzed using the 2^-ΔΔCt method. The DDX11-AS1 primers are as follows, the forward primer 5'-ATTCGGAATTCCGTATCTGGCCTTTTGAC-3' and the reverse primer 5'-CGGTTACTCGGCTTACGCTTGGACTG-3'; GAPDH used as an internal control. The primers for GAPDH were 5'-GACTCATGACCACAGTCCATGC-3' and 5'-AGAGGCAGGGATGATGTTCTG-3'.

Western blot

Cells and tissue samples were collected, and total protein was extracted using RIPA lysis buffer (Beyotime). Protein concentration was determined using the BCA Protein Assay Kit (Beyotime). Equal amounts of protein samples were separated by SDS-PAGE and transferred to PVDF membranes (Millipore). After blocking with 5% non-fat milk for 1 hour, the membranes were incubated overnight with primary antibodies and subsequently with HRP-conjugated secondary antibodies for 1 hour. Protein detection was performed using ECL detection reagent (Thermo Scientific), and semi-quantitative analysis was conducted using ImageJ software. The antibodies Flag (cat. #AE169), VEGFA (cat. #A0280), P38 (cat. #A14401), p-P38 (cat. #AP1310), and GAPDH (cat. #AC001) were all purchased from Abclone, and the primary antibody concentration used was 1:1000. The results were quantified using Image J software.

CCK-8 cell proliferation assay

Cells were seeded into 96-well plates at a density of 1000 cells per well. After 24, 48, 72, and 96 hours of culture, 10 μL of CCK-8 reagent (Dojindo) was added to each well and incubated at 37°C for 2 hours. Absorbance at 450 nm was measured, with each condition tested in triplicate.

Colony formation assay

Cells were seeded into 6-well plates at a density of 500 cells per well and cultured for 14

days, with the medium replaced every 3 days. At the end of the culture period, cells were washed twice with PBS, fixed with 4% paraformaldehyde for 15 minutes, and stained with 0.1% crystal violet for 30 minutes. Colonies were counted after washing, with each condition tested in triplicate.

Transwell migration assay

Cells were suspended in 200 μL of serum-free medium at a concentration of 5 × 10^4 cells per well and added to the upper chamber of an 8 μm pore Transwell insert (Corning). The lower chamber was filled with 600 μL of medium containing 10% FBS act as a chemoattractant. After 24 hours of incubation at 37°C, non-migrated cells in the upper chamber were removed with a cotton swab. Migrated cells in the lower chamber were fixed, stained, and counted under a microscope. Each condition was tested in triplicate.

Wound healing assay

Cells were seeded into 6-well plates and cultured to confluence. A straight line was scratched in the cell monolayer using a sterile pipette tip. Detached cells were removed by washing three times with PBS, and serum-free medium was added. The migration of cells into the wound area was photographed at 0 and 24 hours, and wound healing rates were calculated using ImageJ software. Each condition was tested in triplicate.

In vitro tube formation assay

A 24-well plate was pre-coated with 200 μL of Matrigel (BD Biosciences) and incubated at 37°C for 30 minutes to allow solidification. Cells (1×10^4 per well) were suspended in 200 μL of serum-free medium and added to the pre-coated wells. After 6 hours of incubation at 37°C, tube formation was observed and photographed under a microscope. Tube length and branching points were quantified using ImageJ software, with each condition tested in triplicate.

Statistical analysis

All experimental data were statistically analyzed using GraphPad Prism 8.0 software. Results are presented as mean ± standard deviation. For comparisons between paired samples (e.g., colorectal cancer tissues vs. adjacent normal tissues), a paired Student's t-test was applied. Independent samples t-test was used for unpaired comparisons between two groups. Multiple group comparisons were analyzed by one-way ANOVA followed by Dunnett's post hoc test when comparing against a single control group or Tukey's test for all pairwise comparisons. Time-dependent experiments were evaluated using repeated measures ANOVA. Normality and homogeneity of variances were assessed before applying parametric tests; non-parametric alternatives (e.g., Mann-Whitney U test or Kruskal-Wallis test with Dunn's correction) were used if assumptions were violated. A two-tailed *p*-value <0.05 was considered statistically significant.

Results

Upregulation and oncogenic role of DDX11-AS1 in colorectal cancer

Expression levels of DDX11-AS1 mRNA were analyzed in 10 pairs of colorectal cancer tissues using qRT-PCR, revealing a significant upregulation in cancerous tissues (**Figure 1A**). We transfected two DDX11-AS1 interference fragments and assessed the interference efficiency using qRT-PCR. The results showed that both interference fragments were able to inhibit the expression of DDX11-AS1 (Supplementary Figure 1). Functional assays further demonstrated the oncogenic role of DDX11-AS1. Inhibition of DDX11-AS1 expression resulted in decreased proliferation of colorectal cancer cell lines SW480 and HCT116, as shown by CCK8 and colony formation assays (**Figure 1B** and **1C**). Transwell migration and wound healing assays showed a significant reduction in cell migration capabilities following DDX11-AS1 knockdown (**Figures 1D** and **2A**). Additionally, in vitro tube formation assays showed that interfering with DDX11-AS1 inhibited capillary tube formation in human umbilical vein endothelial cells (HUVECs), underscoring its role in promoting angiogenesis (**Figure 2B**).

Translation of peptide DDX11-AS1-ORF from DDX11-AS1

Preliminary bioinformatics analysis using the GetORF tool (http://emboss.bioinformatics.nl/

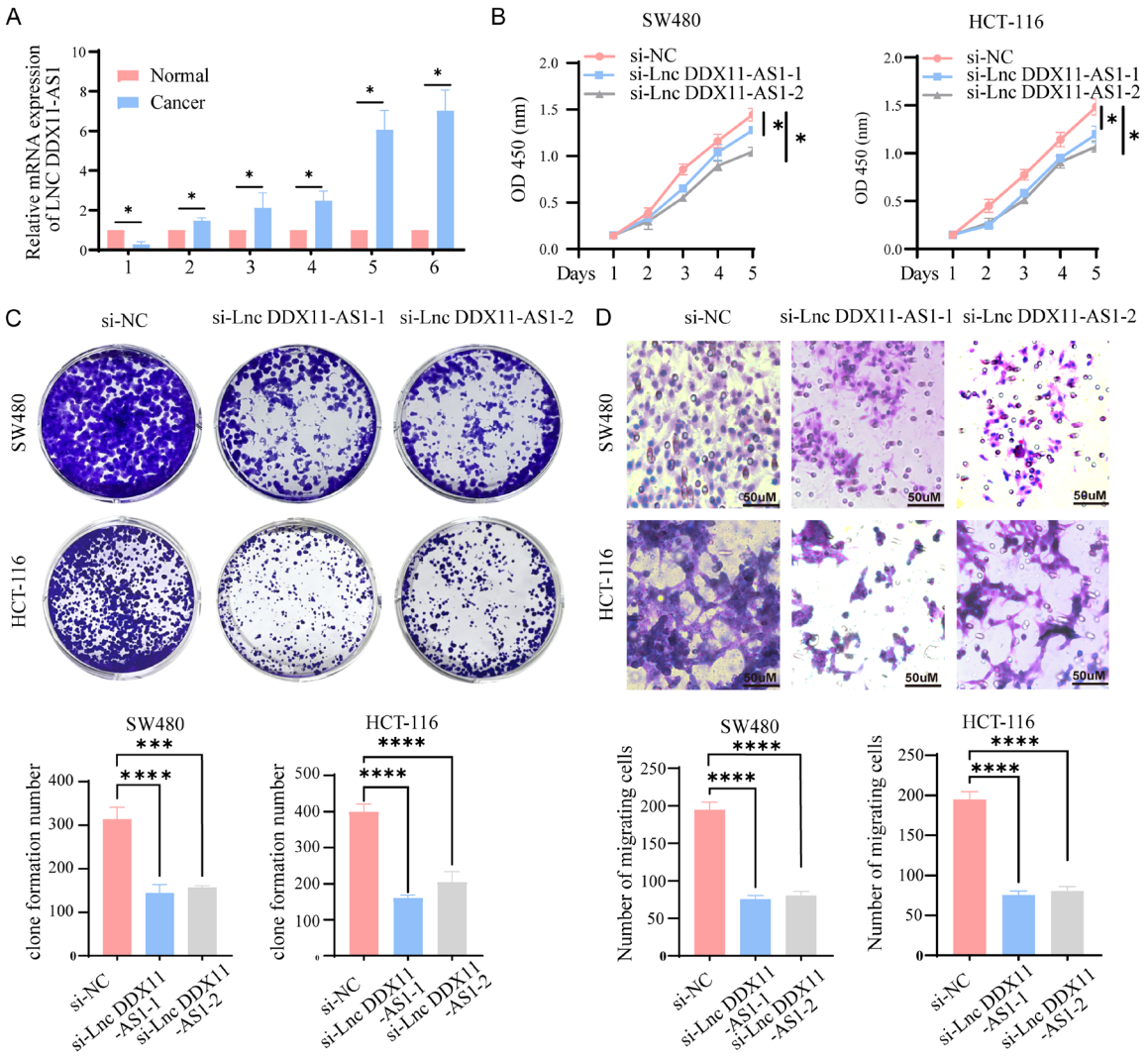

Figure 1. Expression of DDX11-AS1 in colorectal cancer tissues and its impact on cell proliferation and migration. A. qRT-PCR analysis of DDX11-AS1 mRNA expression in 10 pairs of colorectal cancer tissues. Results show significant upregulation of DDX11-AS1 in cancerous tissues. Statistical analysis was performed using independent samples t-test. B. Transfection of interference fragments of DDX11-AS1 in colorectal cancer cell lines SW480 and HCT116, with proliferation assessed by CCK8 assay. Statistical analysis was performed using repeated measures ANOVA. C. Colony formation assay results indicating a significant decrease in the proliferation of SW480 and HCT116 cells following DDX11-AS1 knockdown. One-way ANOVA was used for statistical analysis. D. Transwell migration assay demonstrating a significant reduction in the migratory ability of colorectal cancer cells post-DDX11-AS1 interference. One-way ANOVA was used for statistical analysis. *P<0.05, ***P<0.001, ****P<0.0001.

cgi-bin/emboss/getorf) suggested the capability of DDX11-AS1 to translate a peptide. Constructs ORF-WT-3*flag and ORF-MUT-3*flag were transfected into HCT116 and SW480 cells, and the expression of the ORF was detected by Western blot and immunofluorescence assays, confirming the translation of an 89-amino acid peptide, DDX11-AS1-ORF. This finding indicates that DDX11-AS1 not only acts as an lncRNA but may also contribute to colorectal cancer progression through its encoded peptide (**Figure 3A** and **3B**).

Functionality of peptide DDX11-AS1-ORF

Following DDX11-AS1 interference and subsequent overexpression of DDX11-AS1-ORF (**Figure 4A**) in HCT116 and SW480 cells showed that DDX11-AS1-ORF independently promoted the proliferation of colorectal cancer cells, as evidenced by CCK8 and colony formation

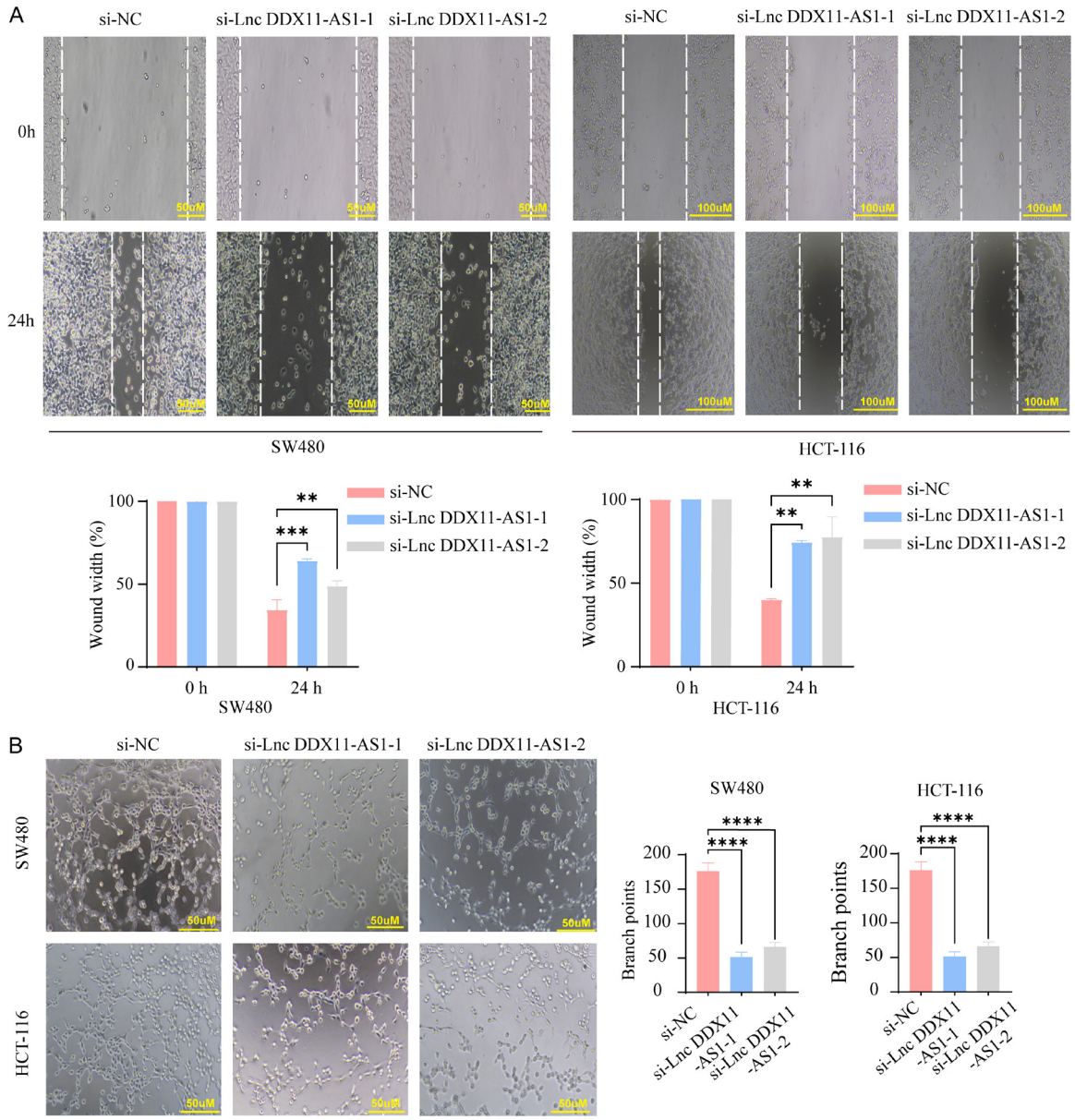

Figure 2. Effects of DDX11-AS1 on migration and angiogenesis in colorectal cancer cells. A. Wound healing assay results showing a significant reduction in the migratory ability of colorectal cancer cells following DDX11-AS1 interference. One-way ANOVA was used for statistical analysis. B. In vitro tube formation assay indicating that DDX11-AS1 interference inhibited capillary tube formation in human umbilical vein endothelial cells (HUVECs). Statistical analysis was performed using one-way ANOVA followed by Dunnett's test. **P<0.01, ***P<0.001, ****P<0.0001.

assays (**Figure 4B** and **4C**). Further, Transwell migration and wound healing assays demonstrated enhanced migratory abilities of cancer cells independent of DDX11-AS1 (**Figures 4D** and **5A**). In vitro tube formation assays indicated that DDX11-AS1-ORF independently promoted capillary tube formation in HUVECs (**Figure 5B**), highlighting its role in angiogenesis. Similar to DDX11-AS1, the peptide DDX11-AS1-ORF independently enhances cell proliferation, migration, and angiogenesis in colorectal cancer cells.

Activation of the p38-MAPK pathway by peptide DDX11-AS1-ORF through VEGFA

Preliminary analysis in the GEPIA database indicated an association between DDX11-AS1 and VEGFA, but not with VEGFB or VEGFC (Supplementary Figure 2). The effects of

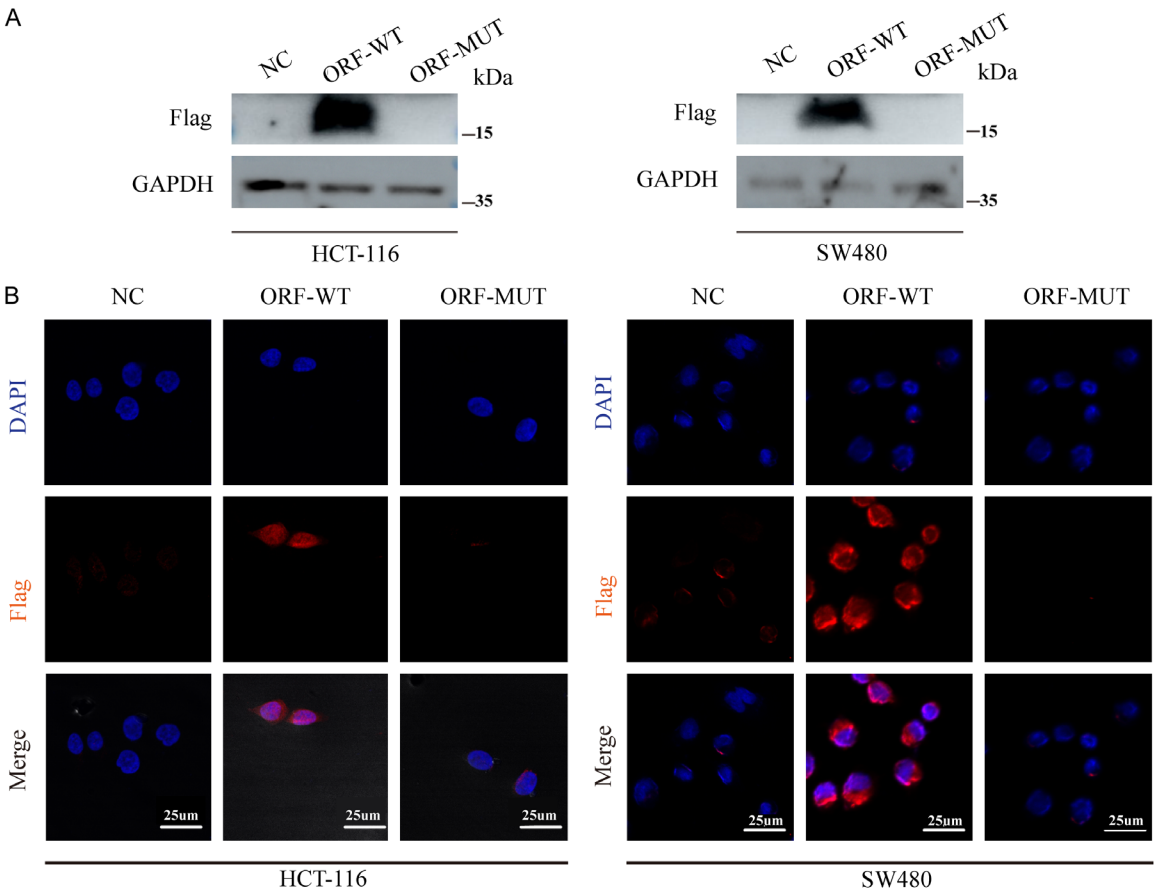

Figure 3. Verification of peptide DDX11-AS1-ORF translated from DDX11-AS1. A. Western blot analysis to detect whether DDX11-AS1-ORF can be translated into a peptide. Results confirm the translation of an 89 amino acid peptide, DDX11-AS1-ORF. B. Immunofluorescence experiments further verifying the expression of DDX11-AS1-ORF in HCT116 and SW480 cells. Results demonstrate the translation of peptide DDX11-AS1-ORF.

DDX11-AS1-ORF on VEGFA were assessed through qRT-PCR and western blot experiments. After overexpressing the DDX11-AS1-ORF plasmid, qRT-PCR analysis showed no statistically significant difference in VEGFA mRNA expression between the DDX11-AS1-ORF overexpression group and the control group (Supplementary Figure 3). However, western blot results demonstrated that VEGFA protein expression was upregulated following DDX11-AS1-ORF overexpression (**Figure 6A**). These results suggest that DDX11-AS1-ORF may primarily regulate VEGFA at the translational or post-translational level. Further investigation of the pathogenic mechanisms of DDX11-AS1-ORF, derived from DDX11-AS1, involved GSEA analysis of colorectal cancer TCGA samples, which indicated a positive correlation of high DDX11-AS1 expression with enrichment in the p38-MAPK and PI3K pathways (Supplementary Figure 4). Western blot analysis revealed significant activation of the p38-MAPK pathway by DDX11-AS1-ORF (**Figure 6B**). This suggests that DDX11-AS1-ORF may exert its oncogenic effects in colorectal cancer through the p38-MAPK pathway. Interference with VEGFA expression post-transfection of DDX11-AS1-ORF plasmid reduced the activation of the p38-MAPK pathway (**Figure 6C**).

Functionality of peptide DDX11-AS1-ORF through the p38-MAPK pathway

Functionality tests further validated the oncogenic role of DDX11-AS1-ORF mediated through the p38-MAPK pathway. Inhibition of the p38-MAPK pathway using the inhibitor SB203580 showed a marked decrease in the proliferation and migration of colorectal cancer cells, as evidenced by CCK8, colony formation, Transwell,

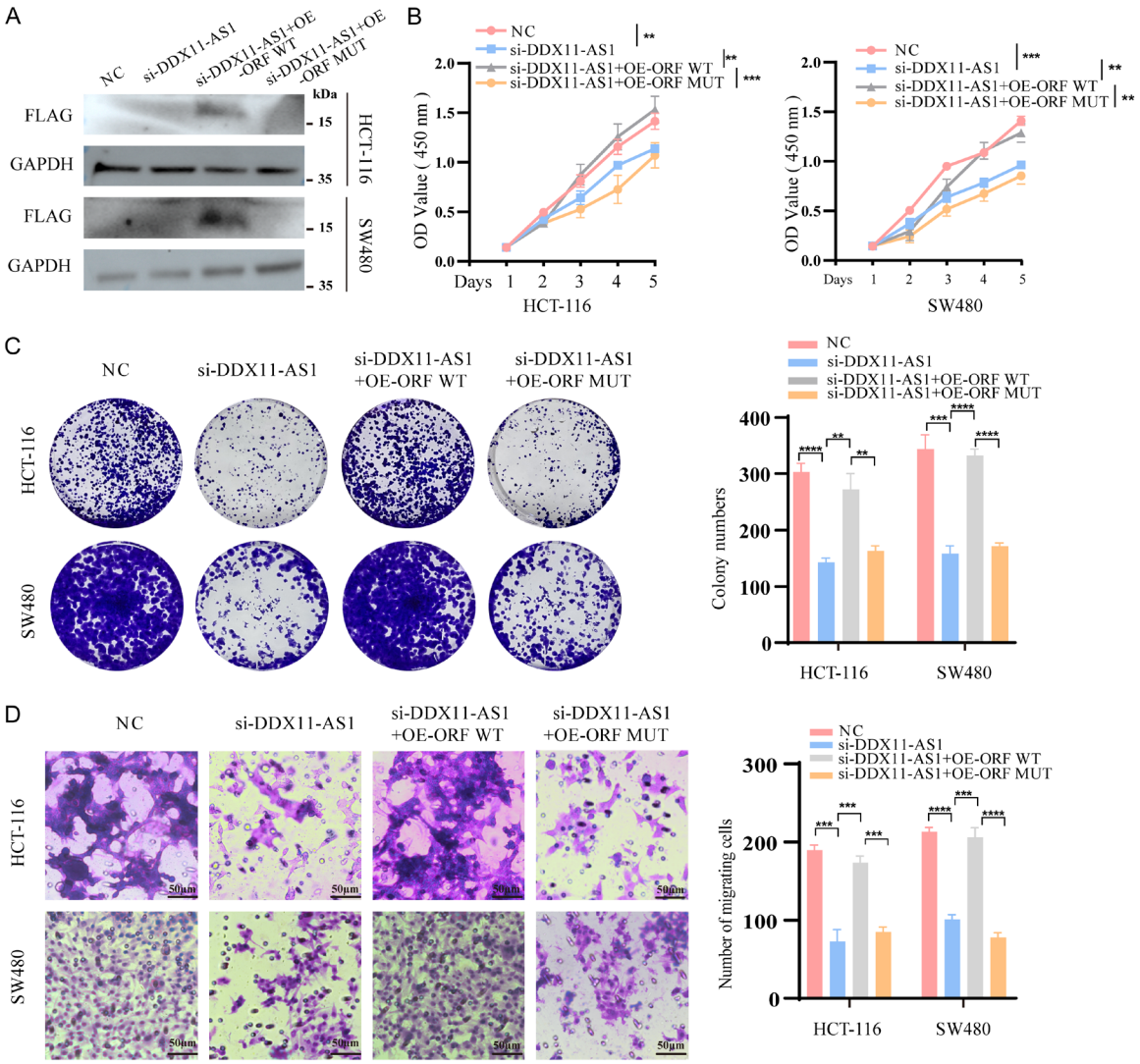

Figure 4. Functional validation of peptide DDX11-AS1-ORF. A. Overexpression of DDX11-AS1-ORF following interference of DDX11-AS1. Western blot analysis performed to verify protein expression of DDX11-AS1-ORF. B. CCK8 assay to assess the proliferative capability of DDX11-AS1-ORF in colorectal cancer cells HCT116 and SW480. C. Colony formation assay confirming the impact of DDX11-AS1-ORF on the proliferation of colorectal cancer cells. D. Transwell migration assay evaluating the influence of DDX11-AS1-ORF on the migratory ability of colorectal cancer cells. For repeated data measured at multiple time points from the same group of subjects, use Repeated Measures ANOVA for analysis, Statistical analysis for other comparisons between groups was performed using one-way ANOVA followed by Dunnett's test. **P<0.01, ***P<0.001, ****P<0.0001.

and wound healing assays (**Figure 6D-G**). Tube formation assays also demonstrated diminished angiogenic capabilities following p38-MAPK pathway inhibition (**Figure 6H**). These results confirm that DDX11-AS1-ORF promotes colorectal cancer progression by activating the p38-MAPK pathway via VEGFA.

Discussion

Colorectal cancer (CRC) remains a major global health challenge, ranking third in terms of incidence and second in mortality among all cancers worldwide [14]. Despite advances in screening techniques and improved therapeutic strategies, the prognosis for CRC patients, especially those with metastatic disease, remains poor [15]. The complexity of tumor biology and the heterogeneity of the disease contribute significantly to treatment resistance and relapse [16]. Therefore, understanding the molecular mechanisms underlying CRC progression is critical for developing novel therapeutic targets [17].

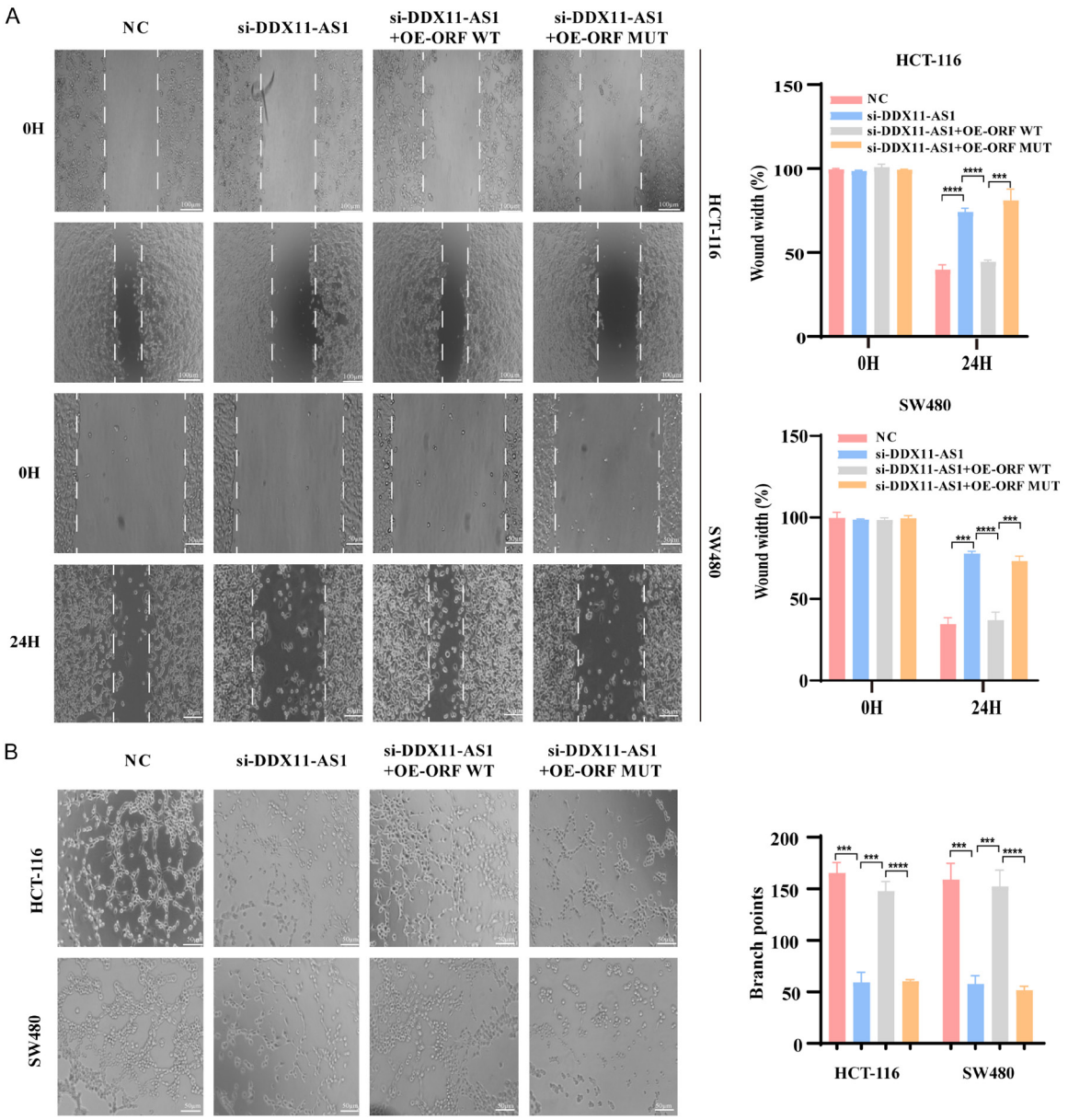

Figure 5. Impact of DDX11-AS1-ORF on migration and angiogenesis in colorectal cancer cells. A. Wound healing assay verifying the effect of DDX11-AS1-ORF on the migratory ability of colorectal cancer cells HCT116 and SW480. Statistical analysis was performed using repeated measures ANOVA. B. In vitro tube formation assay assessing whether DDX11-AS1-ORF can independently promote capillary tube formation in human umbilical vein endothelial cells (HUVECs). One-way ANOVA followed by Dunnett's test was used for statistical analysis. ***P<0.001, ****P<0.0001.

Our findings demonstrate that the long noncoding RNA (lncRNA) DDX11 antisense RNA 1 (DDX11-AS1) is upregulated in colorectal cancer tissues and cell lines, indicating its potential role in tumorigenesis. Functional assays revealed that DDX11-AS1 enhances CRC cell proliferation, migration, and angiogenesis. These results align with emerging evidence that lncRNAs can act as crucial regulators of cancer biology, impacting tumor growth, metastasis, and angiogenesis [18-22]. The promotion of endothelial tube formation by DDX11-AS1 implicates it in angiogenic processes, which are essential for tumor growth and metastasis.

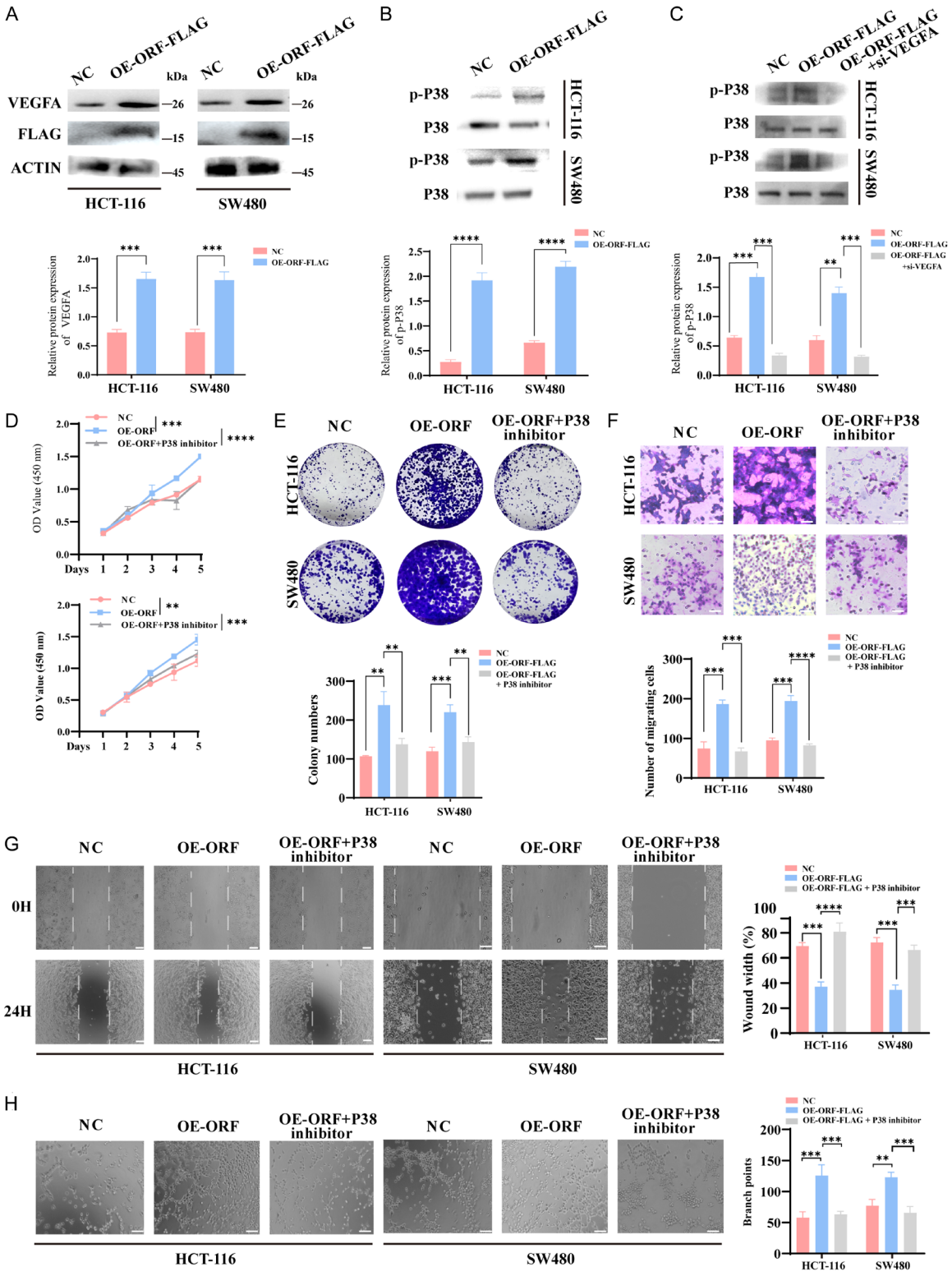

Figure 6. Oncogenic activation of the p38-MAPK pathway by peptide DDX11-AS1-ORF via VEGFA. A. Western blot analysis of VEGFA protein expression following overexpression of DDX11-AS1-ORF. Statistical analysis was performed using independent samples t-test. B. Western blot analysis evaluating the activation of p38-MAPK and PI3K pathways by DDX11-AS1-ORF. Independent samples t-test was used for statistical analysis. C. Post-transfection of DDX11-AS1-ORF plasmid and interference with VEGFA expression, Western blot analysis assessing the impact on p38-MAPK pathway activation. Statistical analysis was performed using one-way ANOVA followed by Dunnett's test.

D. CCK8 assay evaluating the proliferation of colorectal cancer cells following inhibition of the p38-MAPK pathway using the inhibitor SB203580. Statistical analysis was performed using repeated measures ANOVA. E. Colony formation assay showing that inhibition of the p38-MAPK pathway reduces the proliferative effect of DDX11-AS1-ORF on colorectal cancer cells. One-way ANOVA was used for statistical analysis. F. Transwell migration assay examining the effect of DDX11-AS1-ORF on colorectal cancer cell migration following p38-MAPK pathway inhibition. One-way ANOVA was used for statistical analysis. G. Wound healing assay further confirming the impact of DDX11-AS1-ORF on the migratory ability of colorectal cancer cells post-p38-MAPK pathway inhibition. Statistical analysis was performed using repeated measures ANOVA. H. Tube formation assay indicating that inhibition of the p38-MAPK pathway reduces the angiogenic capabilities of DDX11-AS1-ORF in human umbilical vein endothelial cells (HUVECs). Statistical analysis was performed using one-way ANOVA followed by Dunnett's test. **P<0.01, ***P<0.001, ****P<0.0001.

These findings suggest that targeting DDX11-AS1 could be a promising strategy to curb CRC progression.

The discovery of the translated peptide DDX11 Antisense RNA 1 - Open Reading Frame (DDX11AS1-ORF) from the lncRNA DDX11-AS1 is a significant advancement in understanding the complexities of non-coding RNA functions. Our study demonstrates that DDX11-AS1-ORF can independently promote the proliferation and migration of colorectal cancer cells. Notably, DDX11-AS1-ORF enhances the angiogenic capabilities of human umbilical vein endothelial cells (HUVECs), suggesting its crucial role in tumor angiogenesis. Gene set enrichment analysis (GSEA) of colorectal cancer TCGA samples showed that DDX11-AS1 expression correlates with p38 mitogen-activated protein kinase (p38-MAPK) and Phosphoinositide 3-Kinase (PI3K) pathway activation. Western blot analysis showed that DDX11-AS1-ORF significantly activates the p38-MAPK signaling pathway, indicating that DDX11-AS1-ORF may promote the development of CRC through this pathway. In further experiments, we explored the relationship between DDX11-AS1-ORF and Vascular Endothelial Growth Factor A (VEGFA). Analysis using the GEPIA database indicated a correlation between DDX11-AS1 and VEGFA, implying that VEGFA may be a critical mediator of DDX11-AS1-ORF's function. By overexpressing DDX11-AS1-ORF, we found that VEGFA expression simultaneously increased. Furthermore, Western blot experiments confirmed that upregulated VEGFA expression enhanced the activity of the p38-MAPK pathway. When we used specific small interfering RNA (siRNA) to knock down VEGFA expression, the ability of DDX11-AS1-ORF to activate the p38-MAPK pathway was inhibited, further confirming the pivotal role of VEGFA in DDX11-AS1-ORF-mediated activation of the p38-MAPK pathway. To gain a deeper understanding of the function of DDX11-AS1-ORF through the p38-MAPK pathway, we conducted experiments using the p38-MAPK pathway inhibitor SB203580. The results showed that inhibition of the p38-MAPK pathway significantly attenuated the promotion of CRC cell proliferation and migration by DDX11-AS1-ORF. Additionally, tube formation assay results indicated that the angiogenic capability was markedly reduced following disruption of the p38-MAPK pathway. These experimental results indicate that DDX11-AS1-ORF exerts a protumorigenic effect in CRC by activating the p38-MAPK pathway via VEGFA, providing a scientific basis for developing therapeutic strategies targeting this novel protein in the future.

In conclusion, our study reveals that the peptide DDX11-AS1-ORF, derived from the lncRNA DDX11-AS1, acts as a potent oncogenic factor in colorectal cancer by promoting cell proliferation, migration, and angiogenesis through the activation of the VEGFA-p38-MAPK signaling axis. These findings underscore the potential of DDX11-AS1-ORF as a target for therapeutic strategies aimed at disrupting these pathways. The ability to modulate such a pivotal mechanism opens new avenues for therapeutic interventions in colorectal cancer, potentially improving outcomes for patients suffering from this challenging disease.

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Disclosure of conflict of interest

None.

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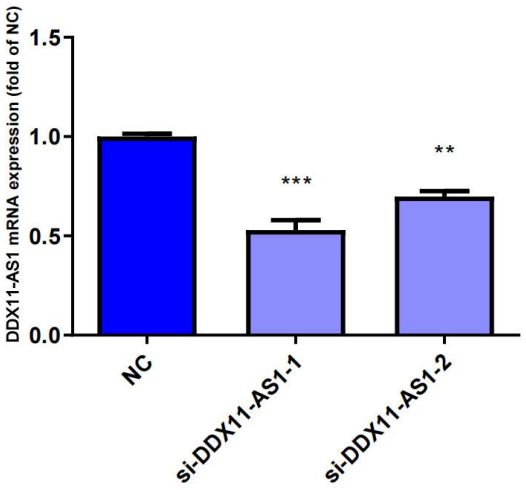
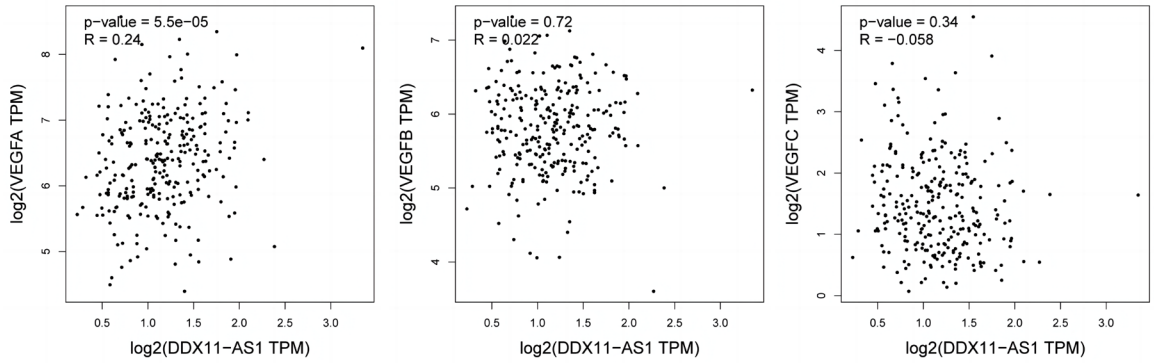
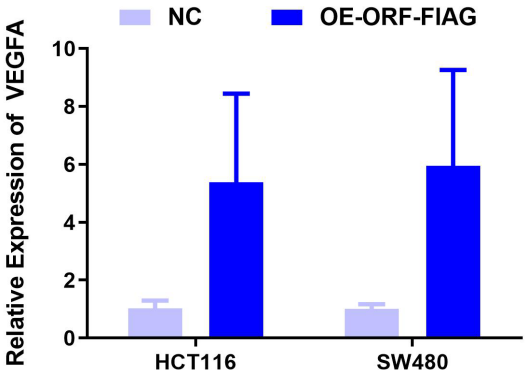


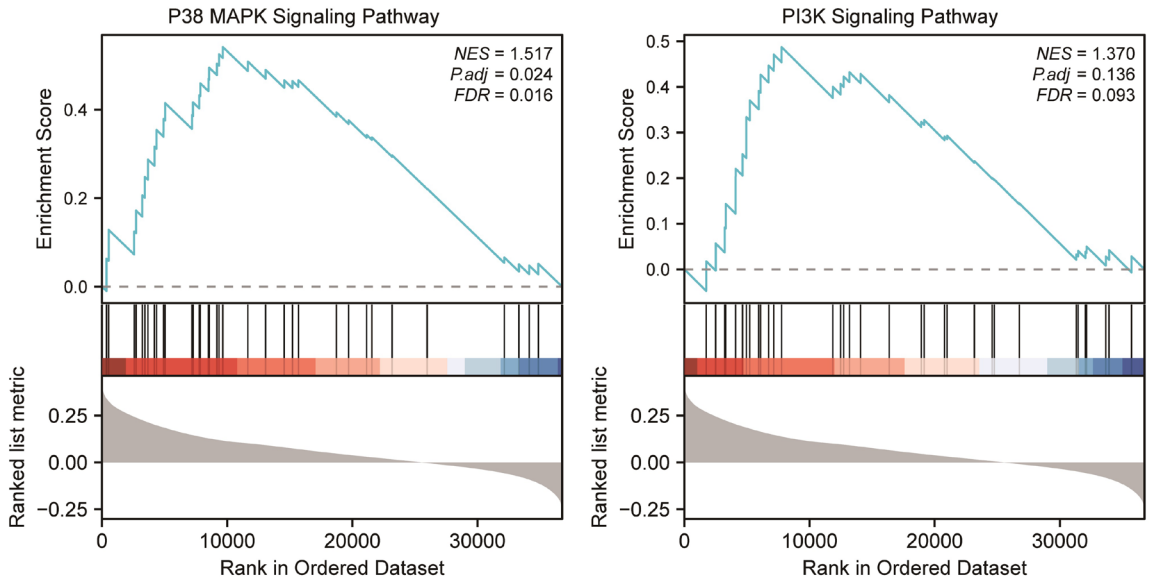
Supplementary Figure 1. Transfection of interference fragments (si-DDX11-AS1-1 and si-DDX11-AS1-2) in colorectal cancer cell lines SW480 and HCT116, with qRT-PCR results demonstrating significant reduction in DDX11-AS1 expression.



Supplementary Figure 2. Correlation analysis between DDX11-AS1 and VEGFA, VEGFB, VEGFC in the GEPIA database.



Supplementary Figure 3. qRT-PCR analysis VEGFA mRNA expression between the DDX11-AS1-ORF overexpression group and the control group.



Supplementary Figure 4. GSEA analysis showing enrichment of DDX11-AS1 high expression in p38-MAPK and PI3K pathways.