miR-627-5p inhibits malignant progression of cervical cancer by targeting ANGPTL4

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ABSTRACT

In recent years, accumulating evidence has highlighted the critical role of miR-627-5p in the occurrence and progression of various cancers. However, its specific role and mechanism in cervical cancer (CC) remain unclear. This study aimed to elucidate the mechanism by which miR-627-5p inhibits the malignant progression of CC and assess its potential clinical implications. In C33A cells, the mRNA expression levels of ANGPTL4 and miR-627-5p were analyzed using qRT-PCR. The miR-627-5p mimics and their control (miR-NC) were transfected into C33A cells to determine whether miR-627-5p directly regulates ANGPTL4 expression. A comprehensive suite of assays, including CCK-8, migration, transwell, flow cytometry, and Western blotting, was conducted to evaluate how miR-627-5p modulates the malignant biological behavior of CC cells. Rescue experiments were performed by overexpressing ANGPTL4. In C33A cells, miR-627-5p expression was reduced, whereas ANGPTL4 expression was elevated. Further analysis confirmed that miR-627-5p negatively regulates ANGPTL4 by directly targeting its 3'-UTR. Functional assays demonstrated that miR-627-5p inhibits proliferation, invasion, migration, and epithelial-mesenchymal transition (EMT) while promoting apoptosis and S-phase arrest in C33A cells, effects that were reversed by ANGPTL4 overexpression. These findings highlight the potential of miR-627-5p as both a biomarker and a therapeutic target for CC. By inhibiting EMT and regulating ANGPTL4 expression, miR-627-5p may provide a novel avenue for improving therapeutic strategies, particularly in advanced or metastatic CC. Moreover, miRNA-based therapies, supported by advanced delivery systems such as nanoparticle carriers, could enhance the stability and precision of miR-627-5p applications. This study lays the groundwork for future research integrating miR-627-5p into precision medicine approaches for CC treatment.

Key words: miR-627-5p; epithelial-mesenchymal transition; cervical cancer; ANGPTL4.

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Introduction

Cervical cancer (CC) is one of the most common gynecological malignancies worldwide,[1,2] causing an estimated 311,000 deaths in 2018 and ranking as the fourth leading cause of cancer-related mortality.[3] Despite advances in screening and vaccination programs, the clinical outcomes of CC remain highly variable and difficult to predict.[4] Drug resistance, immune escape, and the invasive and migratory behavior of tumor cells are recognized as major contributors to poor prognosis, high recurrence rates, and increased mortality in CC patients.[5] This underscores the urgent need to identify novel therapeutic targets and elucidate the molecular mechanisms underlying CC progression.

MicroRNAs (miRNAs), small non-coding RNAs that post-transcriptionally regulate gene expression, have emerged as crucial regulators in cancer biology and are increasingly being recognized as tools in cancer diagnostics and therapeutics.[6] By binding to the 3'-UTR of their target gene mRNA, miRNAs can inhibit translation or induce mRNA degradation, thereby influencing a variety of cellular processes.[7]

Recent studies have demonstrated that miR-627-5p plays a significant role in inhibiting the proliferation, invasion, and epithelial-mesenchymal transition (EMT) of cancer cells, while promoting apoptosis in various malignancies, including CC, oral squamous cell carcinoma, liver cancer, and glioma.[8-12] Furthermore, miR-627-5p has been identified as a potential biomarker for colorectal cancer and has been shown to suppress liver cancer cell proliferation by targeting BCL3.[13,14] Despite these findings, the specific mechanisms through which miR-627-5p influences CC progression remain largely unexplored.

Angiopoietin-like protein 4 (ANGPTL4), a secretory glycoprotein expressed in various tissues such as the liver, heart, and adipose tissue, has been implicated in diverse physiological and pathological processes, including protein transport and apoptosis. Its structural similarity to angiopoietins enables ANGPTL4 to regulate cell membrane localization and degrade misfolded proteins.[15] In cancer biology, ANGPTL4 is known to promote tumor progression through multiple pathways. For instance, ANGPTL4 activates the ERK1/2 pathway to facilitate ovarian cancer progression and enhances angiogenesis and invasion in head and neck squamous cell carcinoma.[15-17] These findings suggest that ANGPTL4 plays a multifaceted role in tumorigenesis and could serve as a potential therapeutic target.

Using bioinformatics tools such as Starbase, we identified binding sites between miR-627-5p and ANGPTL4, suggesting a potential regulatory relationship. However, whether miR-627-5p can suppress the malignant progression of CC cells by targeting ANGPTL4 remains to be fully elucidated. This study aims to investigate the interaction between miR-627-5p and ANGPTL4 and to explore their roles in modulating the biological behavior of CC cells, thereby providing insights into novel therapeutic strategies for CC.

Materials and Methods

Cell culture

Human CC cells (C33A) and normal human cervical epithelial cells (H8) were obtained from Wuhan Punosai Life Tech Co., Ltd. (Wuhan, China). Cells were cultured in a medium containing 10% fetal bovine serum (FBS) and maintained at 37°C with 5% CO_2.

Cell transfection

miR-NC and miR-627-5p mimics were purchased from Guangzhou Ruibo Biotechnology Co., Ltd. (Guangzhou, China). Overexpression plasmids for ANGPTL4 (oe-ANGPTL4) and empty vectors (pLV-Puro) were synthesized by Suzhou Jima Gene Co., Ltd. and packaged into lentivirus. Cells were transfected using Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. The final concentration of miR-627-5p mimics was 50 nM, and cells were incubated for 48 h post-transfection before analysis. Transfection efficiency was confirmed by qRT-PCR.

Assay for dual luciferase reporter (DLR)

Wild-type (PmirGLO-ANGPTL4-WT) and mutant (PmirGLO-ANGPTL4-MUT) dual-luciferase reporter vectors were constructed by Shanghai Shengong Bioengineering Company (Shanghai, China). miR-NC or miR-627-5p mimics (50 nM) were co-transfected into cells along with luciferase reporter vectors. Cells were incubated for 48 h, and luciferase activity was measured using a Fluoroskan FL microplate fluorescence analyzer (Thermo Fisher, Waltham, MA, USA) following the manufacturer's protocol.

CCK-8 experiment

Cells treated with miR-627-5p mimics or controls were seeded in 96-well plates and incubated for 24 h. The CCK-8 reagent (10 µL/well) was added and incubated at 37°C for 1 h. Absorbance was measured at 450 nm using a microplate reader (Rayto, Guangzhou, China).

Clone formation experiment

After transfection, cells were seeded into 6-well plates at a density of 200 cells/well and cultured for 10-14 days. Colonies were fixed with 4% paraformaldehyde for 20 min, stained with 0.2% crystal violet for 5 min, washed with tap water, and air-dried. The number of colonies was counted manually.

Cell migration experiment

Cell migration was assessed using a wound-healing assay. A 200 µL pipette tip was used to create a scratch in a confluent cell monolayer. The debris was washed away with serum-free DMEM. Images of the scratch were captured at 0 and 24 h under a microscope (Shanghai Optical Instrument Factory 1, Shanghai, China). The migration distance was measured to evaluate wound closure.

Transwell invasion experiment

The upper chamber of Transwell inserts was coated with Matrigel to assess invasion. Cells (5×10^4) were suspended in serum-free DMEM and seeded into the upper chamber. The lower chamber was filled with 0.6 mL DMEM containing 50% FBS. After 24 h of incubation, non-invaded cells were removed, and invaded cells were stained with 0.2% crystal violet. Representative images were captured, and the number of invaded cells was counted.

Cell apoptosis

Apoptosis was measured using a flow cytometer with Annexin V-FITC and PI staining. Transfected cells were collected, washed with cold PBS, and resuspended in 1× Annexin V Binding Solution. Annexin V-FITC and PI were added and incubated for 15 min at room temperature in the dark. Stained cells were analyzed using a flow cytometer (Invitrogen).

Cell cycle analysis

Transfected cells were fixed with 70% ethanol at 4°C for 2 h. After washing, cells were stained with propidium iodide (PI) containing RNase for 30 min at 37°C. Cell cycle distribution was analyzed by flow cytometer.

qRT-PCR

Total RNA was extracted using TRIzol reagent, and cDNA was synthesized using a reverse transcription kit (Vazyme, Nanjing, China). Gene expression levels were quantified using qRT-PCR with GAPDH as the internal control. Primer sequences are provided in Table 1. Relative expression levels were calculated using the $2^{-\Delta\Delta Ct}$ method.

Western blot

Total protein was extracted using RIPA lysis buffer supplemented with protease inhibitors. Equal amounts of protein were separated by SDS-PAGE and transferred to PVDF membranes. Membranes were blocked and incubated overnight at 4°C with primary antibodies (Table 2), followed by HRP-conjugated secondary antibodies for 1 h at room temperature. Protein bands were visualized using enhanced chemiluminescence (ECL) on a JP-K6000 imaging system (Shanghai Jiapeng, Shanghai, China).

Statistical analysis

Data were analyzed using GraphPad Prism 9 and presented as mean ± SD. Differences between groups were assessed using *t*-tests or one-way ANOVA. Statistical significance was defined as $p<0.05$.

Results

MiR-627-5p level and ANGPTL4 interaction in C33A cells

To understand the expression of miR-627-5p and ANGPTL4 in cancer cells, we measured the mRNA expression of miR-627-5p and ANGPTL4 in C33A and H8. The results (Figure 1A-B) showed that compared with H8, the level of miR-627-5p mRNA in C33A cells was reduced ($p<0.01$), while the level of ANGPTL4 mRNA was markedly increased ($p<0.001$). To investigate the interaction between miR-627-5p and ANGPTL4, TargetScan was used to predict the binding sites of the two (Figure 1C). The DLR method was applied to verify these predictions. MiR-627-5p mimics were found to inhibit the luciferase activity of WT-ANGPTL4 in C33A cells ($p<0.001$) but had no effect on the luciferase activity of MUT-ANGPTL4 (Figure 1C). These findings suggested that miR-627-5p and ANGPTL4 have a negative regulatory relationship. To further confirm this relationship, we overexpressed miR-627-5p in C33A cells. As shown in Figure 1D, the mRNA levels of miR-627-5p did not differ between the miR-NC mimic and the control group ($p>0.05$). However, the miR-627-5p mimic group exhibited increased miR-627-5p mRNA expression compared to the miR-NC mimic group ($p<0.01$), indicating successful cell transfection. Additionally, the mRNA and protein expression levels of ANGPTL4 were lower in the miR-627-5p mimic group than in the miR-NC mimic group (Figure 1 E-F, $p<0.01$), confirming a negative regulatory relationship between miR-627-5p and ANGPTL4.

MiR-627-5p impact on CC cell malignant development

MiR-627-5p mimics, and miR-NC mimics were transfected into cells to investigate the effects of miR-627-5p on the malignant properties of cells. The results (Figure 2 A-D) showed that miR-627-5p mimics inhibited the proliferation, migration, and invasion of C33A cells ($p<0.05$). Furthermore, the miR-627-5p mimic group exhibited lower levels of N-cadherin and vimentin protein expression and higher levels of E-cadherin protein expression compared to the miR-NC mimic group (Figure 2E, $p<0.01$). These findings suggest that miR-627-5p mimics inhibit EMT and the malignant progression of cells.

Impact of miR-627-5p on CC cell cycle and apoptosis

Apoptosis was assessed using flow cytometry. The results (Figure 3A) showed that miR-627-5p mimics increased the apoptosis rate ($p<0.001$). Moreover, the expression of Bcl-2 protein was decreased, while Bax protein expression was increased, further supporting that miR-627-5p promotes apoptosis. Cell cycle analysis using FC (Figure 3C) revealed that miR-627-5p mimics impaired DNA replication and induced S-phase arrest ($p<0.01$).

Table 1. Primers.

Gene		Sequences (5'-3')
ANGPTL4	F	GCCTATAGCCTGCAGCTCAC
	R	AAACCACCAGCCTCCAGAGA
GAPDH	F	AATGGGCAGCCGTTAGGAAA
	R	GCCCAATACGACCAAATCAGAG

Table 2. Protein antibody.

Antibodies	Dilution (application)	Lot	Corporation
ANGPTL4	1:800 (WB)	ab196746	Abcam (UK)
E-cadherin	1:2000 (WB)	60335-1-Ig	Abcam
N-cadherin	1:1000 (WB)	ab280375	Abcam
Vimentin	1:2000 (WB)	ab92547	Abcam
Bcl-2	1:1000 (WB)	ab194583	Abcam
Bax	1:1000 (WB)	#2772	Cell Signaling Technology (USA)
GAPDH	1:1000 (WB)	bsm-33033M	Bioss (China)
Goat Anti-Rabbit IgG H&L(HRP)	1:20000 (WB)	bs-0295G-HRP	Bioss
Goat Anti-Mouse IgG H&L(HRP)	1:20000 (WB)	bs-0296G-HRP	Bioss

MiR-627-5p controls ANGPTL4 to inhibit the growth of C33A cells

The results suggested that miR-627-5p inhibits EMT and malignant proliferation of C33A cells while promoting apoptosis and S-phase arrest, likely through the negative regulation of ANGPTL4. To verify this, ANGPTL4 was overexpressed (oe-ANGPTL4) in C33A cells. The results showed that the ANGPTL4 mRNA expression in the oe-ANGPTL4 group was higher than in the oe-NC group ($p<0.001$), counteracting the inhibitory effects of miR-627-5p mimics ($p<0.05$). Overexpression of ANGPTL4 enhanced cell viability and promoted cell invasion, migration, proliferation, and EMT (Figure 4 B-F, $p<0.05$). In comparison to the oe-ANGPTL4 group, miR-627-5p mimics+oe-ANGPTL4 inhibited ANGPTL4 mRNA expression and suppressed cell proliferation, invasion, migration, and EMT ($p<0.05$). However, compared to the miR-627-5p mimic group, ANGPTL4 mRNA expression and malignant progression were increased in the miR-627-5p mimics+oe-ANGPTL4 group ($p<0.01$). These results indicate that oe-ANGPTL4 reverses the inhibitory effects of miR-627-5p mimics on the malignant progression of C33A cells.

MiR-627-5p controls ANGPTL4 to induce apoptosis and S-phase arrest in C33A cells

The findings (Figure 5 A-C) revealed that oe-ANGPTL4 reduced the apoptosis rate, increased Bcl-2 protein expression, decreased Bax protein expression, and alleviated S-phase arrest ($p<0.05$). Conversely, miR-627-5p mimics+oe-ANGPTL4 induced apoptosis and S-phase arrest compared to the oe-ANGPTL4 group ($p<0.05$). However, miR-627-5p mimics+oe-ANGPTL4 exhibited reduced apoptosis and S-phase arrest compared to the miR-627-5p mimic group ($p<0.01$). These results demonstrate that oe-ANGPTL4 counteracts the promoting effects of miR-627-5p mimics on apoptosis and S-phase arrest in C33A cells.

Discussion

CC is a major threat to women's lives, health, and quality of life.[18] With HPV vaccination, CC screening, and colposcopic cervical tissue biopsy, an increasing number of cervical lesions are treated without progression to cancer.[19-21] However, due to large differences in population distribution and urban and rural levels of CC, 85% to 90% of cases occur in low- and middle-income countries, resulting in an annual increase in the incidence rate and mortality of CC.[22] Although the 5-year survival rate after surgery for early CC is satisfactory, the prognosis for recurrent and metastatic CC remains poor.[23] CC develops and progresses through intricate processes involving multiple variables, stages, and genes.[24] Therefore, it is critical to study the pathogenesis of CC and explore novel biomarkers and therapeutic strategies. Research has demonstrated that miRNAs play a central role in regulating various biological processes, with aberrant expression associated with cancer onset and progression. For instance, miR-627-5p targets Wnt2 to inhibit the malignant development of colorectal cancer cells.[25] In breast cancer cells, miR-627-5p limits radiation resistance.[26] Oral squamous cell carcinoma migration and proliferation are also inhibited by miR-627-5p.[8] This study found reduced expression of miR-627-5p in CC cells compared to H8 cells, consistent with previous findings. Transfection of miR-627-5p mimics confirmed that it accelerates S-phase arrest and apoptosis while inhibiting invasion, migration, proliferation, and EMT in C33A cells. We previously confirmed that miR-627-5p negatively regulates ANGPTL4 in C33A cells through bioinformatics prediction and DLR experiments. Furthermore, ANGPTL4 expression was elevated in C33A cells. Validation experiments showed that miR-627-5p mimics downregulated ANGPTL4 mRNA and protein expression, indicating a direct regulatory relationship. Rescue experiments demonstrated that

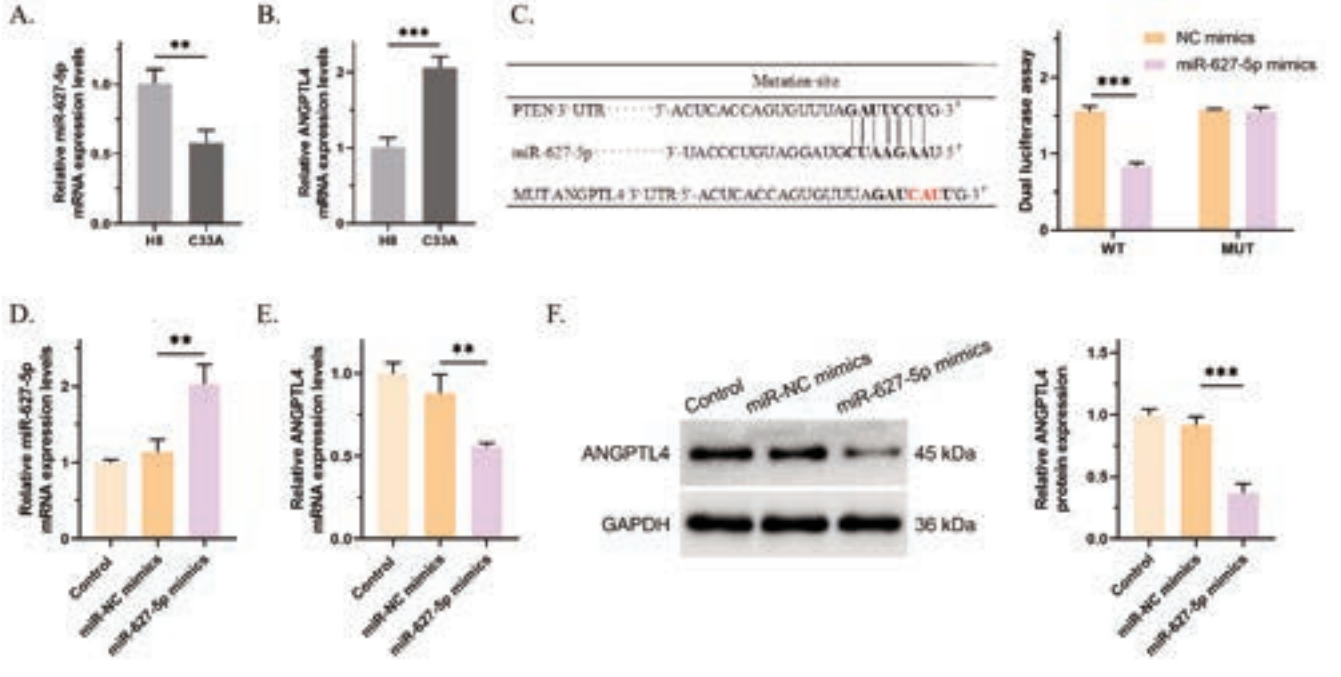

Figure 1. Expression and interaction of miR-627-5p and ANGPTL4 in C33A cells. **A,B**) qRT-PCR was used to detect the mRNA levels of miR-627-5p and ANGPTL4 in H8 and C33A cells, showing lower miR-627-5p expression and higher ANGPTL4 expression in C33A cells compared to H8 cells. **C**) DLR assays and bioinformatic analysis confirmed that miR-627-5p directly targets ANGPTL4 through binding to its 3'-UTR. **D-F**) qRT-PCR and WB were performed after transfection with miR-627-5p mimics. The results indicated that miR-627-5p mimics upregulated miR-627-5p expression while downregulating ANGPTL4 mRNA and protein levels, confirming their negative regulatory relationship in C33A cells. $^{**}p<0.01$; $^{***}p<0.001$.

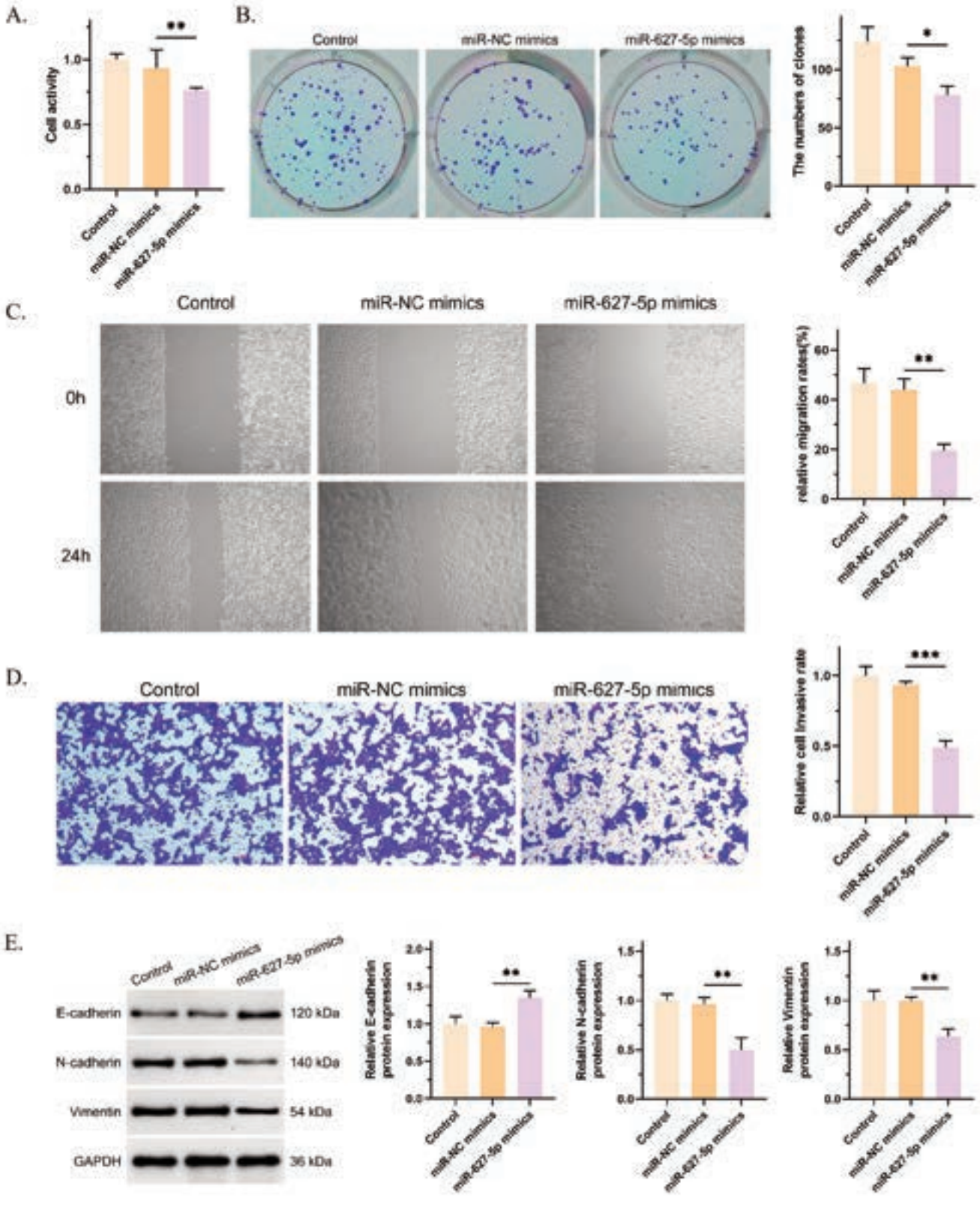

Figure 2. MiR-627-5p impact on C33A cell malignant evolvement. **A-D**) CCK-8, clonal formation, wound-healing, and Transwell assays were used to evaluate the effects of miR-627-5p mimics on C33A cell proliferation, migration, and invasion. The results showed that miR-627-5p inhibited proliferation, slowed wound healing, and reduced invasive ability in C33A cells; scale bars (50 μm) were added to all relevant images, and representative images were chosen based on reproducible outcomes across at least three independent experiments. **E**) WB analysis demonstrated that miR-627-5p mimics upregulated E-cadherin protein expression while downregulating N-cadherin and vimentin levels, indicating inhibition of EMT. *p<0.05; **p<0.01; ***p<0.001.

ANGPTL4 overexpression neutralized the inhibitory effects of miR-627-5p mimics on malignant progression and EMT while reducing apoptosis and S-phase arrest. Collectively, these findings suggest that miR-627-5p suppresses CC progression by targeting ANGPTL4. From a clinical perspective, miR-627-5p holds significant potential as both a biomarker and a therapeutic target for CC treatment. Recent reviews highlight the functional role of miRNA clusters in CC, emphasizing their potential as prognostic markers and therapeutic targets.[27] Advances in diagnostic tools, such as exosome biomarkers, provide further evidence for integrating novel molecular regulators like miR-627-5p into comprehensive diagnostic and therapeutic strategies.[28] By effectively inhibiting EMT, a key driver of tumor metastasis, miR-627-5p could mitigate cancer progression and improve patient outcomes. Additionally, targeting ANGPTL4, a critical player in tumor biology, provides an opportunity to enhance current therapeutic strategies, particularly for individuals with advanced or metastatic CC.

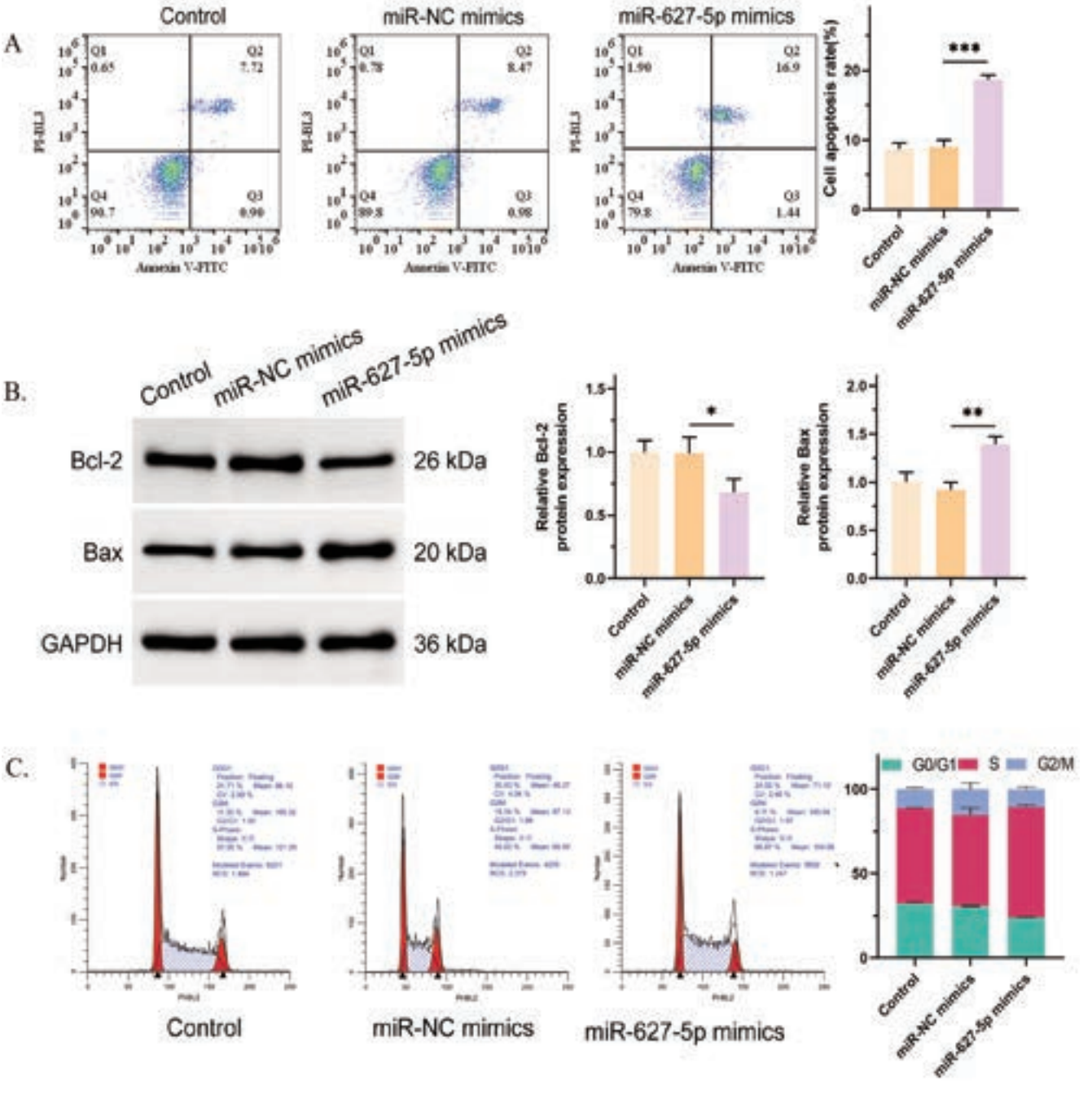

Figure 3. MiR-627-5p impact on C33A cycle and apoptosis. **A,B**) Flow cytometer and WB were used to assess apoptosis rates and apoptosis-related protein expression in C33A cells transfected with miR-627-5p mimics. miR-627-5p promoted apoptosis by upregulating Bax and downregulating Bcl-2 protein levels. **C**) Flow cytometer analysis revealed that miR-627-5p induced S-phase arrest, suggesting its role in disrupting cell cycle progression. *p<0.05; **p<0.01; ***p<0.001.

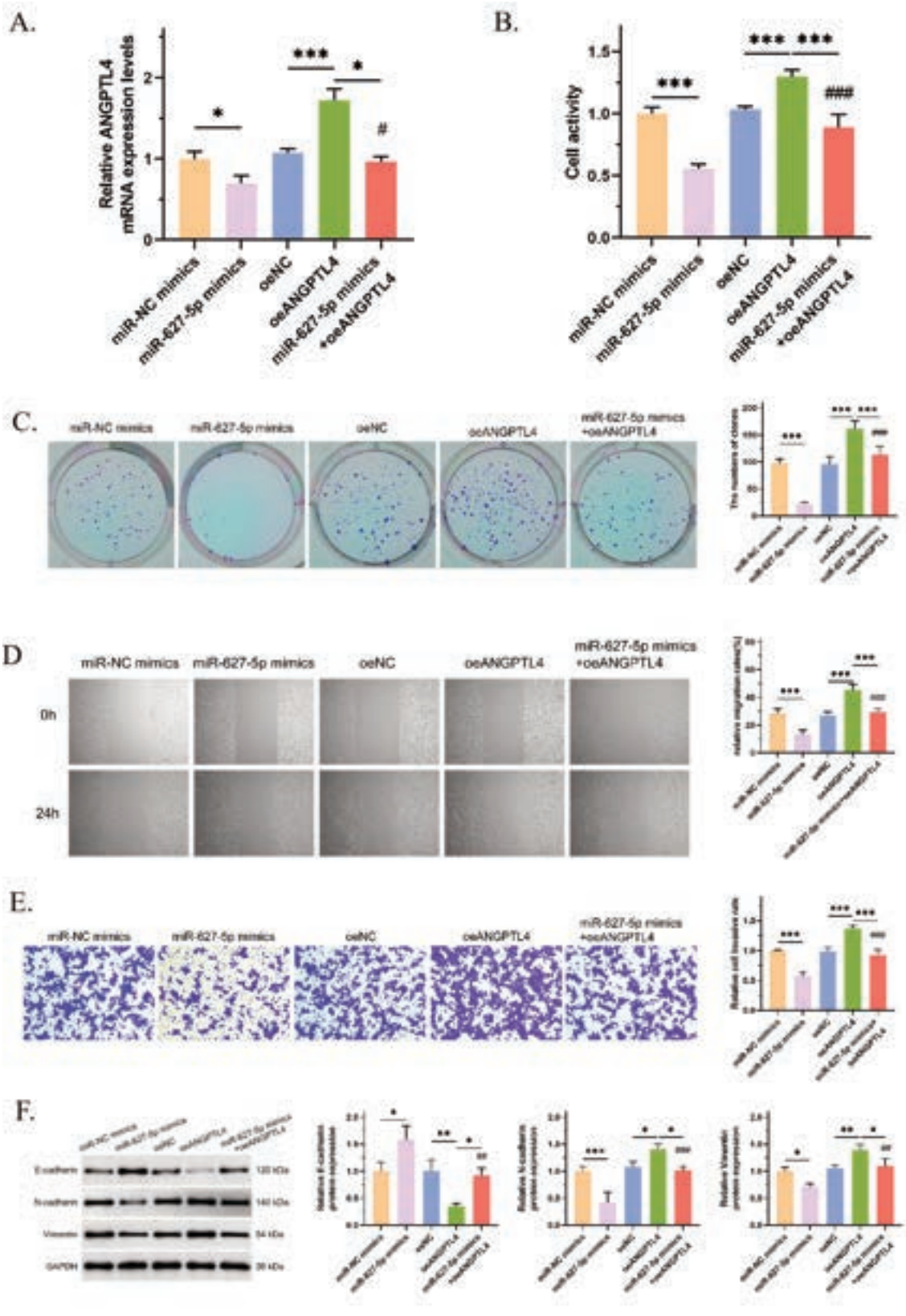

Figure 4. MiR-627-5p controls ANGPTL4 to inhibit the growth of C33A cells. **A**) qRT-PCR analysis confirmed the successful overexpression of ANGPTL4 in C33A cells transfected with oe-ANGPTL4. **B-E**) Functional assays, including CCK-8, clonal formation, wound-healing, and Transwell assays, demonstrated that ANGPTL4 overexpression counteracted the inhibitory effects of miR-627-5p mimics on cell proliferation, migration, and invasion; microscopy images now include scale bars for improved precision; selected images represent typical outcomes observed across three independent experiments, ensuring reproducibility; scale bars: 50 μm. **F**) Western blot analysis showed that ANGPTL4 overexpression restored EMT-related protein levels, reversing the effects of miR-627-5p mimics. *p<0.05; **p<0.01; ***p<0.001.

Despite its promise, translating these findings into clinical applications presents significant challenges. The instability and susceptibility of miRNAs to enzymatic degradation pose obstacles to effective delivery. Advanced delivery technologies, such as nanoparticle-based systems, have shown potential to address these issues by enhancing miRNA stability, targeting precision, and therapeutic efficacy. Moreover, ANGPTL4, as a multifaceted therapeutic target, is involved in several pathways contributing to tumor progression, necessitating thorough investigation to assess its downstream effects and off-target risks. Addressing these challenges is essential for clinical translation.

In the broader context, these findings align with the evolving paradigm of personalized medicine, which emphasizes tailored therapeutic approaches based on molecular and genetic profiling, as demonstrated by the expanding role of non-coding RNAs in gynecological tumors.[29] Ethical considerations, such as patient consent, data security, and fertility preservation in young CC patients, must also be addressed. For example, fertility preservation has been identified as a critical component of comprehensive care for female cancer patients undergoing innovative treatments, including miRNA-based therapies.[30] Regulatory frameworks and evidence-based guidelines will be necessary to integrate miR-627-5p-targeted therapies into clinical practice effectively.

In addition to delivery challenges, regulatory and clinical validation represents a crucial step for translating these findings into therapeutic applications. Rigorous preclinical studies, including *in vivo* experiments using relevant animal models, are essential to establish the safety and efficacy of miR-627-5p and ANGPTL4-targeted therapies. Ethical considerations, such as patient consent and data security in the use of innovative approaches, must also be addressed to ensure the responsible implementation of these therapies. Moreover, aspects like fertility preservation in young CC patients undergoing miRNA-based therapies need to be incorporated into clinical guidelines. These foundational studies will be instrumental in designing clinical trials and integrating these targets into precision medicine strategies for CC treatment.

One limitation of this study is the lack of *in vivo* validation to confirm the proposed mechanism. Future research will address this by developing a CC mouse model using tumor-bearing techniques. By creating a model with miR-627-5p overexpression and conducting rescue experiments, we aim to validate further that miR-627-5p inhibits the malignant progression of CC through the regulation of ANGPTL4.

In conclusion, miR-627-5p level was low in C33A cells, while ANGPTL4 expression was high. miR-627-5p can specifically inhibit ANGPTL4, thus inhibiting the malignant biological behavior of CC. A shortcoming of this study is that this mechanism has not been verified through *in vivo* experiments. In the future, a mouse model of CC will be established by bearing tumor method. Through the overexpression model mouse miR-627-5p gene and rescue experiment, it was further verified that miR-627-5p inhibited the pernicious progression of CC by targeting ANGPTL4.

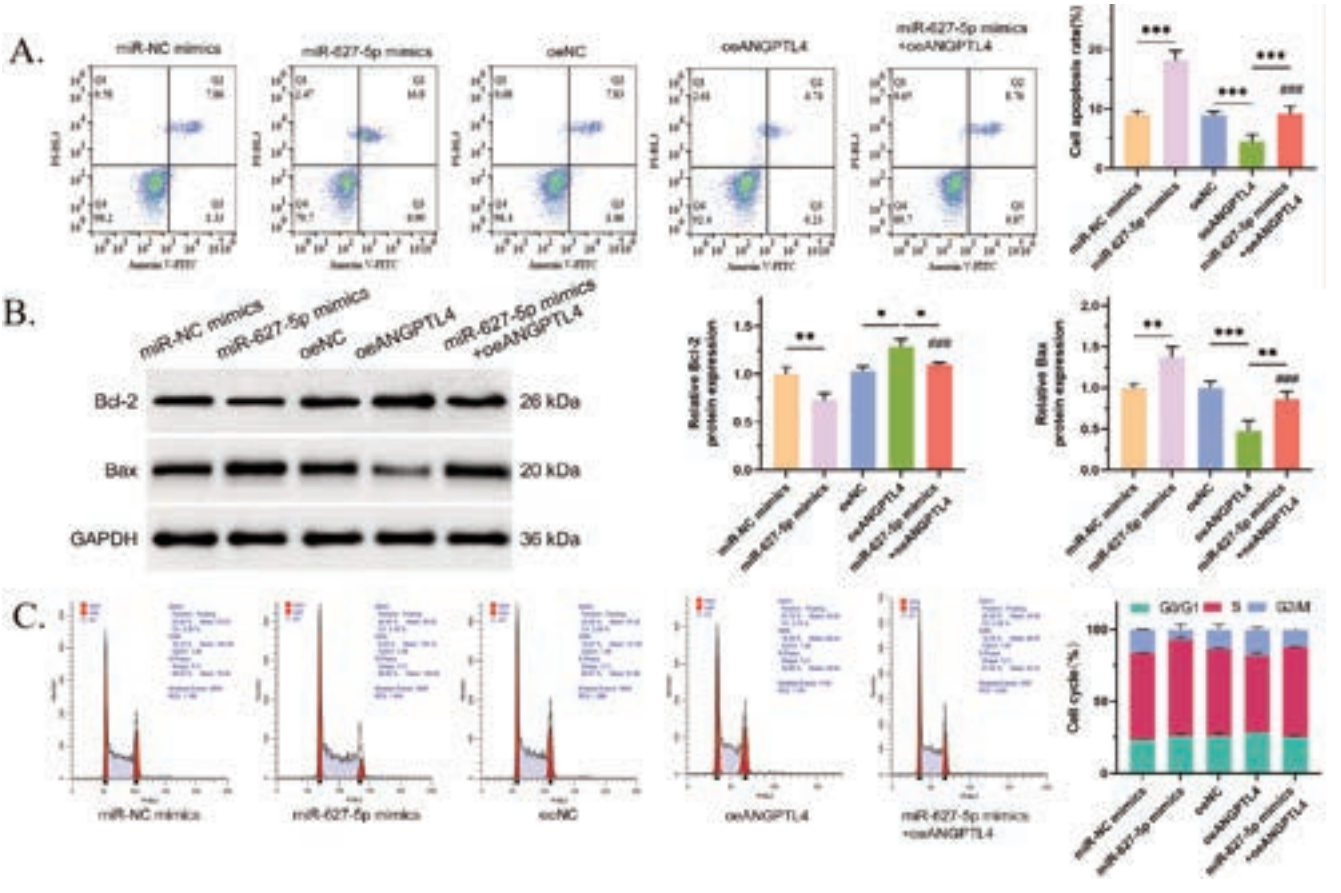

Figure 5. MiR-627-5p promotes apoptosis and S phase arrest in C33A cells by regulating ANGPTL4. **A,B**) Flow cytometer and WB showed that ANGPTL4 overexpression reduced apoptosis and S-phase arrest, counteracting the effects of miR-627-5p mimics; ANGPTL4 overexpression increased Bcl-2 levels while decreasing Bax levels, reducing apoptosis. **C**) Flow cytometer confirmed that ANGPTL4 overexpression alleviated the S-phase arrest induced by miR-627-5p, further highlighting their regulatory relationship in cervical cancer cells. *p<0.05; **p<0.01; ***p<0.001.

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