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miR-146a-5p suppresses migration and downregulates vimentin and MMP-9 expression in gastric cancer cells

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Abstract

Gastric cancer (GC) is a significant global health issue, characterized by poor prognosis due to its metastatic nature. This study investigates the role of microRNA-146a-5p (miR-146a-5p) in regulating migration and invasion of KATO III GC cells by targeting vimentin and matrix metalloproteinase-9 (MMP-9), critical mediators of epithelial–mesenchymal transition (EMT). miR-146a-5p expression was analyzed in GC cell lines, and functional assays were performed after transfection with a miR-146a-5p mimic. Results showed that miR-146a-5p expression was significantly reduced in GC cells, particularly in KATO III. Transfection with the mimic reduced cell viability, increased apoptosis, and inhibited migration, as shown by wound-healing assays. Additionally, miR-146a-5p downregulated vimentin and MMP-9 mRNA expression. These findings suggest that miR-146a-5p may influence metastatic behavior in GC cells through regulation of EMT-related genes. However, further studies, including protein-level validation and direct target confirmation, are needed. These results provide a basis for future investigation into the potential therapeutic role of miR-146a-5p in GC.

Keywords MiR-146a-5p, Gastric cancer (GC), Migration, Invasion, Vimentin, MMP-9, Epithelial-mesenchymal transition (EMT)

1 Introduction

Gastric cancer (GC) is one of the most frequent types of cancer which remains a critical international health concern, constituting the fifth most prevalent malignancy and one of the leading causes of cancer-related deaths [1]. A recent evaluation of GC patients evidenced that the prevalence of this cancer is steadily rising in youth [2]. The absence of recognizable clinical manifestations in the preliminary stages of this disease leads to delayed diagnosis and treatment [3]. Despite advances in early identification and treatment options, GC's prognosis remains poor with a low survival rate in upcoming years [4]. This is largely due to high rates of metastasis of GC cells to the other organs which is a key factor in determining the cancer's outcome [5].

The metastasis cascade is a sequence of complex processes, including invasion, intravasation into the circulatory system, survival, maintenance, extravasation, and outgrowth in the distant organ [6]. One of the crucial steps in this process is the epithelial–mesenchymal transition (EMT), an evolutionarily conserved developmental program, that plays a pivotal role in carcinogenesis by endowing cancer cells with metastatic potential. This process enhances cellular motility, invasiveness, and resistance to apoptotic signals. During this process, cancer cells lose their connections between themselves and the cell's polarity, while gaining more motility and the ability to degrade the extracellular matrix, which allows cancer cells to spread away and metastasize from the primary cancer site [7].

One of the key regulators of the EMT process is an important type III intermediate filament protein named vimentin, expressed in mesenchymal cells [8]. Vimentin plays a critical role in remodeling the cytoskeleton, interlinking the cytoskeleton with the Extracellular matrix, and the acquisition of cancer cell migration and invasion [9]. Moreover, matrix metalloproteinases (MMPs), such as MMP-9, have emerged as potential factors for cancer cell invasion. MMPs are zinc-dependent endopeptidases which can degrade the extracellular matrix and play a pivotal role in cancer progression [10].

Recently microRNAs (miRNAs) have become as important regulators in gene expression, with the ability to serve as a tumor-suppressive agent in multiple tumors [11]. One miRNA which is particularly noteworthy in the context of cancer is miRNA-146a-5p which has been shown to adjust cell migration and invasion in different cancers [12, 13]. MiR-146a-5p is a member of the microRNA-146 family that can target and impede the expression of various genes in the EMT process, such as SOX5, Notch2, etc [14–16]. Furthermore, miRNA-146a-5p has been proven to suppress MMP-9 expression, reducing cancer cells' invasion [17].

While several studies demonstrated miRNA-146a-5p' tumor suppressive effect in GC inducing cell cycle arrest and triggering apoptosis in GC cells [18], the exact molecular mechanisms mediating these effects Have not yet been completely clarified. Therefore, in this research, we aimed to evaluate miRNA-146a-5p impact on the capacity of the migration of human KATO III cancer cells and to explain the probable mechanisms involved, with a particular emphasis on the control of vimentin and MMP-9 production. miRNA-146a-5p could be a promising biomarker for early GC treatment. By understanding the role of miRNA-146a-5p in gastric cancer metastasis, our study may contribute to a novel therapeutic strategy targeting this malignancy.

2 Materials and methods

2.1 Bioinformatic analysis

To investigate the potential regulatory mechanisms of miR-146a-5p, we conducted an in silico analysis using several widely used databases. Predicted mRNA targets of miR-146a-5p were retrieved from miRDB (http://mirdb.org). These targets were co mpiled and subjected to KEGG pathway enrichment analysis using the Enrichr tool (https://maayanlab.cloud/Enrichr/). Pathways with a p-value less than 0.05 were consi dered significantly enriched. Additionally, miRTarBase (https://mirtarbase.cuhk.edu.cn/) and TargetScan (http://www.targetscan.org) were queried to determine whether vimentin (VIM) or MMP-9 are predicted or experimentally validated direct targets of miR-146a-5p.

2.2 Cell culture

Human GC cell lines AGS, MKN-45, and KATO III were obtained from the Pasteur Institute of Iran. They were grown in RPMI media with 10% fetal bovine serum (FBS) (Gibco, USA), 100 IU/mL penicillin, and 100 µg/mL streptomycin. The cultures were stored in a 37 °C incubator (Memmert, Schwabach, Germany) in a humidified atmosphere containing 5% CO_2 and used throughout the logarithmic phase of cell growth.

2.3 RNA isolation and cDNA synthesis

To evaluate the expression levels of miR-146a-5p and its potential target genes, vimentin and MMP-9, total RNA was extracted from the three GC cell lines using TRIzol reagent (RiboEx). cDNA synthesis was performed using 1 µg of RNA and a cDNA synthesis kit (Biofact, South Korea). qRT-PCR was carried out on a LightCycler 96 system (Roche Diagnostics, Mannheim, Germany) following standard protocols. Data analysis was performed using the $2^{-\Delta\Delta CT}$ method. U6 and β-actin were used as internal controls for miRNA and housekeeping genes, respectively. The primer sequences for both the target genes and internal controls are provided in Table 1.

2.4 MiRNA transfection

Following an initial evaluation of miR-146a-5p expression across the three GC cell lines, the cell line exhibiting the least miRNA expression was chosen for further experimentation. The miR-146a-5p mimic and negative control miRNA (miR-NC) were obtained from Microcynth (AG, Switzerland). The chosen cell line was maintained in an antibiotic-free medium at a density of 3×10^5 cells/well in six-well plates. Transfection was performed when cells reached approximately 80% confluency using varying concentrations of the miRNA mimic (50 nM, 75 nM, and 100 nM) and the jetPEI reagent (Polyplus, France), as per the manufacturer's instructions. The optimal concentration of 100 nM miR-146a-5p mimic, which resulted in the highest expression levels, was used for subsequent assays. After 6 h of incubation, the medium was replaced with RPMI containing 20% FBS, and the cells were incubated for an additional 48 h before proceeding with the MTT assay, wound healing assay, and qRT-PCR.

2.5 Apoptosis assay

To assess the effects of miR-146a-5p on apoptosis, cells were subjected to flow cytometry (FCM) using an Annexin V/PI double-staining kit (EXBIO, Czech Republic). KATO III cells were seeded in six-well plates at 2×10^5 cells/well and treated with either 100 nM miR-146a-5p mimic or miR-NC. After 48 h, cells were stained according to the manufacturer's protocol, and apoptotic cells were analyzed using an FCM instrument

Table 1 Primer sets for quantification of target genes' mRNA expression

Genes	Chain	Sequences
MMP-9	Forward	5′-ATTTCTGCCAGGACCGCTTCTAC-3′
	Reverse	5′-ATCCGGCAAACTGGCTCCTTC-3′
Vimentin	Forward	5′-AATCGTGTGGGATGCTACCT-3′
	Reverse	5′-CAGGCAAAGCAGGAGTCCA-3′
β-Actin	Forward	5′-TCCCTGGAGAAGAGCTACG-3′
	Reverse	5′-GTAGTTTCGTGGATGCCACA-3′
U6	Forward	5′-CTTCGGCAGCACATATACTAAAATTGG-3′
	Reverse	5′-TCATCCTTGCGCAGGGG-3′

(FACSQuant; Milteny Biotec, Germany). The apoptotic rates were determined, and the data were analyzed using FlowJo software (Tree Star, Inc., San Carlos, CA).

2.6 Cell viability assay

The viability of the cells was assessed using the MTT assay. KATO III cells were plated at a density of 15,000 cells per well in 96-well plates and incubated for a period of 24 h. The cells were then treated with 100 nM miR-146a-5p mimic or miR-NC for 48 h. Following treatment, the culture medium was discarded, and the cells were incubated with 2 mg/mL MTT (Sigma, Germany) for 4 h at 37 °C. The resulting formazan crystals were solubilized using 200 µL of dimethyl sulfoxide (DMSO), and absorbance was measured at 570 nm using a Sunrise™ microplate reader (Tecan, Switzerland).

2.7 Migration assay

Migration of the cells was assessed using the scratch assay. KATO III cells were plated in 24-well plates at 2×10^5 cells/well and cultured for 24 h to achieve confluence. A wound was created by scratching the surface of the monolayer with a micropipette tip. Following the removal of cell debris, the cells were treated with 100 nM miR-146a-5p mimic or miR-NC and incubated for 48 h. Images of the wound gap were captured at 0, 24, and 48 h post-treatment. The migration rate was quantified by measuring the closure of the wound gap using ImageJ software.

2.8 Statistical analysis

Statistical assessments were carried out utilizing GraphPad Prism 6 software (San Diego, CA, USA). One-way analysis of variance (ANOVA) was conducted to compare differences between experimental groups, followed by Tukey's post-hoc test for multiple comparisons. A p-value of less than 0.05 was considered statistically significant.

3 Results

3.1 Bioinformatic analysis

Database searches using miRDB, miRTarBase, and TargetScan revealed that neither vimentin nor MMP-9 were predicted or validated as direct targets of miR-146a-5p. No seed sequence binding sites or experimental evidence of direct interaction were identified for these genes.

However, KEGG pathway enrichment analysis of the predicted targets of miR-146a-5p revealed significant associations with several cancer-related signaling pathways. These included the NF-κB signaling pathway, PI3K-Akt signaling pathway, TGF-β signaling pathway, and cell adhesion molecules. These pathways are known to regulate critical processes involved in cancer progression, including inflammation, cell proliferation, migration, invasion, and epithelial–mesenchymal transition [19–22]. Notably, vimentin and MMP-9 are well-established markers and functional mediators of EMT and cancer cell invasion, which are key steps in tumor metastasis.

Based on these findings, we hypothesize that miR-146a-5p may influence the expression of vimentin and MMP-9 indirectly, through modulation of upstream signaling pathways involved in EMT and metastatic progression.

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3.2 miR-146a-5p downregulation in GC cell lines

Among the cell lines evaluated (AGS, MKN-45, and KATO III), KATO III exhibited the lowest expression level of miR-146a-5p. Based on this observation, the KATO III cell line was selected for subsequent functional experiments (Fig. 1).

3.3 miR-146a-5p upregulation after the KATO III GC cells transfection

miR-146a-5p mimic transfection carried out for a duration of 24, 48, and 72 h and the results indicated that the optimal upregulation was at 48 h. Following dose optimization, GC cells were transfected with 50 nM and 100 nM concentrations of the miR-146a-5p mimic ($P < 0.0001$) (Fig. 2). Based on the findings, a concentration of 100 nM miR-146a-5p mimic was determined to be the optimal condition for subsequent experiments.

3.4 Transfection with miR-146a-5p resulted in a significant impact on apoptosis and cell viability

The MTT test was employed to assess the miR-146a-5p mimic's transfection impact on the viability of KATO III cells. Unlike other doses, treatment with 100 nm miR-146a-5p exerted a significant impact on the viability of KATO III cells, with significant proliferative changes ($P < 0.05$) (Fig. 3A). Moreover, FCM test revealed that miR-146a-5p mimic significantly impacted apoptosis in KATO III cells ($^{**}P < 0.01$) (Fig. 3B). Given that the KATO III cells are a metastatic cell line, we concentrated the rest of the research on determining the impacts of miR-146a-5p mimic on their migration rates.

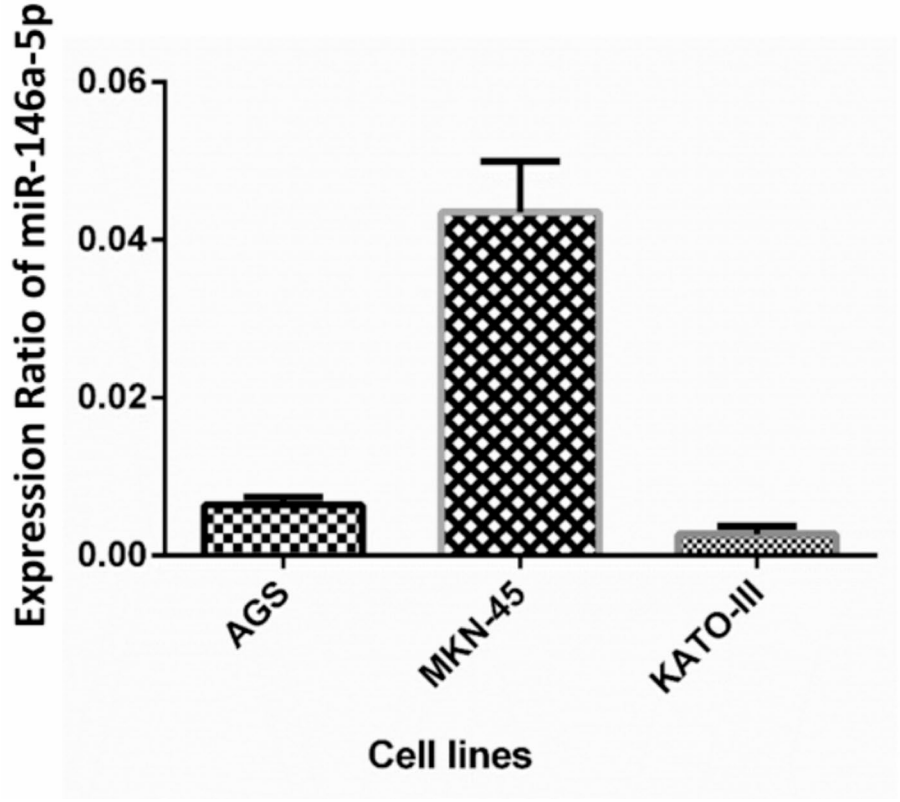


Fig. 1 Relative expression of miR-146a-5p in GC cell lines (AGS, MKN-45, and KATO III) analyzed by qRT-PCR. Among the tested cell lines, KATO III showed the lowest expression level of miR-146a-5p

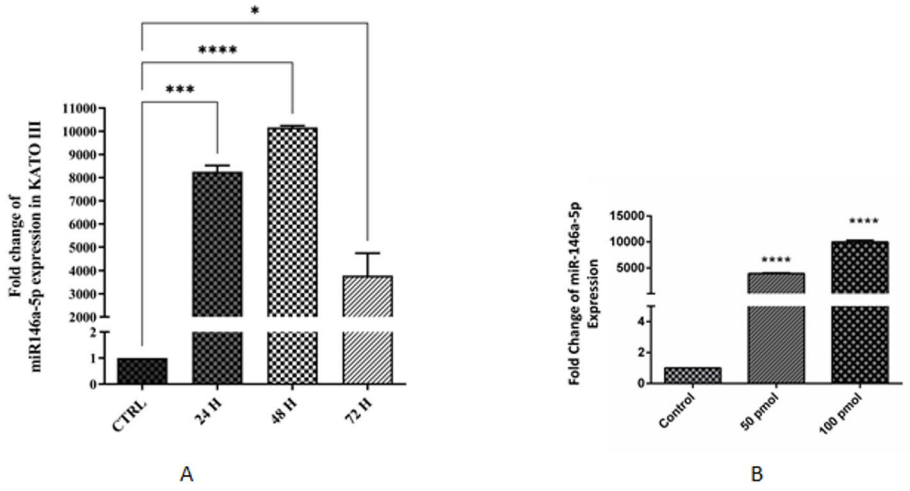


Fig. 2 **A** Time-course analysis of miR-146a-5p expression in KATO III cells following mimic transfection at 24, 48, and 72 h, showing maximum upregulation at 48 h.**B** Dose-dependent qRT-PCR analysis of miR-146a-5p expression after transfection with 50 nM and 100 nM mimics, with significant upregulation observed compared to the control group (***P < 0.0001)

3.5 Suppression of migration in the KATO III cell line after the overexpression of miR-146a-5p

A scratch assay was used to compare the cells' rate of migration of the KATO III cell line in the miRNA-treated group compared to the control group. The wound area was measured at 0, 24, and 48 h. As shown in Fig. 4, miR-146a-5p transfection in KATO III cells caused a considerable decrease in cell migration over 48 h compared to the control cells. After transfection, we assessed the expression of genes associated with migration to evaluate miR-146a-5p's impact on migration.

3.6 miR-146a-5p transfection changes the expression of genes related to metastasis

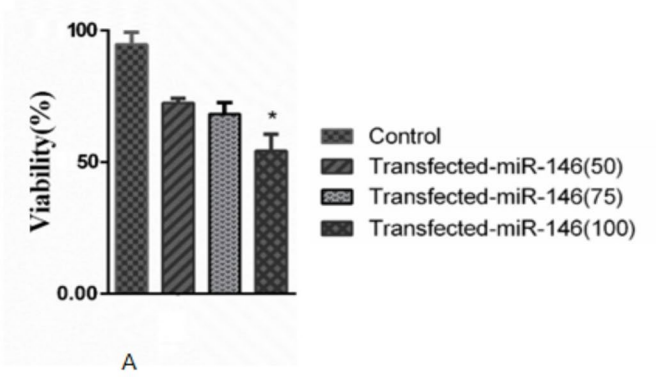
qRT-PCR was used to analyze the impact of miR-146a-5p mimic transfection on vimentin and MMP-9 mRNA expression, which are key metastatic genes (Fig. 5A and B). Transfection with miR-146a-5p mimic sequences significantly inhibited MMP-9 and vimentin production ($P < 0.0001$).

4 Discussion

Gastric cancer is one of the leading causes of cancer-related deaths worldwide. Its poor prognosis is mainly due to late diagnosis and the presence of metastasis. Identifying molecular mechanisms involved in GC progression is essential for improving treatment strategies. This study focused on miR-146a-5p, a microRNA that has been implicated in cancer development and metastasis.

Our findings show that miR-146a-5p expression is reduced in KATO III cells. Transfection with miR-146a-5p mimic increased its expression and led to reduced cell viability, increased apoptosis, and decreased migration. These results are in agreement with previous studies. miR-146a-5p was reported to suppress cell proliferation and promote apoptosis in GC by targeting CDC14A, a regulator of cell cycle transition [18].Wang et al. also showed that miR-146a-5p reduces invasiveness in colorectal cancer cells [23].

After transfection, miR-146a-5p expression was highest at 48 h. The most effective concentration was 100 nM, which produced consistent biological effects. These findings



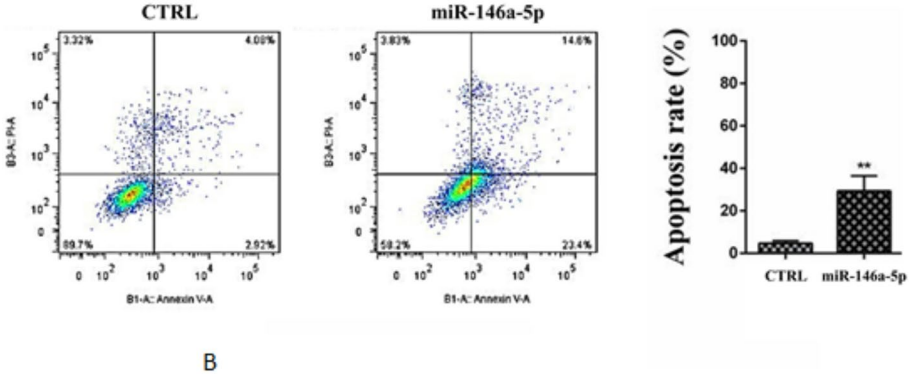


Fig. 3 Effects of miR-146a-5p transfection on cell viability and apoptosis in KATO III cells. **A** MTT assay results showing that 100 nM miR-146a-5p mimic significantly reduced cell viability compared to the control group (*$P < 0.05$), while 50 nM and 75 nM concentrations had no significant effect. **B** Flow cytometry analysis (Annexin V/PI staining) demonstrating a significant increase in apoptosis following transfection with 100 nM miR-146a-5p mimic compared to the control (*$P < 0.01$)

are in line with earlier work indicating that microRNA mimic concentration and timing are important for cellular uptake and gene modulation [24].

The MTT and flow cytometry assays showed that miR-146a-5p reduces cell viability and promotes apoptosis in KATO III cells. These findings are supported by other studies in different cancers. In breast cancer, miR-146a-5p induced apoptosis in vitro [25]. In bladder cancer, it contributed to apoptosis in response to melittin treatment [26]. These effects may involve pathways such as PI3K/Akt, MAPK, and NF-κB, which are known to regulate cell survival and apoptosis [27, 28].

Our data also showed that miR-146a-5p inhibits migration in KATO III cells, as demonstrated by the wound healing assay. This effect is relevant because migration is a key step in the metastatic process [29]. The reduced migration was accompanied by decreased mRNA expression of vimentin and MMP-9, both of which are associated with EMT. Vimentin is a mesenchymal marker that enhances cell motility during EMT [30]. MMP-9 degrades the extracellular matrix and promotes invasion [10]. These findings are consistent with previous research showing that suppression of vimentin and MMP-9 reduces the metastatic potential of cancer cells [31, 32].

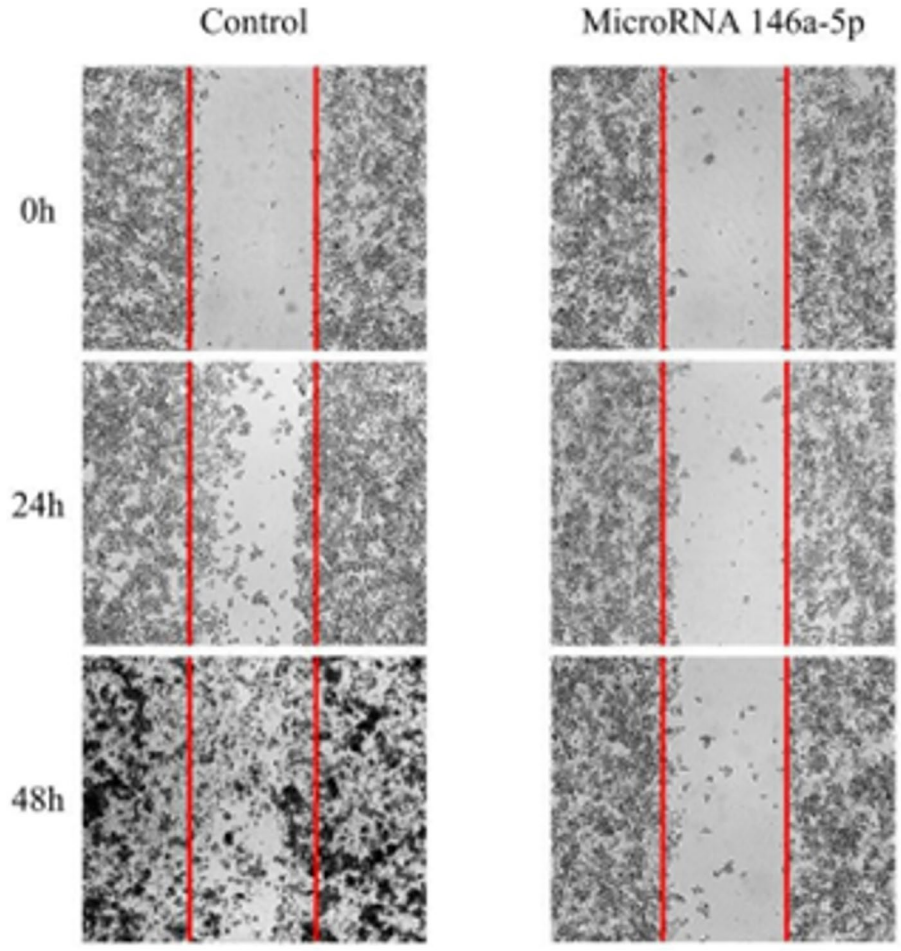


Fig. 4 Wound healing assay to evaluate the migration ability of KATO III cells following miR-146a-5p transfection. Cells treated with miR-146a-5p mimic showed significantly reduced migration at 24 and 48 h compared to cells transfected with the negative control miRNA

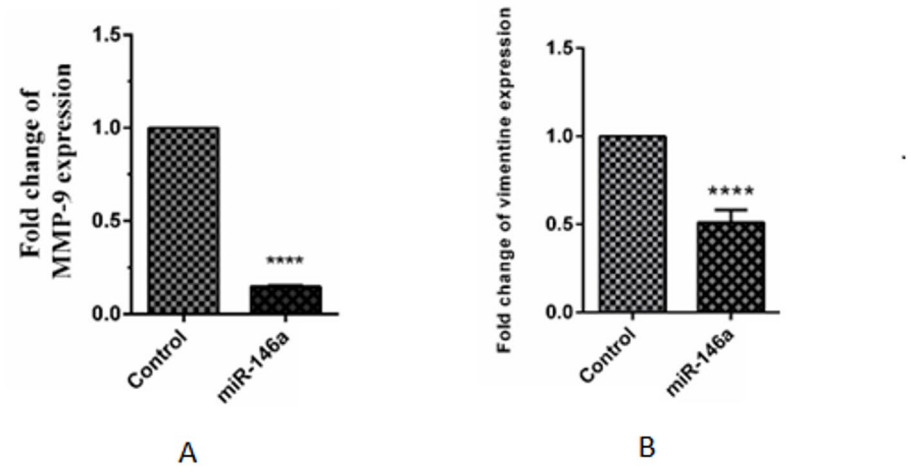


Fig. 5 qRT-PCR analysis of MMP-9 (**A**) and vimentin (**B**) mRNA expression in KATO III cells following transfection with miR-146a-5p mimic. A significant reduction in the expression levels of both genes was observed in miR-146a-5p–transfected cells compared to the control group (***$P < 0.0001$). Cells transfected with control miRNA were used as the baseline

Although in silico tools did not predict vimentin and MMP-9 as direct targets of miR-146a-5p, the observed downregulation suggests that they may be indirectly regulated. This indicates a possible role for miR-146a-5p in modulating EMT-related pathways.

4.1 Limitations and future directions

This study has several limitations. Functional experiments were conducted in only one cell line (KATO III), which may limit the generalizability of the results. Additional GC cell lines should be used in future studies to confirm these findings. Protein-level validation of vimentin and MMP-9 was not performed. Although mRNA levels were measured using qRT-PCR, Western blot analysis is needed to confirm changes at the protein level and is planned in future work.

Direct regulatory interactions between miR-146a-5p and its potential target genes were not evaluated. To address this, future experiments will include dual-luciferase reporter assays and functional recovery studies to determine whether vimentin and MMP-9 are directly regulated by miR-146a-5p. The study also assessed migration using a wound healing assay but did not include invasion-specific assays such as the Transwell assay. Incorporating this method in future experiments will help to better understand the role of miR-146a-5p in GC invasion.

The gene expression analysis was limited to vimentin and MMP-9. Broader transcriptomic profiling using RNA sequencing is necessary to identify additional genes and pathways regulated by miR-146a-5p. Furthermore, as all experiments were conducted in vitro, in vivo studies using animal models are required to validate the biological relevance and therapeutic potential of miR-146a-5p.

The use of synthetic miRNA mimics may not accurately represent physiological conditions. Therefore, future studies should consider using delivery systems that enhance the stability and specificity of miRNAs in vivo. Recent studies have demonstrated that nanoparticle-based delivery systems, including metal-organic frameworks (MOFs) and electrospun nanofibers, can improve the efficacy of chemotherapy agents such as temozolomide, doxorubicin, and platinum-gold nanorods [33, 34]. These technologies may also enhance the delivery and therapeutic application of miR-146a-5p in GC and should be investigated further.

Addressing these limitations in future work will help clarify the function of miR-146a-5p in GC and support its development as a potential therapeutic target.

5 Conclusion

In conclusion, our findings suggest that miR-146a-5p may play a functional role in modulating key characteristics of gastric cancer cells, including migration, apoptosis, and the expression of EMT-associated genes. Overexpression of miR-146a-5p in KATO III cells led to reduced cell viability, increased apoptosis, and decreased migration, accompanied by significant downregulation of vimentin and MMP-9 at the mRNA level. While our results support a potential tumor-suppressive role for miR-146a-5p in gastric cancer, we acknowledge that the mechanisms underlying this regulation—particularly whether these target genes are directly or indirectly affected—require further validation. These preliminary findings highlight miR-146a-5p as a promising candidate for future investigation and warrant additional studies to explore its therapeutic and mechanistic implications in gastric cancer.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions
A.B. conducted the primary analysis and drafted the initial manuscript; Sh.R., S.E, and M.A.Y performed experimental tests ; N.Sh. and A.Sh. carried out the validation experiments; A.Kh. assisted in data organization; B.B. designed the study and revised the final manuscript.

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Data availability
All data generated or analyzed during this study are included in this published article.

Declarations

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The authors declare no competing interests.

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Consent for publication
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During the preparation of this work, the authors utilized ChatGPT for content refinement. After using this tool, the authors reviewed and edited the content as necessary and assume full responsibility for the published material.

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