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Long non-coding RNA PICART1 inhibits cell proliferation by regulating the PI3K/AKT and MAPK/ERK signaling pathways in gastric cancer

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Abstract. – OBJECTIVE: Gastric cancer (GC) is one of the most frequent malignancies and the second leading cause of cancer-related death in the world. The aim of this work was to illustrate the functional role of long non-coding RNA (lnRNA)-PICART1 (p53-inducible cancer-associated RNA transcript 1) in GC, thereby providing novel insights into biomarkers and therapeutic strategies in GC.

PATIENTS AND METHODS: The relative expression level of lncRNA-PICART1 was evaluated by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR). Cell counting kit-8 (CCK-8) assay and colony formation assay were used to determine the ability of cell proliferation. Flow cytometric analysis was performed to detect cell cycle and cell apoptosis. The protein expressions of ERK, p-ERK, AKT and p-AKT were detected by Western blotting. Furthermore, the transfected cells were used to perform tumor xenograft formation assay.

RESULTS: LncRNA-PICART1 was lowly expressed in both GC tissues and cell lines. CCK-8 assay, colony formation assay and flow cytometric analysis validated that up-regulated lncRNA-PICART1 significantly suppressed cell proliferation, whereas promoted cell apoptosis. Besides, the over-expression of lncRNA-PICART1 remarkably inhibited the PI3K/AKT and ERK/MAPK signaling pathways. Tumor xenograft formation assay indicated that lncRNA-PICART1 overexpression significantly inhibited tumor formation.

CONCLUSIONS: Our research illustrated that lncRNA-PICART1 functioned as a tumor suppressor in GC. The regulation of the PI3K/AKT and ERK/MAPK signaling pathways might be the underlying mechanism of the tumor suppressor role of lncRNA-PICART1. In addition, our study might bring novel insights into biomarkers and therapeutic strategies for GC.

Key Words:
LncRNA-PICART1, GC, Proliferation, PI3K/AKT, ERK/MAPK.

Introduction

Gastric cancer (GC) is one of the most frequent malignancies worldwide, which is also the second leading cause of cancer-related deaths[1]. Although significant progress has been made in recent years, the overall 5-year survival rate of GC remains disadvantageous[2]. The main reason for poor prognosis of GC patients is the lack of efficient early diagnosis and significant therapeutic strategies of GC[3].

Long non-coding RNAs (lnRNAs) are RNA transcripts with no protein-coding function, which have more than 200 nucleotides in length[4]. LncRNAs have been reported to have various physiological functions, including cell proliferation, metastasis, invasion, apoptosis and cell cycle[5-7]. Aberrant expression of lncRNAs participates in the progression of many cancer types, such as gastric cancer, colorectal cancer, prostate and cervical cancer[5,8-10]. Therefore, it is essential to understand the mechanism of lncRNAs in tumor progression and to seek novel therapeutic strategies and biomarkers.

In the current study, we recruited several functional assays to determine the role of lncRNA-PICART1 (p53-inducible cancer-associated RNA transcript 1) in GC. Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) assay was used to detect the expression level of lncRNA-PICART1 in GC. The results showed

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that lncRNA-PICART1 was significantly up-regulated in GC tissues and cell lines. Cell proliferation assay and flow cytometric analysis indicated that lncRNA-PICART1 remarkably inhibited the proliferation of GC cells. To elucidate the underlying mechanism, Western blotting was involved in this study. The results showed that lncRNA-PICART1 exerted a tumor suppressor role in GC *via* regulating the PI3K/AKT and MAPK/ERK signaling pathways. All the findings may provide a novel insight into therapeutic strategies and biomarkers of GC.

Patients and Methods

Tissue Specimens

40 pairs of GC tissues and normal tissues were collected in this study. All tissue specimens were obtained from patients who received surgical treatment in The First People's Hospital of Wenling from 2015 to 2016. Collected tissue specimens were immediately preserved in liquid nitrogen. All tumor tissues were confirmed by pathological examination. This study was approved by the Ethics Committee of The First People's Hospital of Wenling. Informed consents were signed from all participants before the study.

Cell Lines

Four GC cell lines (HGC27, BGC823, SGC7901, MGC803) and one non-malignant gastric epithelium cell line were obtained from Shanghai Cell Bank (Shanghai, China). All cells were cultured in Roswell Park Memorial Institute-1640 (RPIM-1640) medium (HyClone, South Logan, UT, USA) containing 10% fetal bovine serum (FBS; Gibco, Grand Island, NY, USA), 100 U/mL penicillin and 100 μg/mL streptomycin in a 37°C, 5% CO_2 incubator.

Cell Transfection

Lentiviral vector was transfected into selected MGC803 cells according to the standard instructions to over-express lncRNA-PICART1. For knockdown of lncRNA-PICART1, HGC27 cells were transfected with shRNA in accordance with the standard protocol. All the plasmids were obtained from GenePharma (Shanghai, China).

Total RNA Extraction and qRT-PCR

Total RNA in tissue specimens cell lines was extracted in strict accordance with TRIzol reagent (Invitrogen, Carlsbad, CA, USA). Complementary DNAs (cDNAs) were synthesized *via* Reverse Transcription Kit (TaKaRa, Otsu, Shiga, Japan) according to the standard protocol. The expression level of lncRNA-PICART1 was detected by SYBR Green Real-Time PCR. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was taken as an internal reference.

Colony Formation Assay

Cells (1.0×10^3) were planted into 60-mm culture plates and cultured for 2 weeks. Then the cells on the plates were washed with phosphate-buffered saline (PBS) (Gibco, Grand Island, NY, USA) twice and fixed with ice-cold 70% methanol for 15 min. Subsequently, formed colonies were stained with Crystal Violet Staining Solution (Beyotime, Shanghai, China). All the colonies were finally captured and calculated.

Cell-Counting Kit-8 Assay (CCK-8)

The CCK-8 assay was used to examine the proliferation of GC cells. The transfected cells were first planted into 96-well plates (6×10^3/well). The CCK-8 solution (Beyotime, Shanghai, China) (10 μL/well) was then added to cells, followed by incubation at 37°C for 2 hours in the dark. The optical density (OD) value (450 nm) was evaluated by a microplate reader.

Flow Cytometric Analysis

For detecting apoptotic cells, the Annexin V-FITC/PI Apoptosis Detection Kit (Vazyme, Nanjing, China) was performed according to the instructions. To examine cell cycle, transfected cells were immersed in 70% ethanol at -20°C overnight, followed by staining with propidium iodide (PI) (Vazyme, Nanjing, China). Flow cytometric analysis was performed by BD FACSCanto II (BD Biosciences, Franklin Lakes, NJ, USA) flow cytometry.

Western Blot

Total protein was isolated by radioimmunoprecipitation assay (RIPA) buffer (Thermo Fisher Scientific, Waltham, MA, USA) and phenylmethanesulfonyl fluoride (PMSF). Extracted protein samples were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred onto polyvinylidene difluoride (PVDF) membranes (Millipore, Billerica, MA, USA). Then the membranes were incubated with primary antibodies at 4°C overnight. Primary rabbit antibodies used in this study included anti-ERK (Cell Signaling Tech-

nology, Danvers, MA, USA), anti-p-ERK (Cell Signaling Technology, Danvers, MA, USA), anti-AKT (Cell Signaling Technology, Danvers, MA, USA), anti-p-AKT (Cell Signaling Technology, Danvers, MA, USA). Rabbit anti-GAPDH (Cell Signaling Technology, Danvers, MA, USA) was taken as a loading control. Relative expression level of proteins was determined by Image Lab software.

Xenograft Model

This study was approved by the Animal Ethics Committee of Shanxi Medical University Animal Center. Transfected MGC803 or HGC27 cells (6×10^5/mL) were subcutaneously injected into two flanks of nude mice (6 weeks old). Tumors growth were monitored and recorded every week. The following formula was used to calculate tumor volume: volume = length×width^2×1/2. Tumors were extracted after 4 weeks.

Statistics Analysis

All experiments in this study were performed at least three times independently. All data were expressed as mean ± standard deviation (SD). Chi-squared test was used to evaluate the significance of differences in Table I. Student's unpaired *t*-test was used to compare the difference between the two groups. $p < 0.05$ was considered statistically significant.

Results

LncRNA-PICART1 Was Lowly-Expressed in Both GC Tissues and Cell Lines

QRT-PCR was performed to determine the expression level of lncRNA-PICART1 in GC tissues and cell lines. As shown in Figure 1A, the expression level of lncRNA-PICART1 in matched normal tissues was significantly higher than that of GC tissues. Consistently, the expression level of lncRNA-PICART1 was significantly down-regulated in GC cell lines (Figure 1B). Meanwhile, the results of clinical data analysis showed that lncRNA-PICART1 was correlated with the progression of GC (Table I). To perform cell functional assays, cell transfection was performed in selected cell lines. As shown in Figure 1C, the expression level of lncRNA-PICART1 in LV-PICART1 group was significantly higher than the LV-vector group. However, the opposite result was found in the Sh-PICART1 group.

LncRNA-PICART1 Inhibited the Proliferation of GC Cells

After transfection in selected cell lines, we used the CCK-8 assay to elucidate the role of lncRNA-PICART1 in cell proliferation. The results showed that over-expressed lncRNA-PICART1 resulted in significantly lower OD values after 5 days. However, down-expression of lncRNA-PI-

Table I. The relationship between the clinical characteristics and lncRNA-PICART1 expression.

Characteristics	Number	LncRNA-PICART1 expression		*p*-value
		High group	Low group	
Age (years)				
< 60	14	8	6	0.970
≥ 60	26	15	11	
Gender				
Male	22	9	13	0.350
Female	18	10	8	
Size (cm)				
< 3	19	7	12	0.010
≥ 3	21	16	5	
Histology grade				
Well-moderately	21	8	13	0.210
Poorly-signet	19	11	8	
Stage				
I/II	22	14	8	0.560
III/IV	18	13	5	
T grade				
T1+T2	24	8	16	0.030
T3+T4	16	11	5	

The LncRNA-PICART1 expression was cut off by the medium expression level of LncRNA-PICART1.

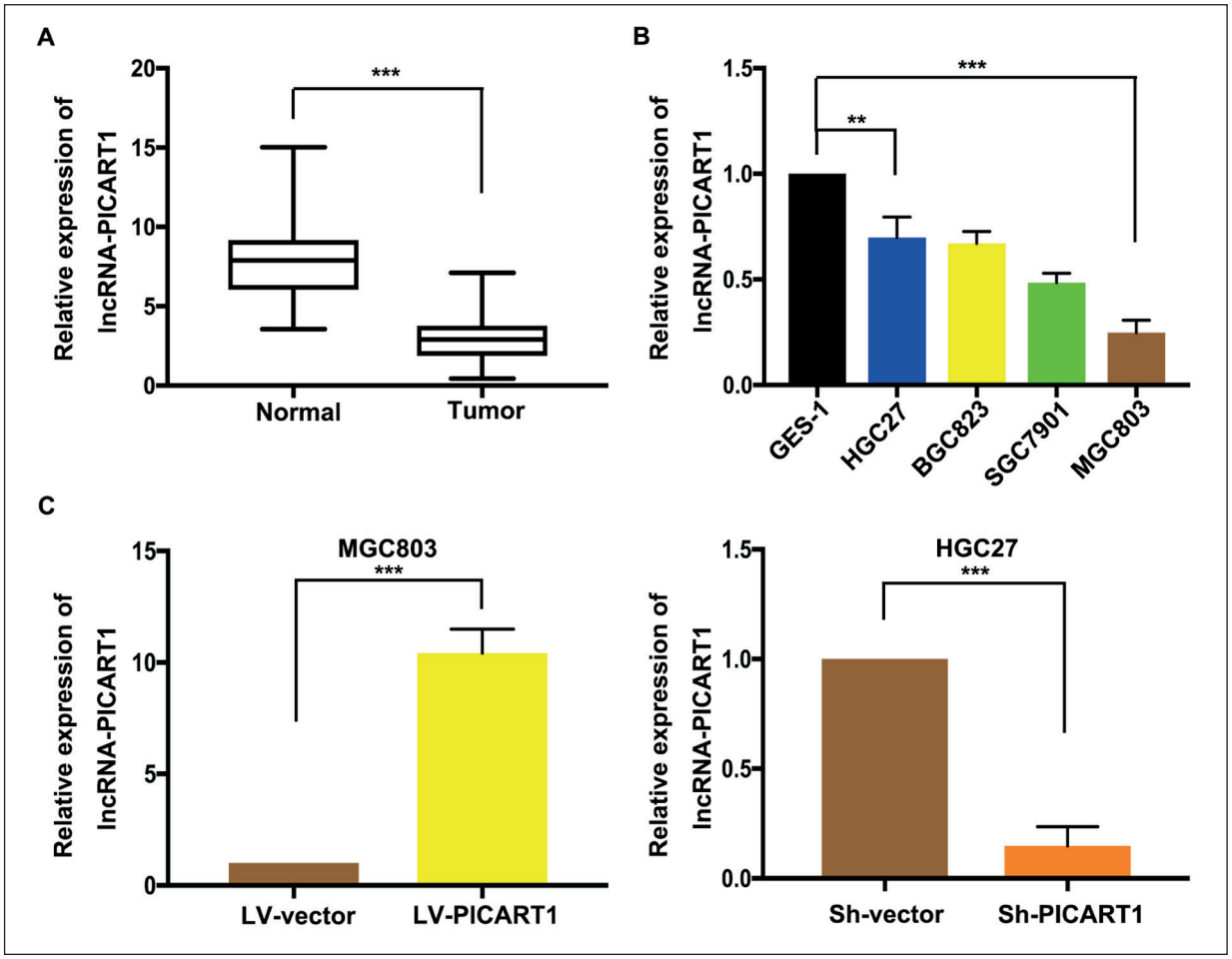

Figure 1. LncRNA-PICART1 was downregulated in both GC tissues and cell lines. ***A,*** The expression level of lncRNA-PICART1 in GC tissues matched normal tissues; ***B,*** Analysis of lncRNA-PICART1 expression level in GC cell lines; ***C,*** Transfection efficiency was evaluated by qRT-PCR. Data were expressed as mean ± SD of three independent experiments. ***$p < 0.001$.

CART1 had a markedly higher OD value after 5 days in comparison with the control group (Figure 2A). After that, we recruited a colony formation assay. As shown in Figure 2B, the number of colonies formed in LV-PICART1 group was significantly higher than that of the control group. Opposite results were found in Sh-PICART1 group. In sum, all results suggested that lncRNA-PICART1 suppressed the proliferation of GC cells.

LncRNA-PICART1 Suppressed Cell Cycle and Promoted Cell Apoptosis in GC

To figure out the role of lncRNA-PICART1 in GC cell cycle and cell apoptosis, flow cytometric analysis was performed. After transfection, cell cycle was arrested in the G1/0 phase in over-expressed lncRNA-PICART1 group when compared with the control group (Figure 3A). Conversely, the over-expression of lncRNA-PICART1 significantly promoted cell cycle progression (Figure 3A). Subsequently, apoptotic cells were detected by flow cytometric analysis. As shown in Figure 3B, the up-regulation of lncRNA-PICART1 led to a significantly lower rate of apoptotic cells in comparison with the control group. However, down-regulated lncRNA-PICART1 remarkably promoted the apoptosis of the GC cells. All data indicated that lncRNA-PICART1 inhibited cell cycle progression and promoted cell apoptosis in GC cells.

Underlying Mechanism of the Functional Role of LncRNA-PICART1 in GC

To illustrate the underlying mechanism of the functional role of lncRNA-PICART1 in the GC development, we speculated that lncRNA-PI-

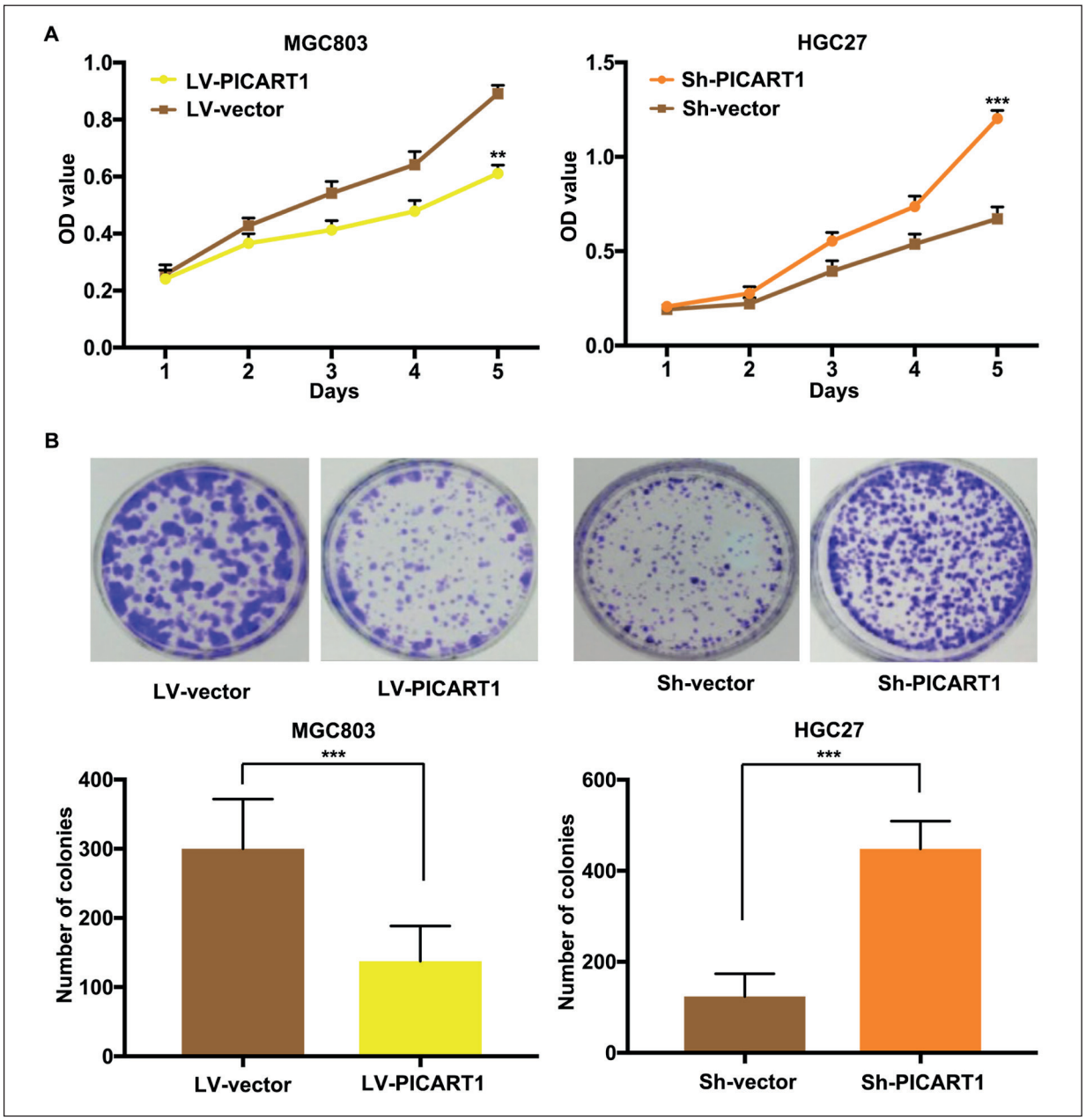

Figure 2. LncRNA-PICART1 inhibited cell proliferation in GC. ***A,*** Cell proliferation ability was determined by CCK-8 assay; ***B,*** Cell proliferation ability was determined by colony formation assay. Data were expressed as mean ± SD of three independent experiments. $^{**}p < 0.01$, $^{***}p < 0.001$.

CART1 exerted its function by regulating the PI3K/AKT and ERK/MAPK signaling pathways. As shown in Figure 4A, the over-expression of lncRNA-PICART1 significantly inhibited the phosphorylation of ERK and AKT in MGC803 cells. However, down-regulated lncRNA-PICART1 markedly activated the two signaling pathways by promoting the phosphorylation of ERK and AKT in HGC27 cells (Figure 4B). Hence, these results demonstrated that over-expressed lncRNA-PICART1 inhibited cell proliferation and promoted cell apoptosis by suppressing the PI3K/AKT and ERK/MAPK signaling pathways.

Overexpression of LncRNA-PICART1 Suppressed Xenograft Tumor Formation

In tumor formation assay *in vivo*, tumor volumes were monitored and recorded. As shown in

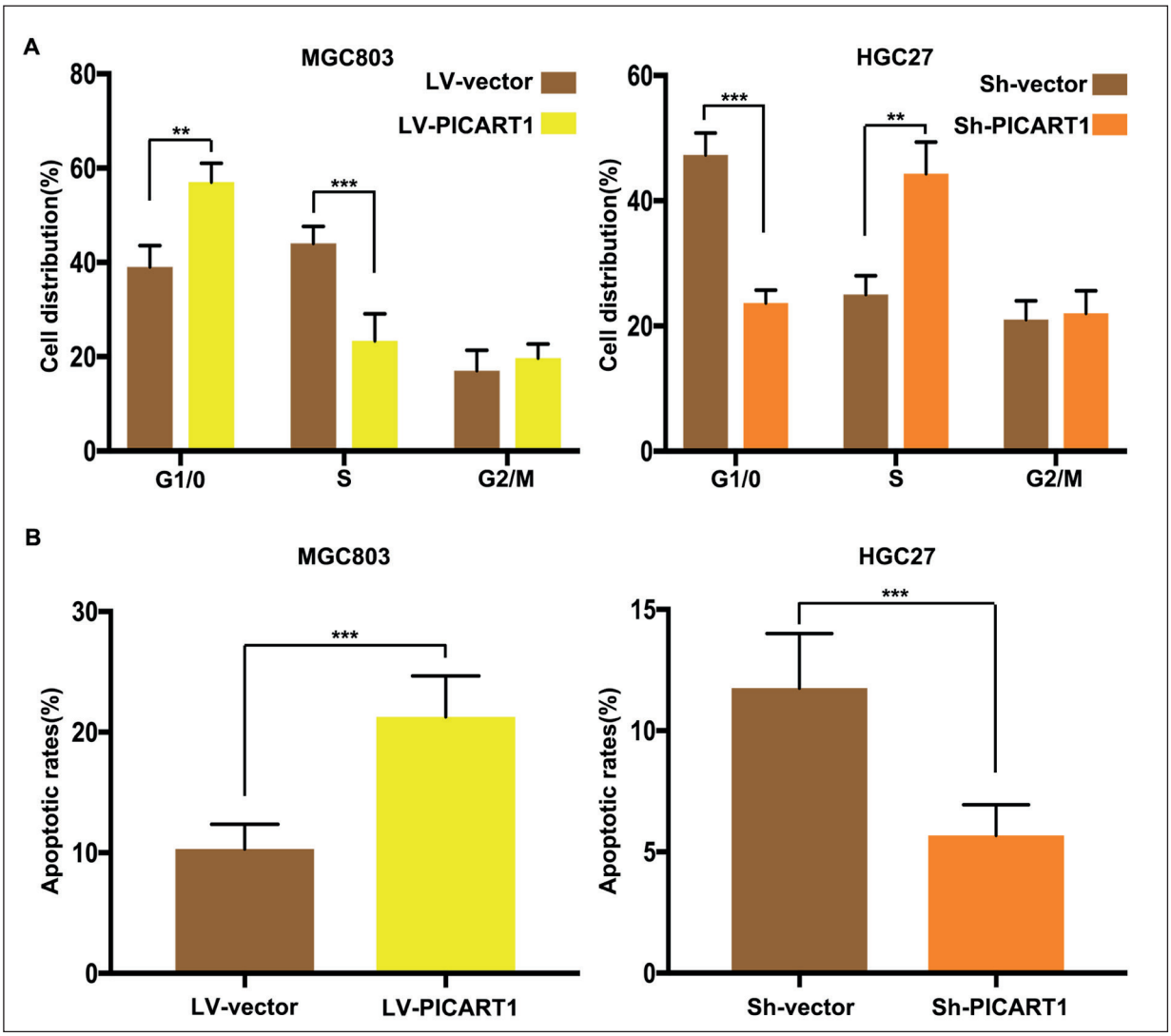

Figure 3. LncRNA-PICART1 suppressed cell cycle and promoted cell apoptosis in GC. ***A,*** Cell cycle progression was detected by flow cytometric analysis in transfected cells; ***B,*** Apoptotic rates in transfected cells was detected by flow cytometric analysis. Data were expressed as mean ± SD of three independent experiments. $^{**}p < 0.01$, $^{***}p < 0.001$.

Figure 5A, over-expressed lncRNA-PICART1 significantly suppressed the ability of tumor formation in GC. However, down-expression of lncRNA-PICART1 promoted tumor growth. Tumor weight in mice with lncRNA-PICART1 overexpression was remarkably lower than control mice. However, it was significantly higher in mice with lncRNA-PICART1 down-regulation (Figure 5B). Subsequently, the expression level of lncRNA-PICART1 was determined by qRT-PCR. The results showed that the expression level of lncRNA-PICART1 was upregulated in the over-expressed lncRNA-PICART1 group, while was down-regulated in the down-expressed lncRNA-PICART1 group. All these data suggested that the over-expression of lncRNA-PICART1 suppressed xenograft tumor formation.

Discussion

GC is still one of the most frequent malignancies in the world. Due to the lack of early diagnosis and efficient treatment strategies, it is essential to find novel biomarkers and therapeutic targets[8,11]. In recent years, numerous studies of lncRNAs have been performed. Meanwhile, the functional role of lncRNAs in cancer progression has been reported. Thus, in the current study, we

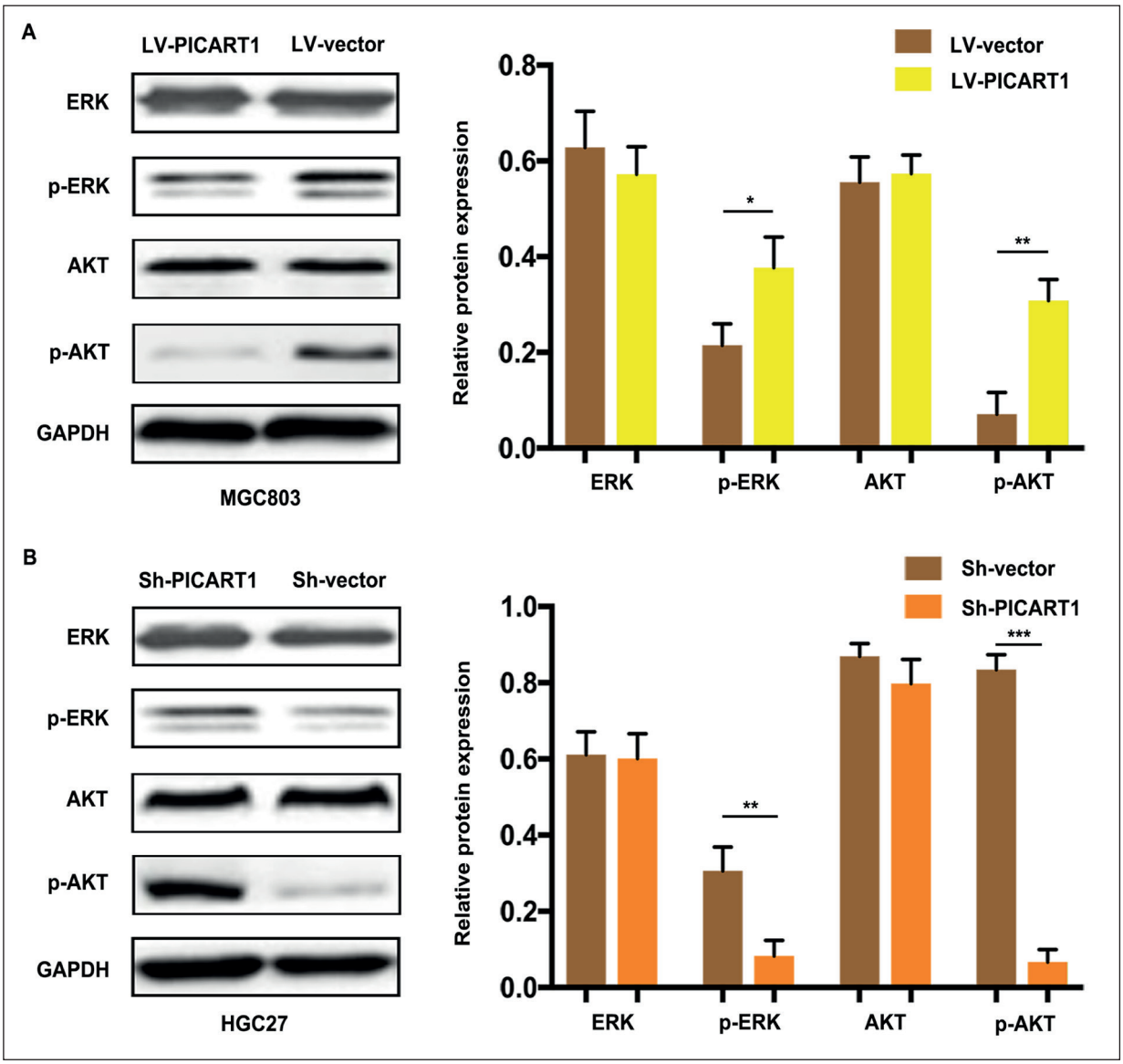

Figure 4. Underlying mechanism of the functional role of lncRNA-PICART1 in GC. ***A,*** AKT, p-AKT, ERK, p-ERK protein expression levels were examined by Western blot in MGC803 cells over-expressing lncRNA-PICART1; ***B,*** AKT, p-AKT, ERK, p-ERK protein expression levels were examined by Western blot in HGC27 cells down-expressing lncRNA-PICART1. Data were expressed as mean ± SD of three independent experiments. $^{**}p < 0.01$, $^{***}p < 0.001$.

investigated the role of lncRNA-PICART1 in GC. We hope our work can bring a novel insight into biomarkers and therapeutic targets in GC.

LncRNAs function as oncogenes or tumor suppressors, which also play an important role in tumorigenesis[12]. LncRNAs exert their functions *via* post-transcriptional regulation, transcriptional regulation or chromatin modification[13]. However, the exact role of lncRNAs in GC progression remains to be elucidated. In the current study, we aimed to explore the physiological role of lncRNA-PICART1 in GC development and to elucidate the underlying mechanism. Mounting evidence has shown that lncRNAs participate in numerous physiological functions of various cancers. It is reported that the down-expression of lncRNA-ANRIL suppresses the proliferation, migration and invasion of cervical cancer[14]. LncRNA-NBR2 has been proved to inhibit epithelial-mesenchymal transition *via* regulating Notch1 signaling in osteosarcoma cells[15]. LncRNA-NEAT1 is re-

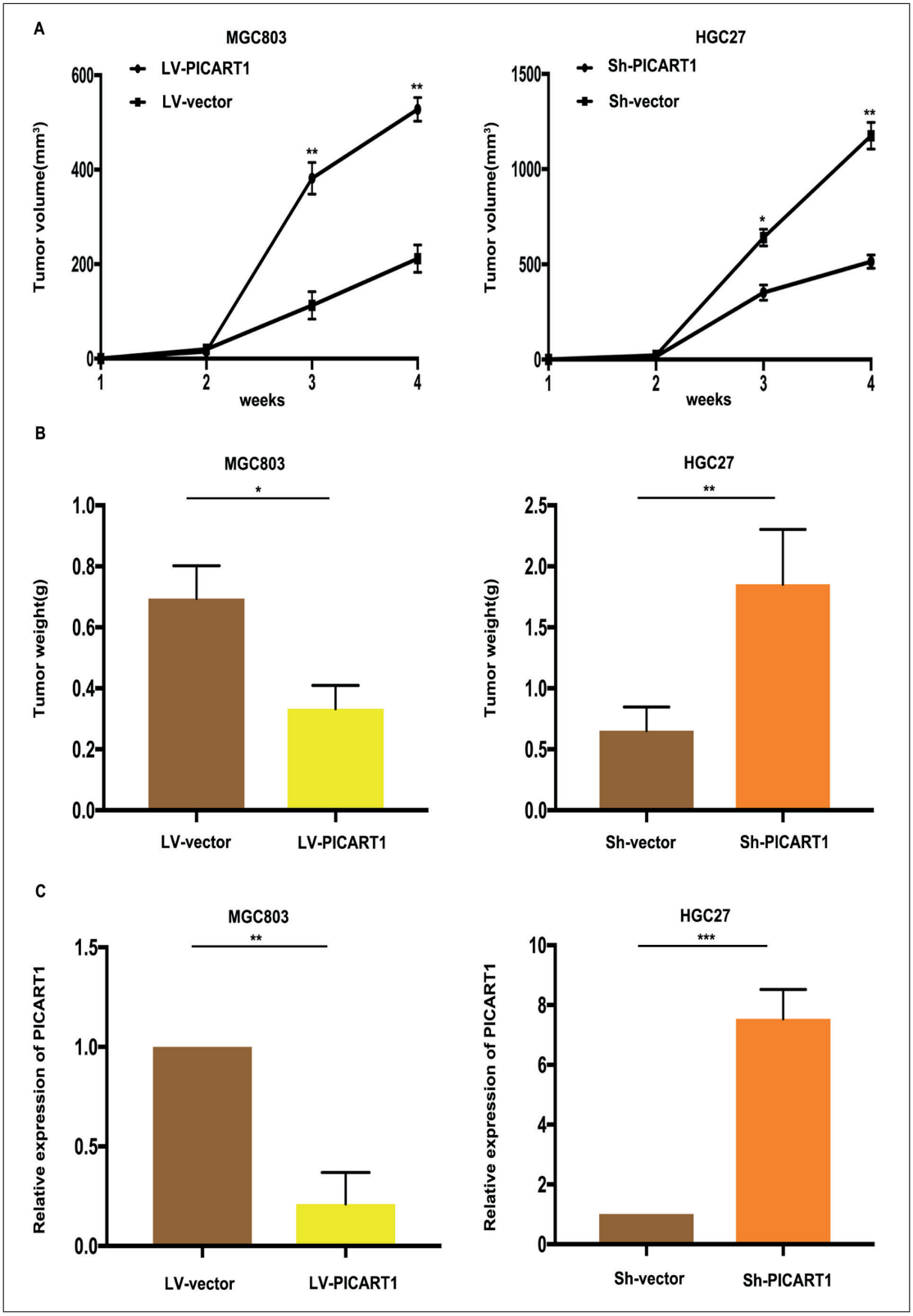

Figure 5. Over-expression of lncRNA-PICART1 suppressed xenograft tumor formation. ***A,*** After tumor extraction, tumor volume was calculated and recorded, respectively; ***B,*** Tumor weight were recorded; ***C,*** The relative expression of lncRNA-PICART1 in tumors were examined by qRT-PCR. Data were expressed as mean ± SD of three independent experiments. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

ported to promote colorectal cancer progression by activating the Wnt/ β-catenin signaling by regulating DDX5[16]. LncRNA-PICART1 is novel transcript with 2.53 kb in length. Its aberrant expression has been reported in lung cancer, breast and colorectal cancer[17,18]. Nevertheless, it is of great significance to elucidate the functional role of lncRNA-PICART1 in GC. Herein, in the current work, a series of physiological assays were performed. All results indicated that lncRNA-PICART1 functioned as a tumor suppressor in GC.

To further investigate the underlying mechanism of lncRNA-PICART1 function in GC, we examined the protein expression changes of the PI3K/AKT and ERK/MAPK signaling pathways. The PI3K/AKT and ERK/MAPK signaling pathways have been considered to play a vital role in various cancers[19-22]. It is reported that these two signaling pathways are mainly correlated with cell proliferation[20,21]. Based on previous studies, Western blotting was used to verify whether lncRNA-PICART1 could regulate both the signaling pathways in MGC803 and HGC27 cells. The results indicated that down-regulated lncRNA-PICART1 could activate the two signaling pathways. Furthermore, tumor xenograft formation assay showed that over-expressed lncRNA-PICART1 could significantly inhibit tumor formation. Hence, all data suggested that the over-expression lncRNA-PICART1 inhibited cell proliferation and promoted cell apoptosis *via* suppressing the PI3K/AKT and ERK/MAPK signaling pathways.

Conclusions

We demonstrated that lncRNA-PICART1 functioned as a tumor suppressor in GC. The regulation of PI3K/AKT and ERK/MAPK might be the underlying mechanism of the tumor suppressor role of lncRNA-PICART1. Our study might bring novel insights into biomarkers and therapeutic strategies in GC.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

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