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Research Article
lncRNA PVT1 Targeting miR-423-5p Regulates Biological Behavior of Gastric Carcinoma Cells

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Abstract

Background and Objective: Gastric Carcinoma (GC) is categorized among malignant tumours with an extremely increased fatality rate, with an incidence constantly rising in recent years. Accumulating studies have pointed out that lncRNA may be the breakthrough in the fight against tumour diseases. The purpose of this investigation was to explore the mechanism of lncRNA PVT1 on gastric carcinoma cells. **Materials and Methods:** SGC7901 and MGC803 GC cell multiplication, invasion and apoptosis were studied under altering expressions of PVT1 and miR-423-5p. The interaction between both was further confirmed by the Dual-Luciferase Reporter Assay (DLRA). **Results:** Silencing PVT1 and increasing miR-423-5p hampered GC cell multiplication and invasiveness capacity and enhanced apoptosis while overexpression had opposite effects ($p<0.05$). The online target gene prediction website identified a reciprocal binding locus between PVT1 and miR-423-5p and DLRA confirmed the targeting relationship ($p<0.05$). After inhibiting PVT1, miR-423-5p in GC cells increased ($p<0.05$). Moreover, the salvage experiment demonstrated that reduced expression levels of PVT1 on GC cells were restored by simultaneously inhibiting miR-423-5p ($p>0.05$). **Conclusion:** PVT1 participates in gastric carcinogenesis and progression through the targeted inhibition of miR-423-5p to promote cell activity and reduce apoptosis, which may be a breakthrough in GC research regarding its diagnosis and treatment.

Key words: lncRNA PVT1, miR-423-5p, gastric cancer, carcinogenesis, apoptosis, invasion, rescue assay

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

GC is currently categorized amongst the most frequent-occurring malignancies, with a high incidence[1,2]. And some data show that GC has an increasing incidence and is prone to occur at younger ages with the alteration of people's diet structure[3,4]. Irrespective of useful clinical treatment effects for early GC, patients with high infiltration or metastasis are confronted with dissatisfactory efficacy[5], with some data indicating that the prognostic mortality rate of advanced GC patients has exceeded 60%[6]. So, early screening for GC and finding new treatment methods are the key breakthroughs to improving the prognosis of patients.

As the research further advances, a developing no of studies have pointed out that long non-coding RNA (lncRNA) may be the key to the future research of neoplastic disease[7,8]. As the genetic material of the human body, lncRNA is essential in the process of genetic information as well as in regulating cell function[9,10]. For example, studies have pointed out that lncRNA PVT1 may be a new potential marker for the prognosis of colorectal cancer and participate in the development of liver cancer[11,12]. In addition, in GC, PVT1 is also found to have obvious abnormal expression[13] but no further study has revealed the connection between PVT1 and GC. Moreover, miR-423-5p is also confirmed to interfere with the onset of GC[14]. And in the research of Lin *et al.*[15], it seems that miR-423-5p has some potential connection with PVT1. Therefore, preliminary screening of the relationship between PVT1 and miR-423-5p was done through an online tool that predicted complementary binding sites which gave initial direction that PVT1 may have an influence on gastric carcinogenesis and progression through miR-423-5p.

Facing the increasingly high incidence of GC in the clinic, it is of extraordinary importance to further understand the relationship between PVT1 and GC for upcoming clinical diagnosis and treatment. Herein, the effect of PVT1 on GC cells and its mechanism were explored, targeting to provide reliable reference and guideline for the new direction of clinical diagnosis and treatment of GC.

MATERIALS AND METHODS

Study area: The study was carried out at the Department of Gastroenterology, Zhongda Hospital Southeast University, Nanjing, Jiangsu, China from January-June, 2021.

Experiment preparation

Cell information: SGC7901 and MGC803, GC cell strains offered by American Type Culture Collection, were grown in 10% FBS-containing RPMI at 37 with 5% CO_2 in the air.

Experimental methods

Cell treatment: Lentivirus vectors including inhibitor (si-PVT1), overexpression (sh-PVT1), control vector (lncRNA-NC), along with miR-423-5p-inhibitor, miR-423-5p-mimics and negative control miR-NC were designed by Thermo Fisher, US. GC cells were transfected with these vectors by using Lipofectamine 2000.

Cell viability detection: Cells were seeded in 96-well plates and cell viability was measured at 24, 48, 72 and 96 hrs, by adding MTT solution (5 mg mL^{-1}) into each well. DMSO (150 µL) was added to stop the reaction after 4 hrs of culture and the reaction was detected (570 nm) using a microplate reader.

Apoptosis rate determination: Cells digested with pancreatin were adjusted to 1×10^6 mL^{-1}. 10 µL of Annexin-V-FITC was added into 100 µL cell suspension, incubated for 15 min and analyzed by stream cytometry to measure apoptosis.

Cell invasiveness detection: The transfected cells were vaccinated in the upper chamber of the Transwell chamber and the 10% FBS-having culture medium was placed into the lower one. After incubating cells for 24 hrs, the transmembrane cells were wiped off with cotton swabs, washed with PBS and stained. Five fields were arbitrarily chosen for counting under the microscope.

Double luciferase reporter assay (DLRA): ENCORI (http://starbase.sysu.edu.cn/), an online target gene prediction website, analyzed the binding complementary sites of PVT1 and miR-423-5p. The mutant sequence (WT) and wild sequence (mut) of PVT1 were constructed and GC cells were co-transfected with miR-423-5p mimics and miR-NC. The fluorescence intensity was calculated after 48 hrs by a firefly luciferase assay kit.

Statistical processing: All tests were run in triplicate in this experiment and the results were averaged and recorded as ($c\pm s$). SPSS 22.0 software was used for analysis. Statistical methods included independent, One-way ANOVA, sample t-test and LSD post hoc test. Pearson correlation coefficient

and ROC curve were employed for analysis. Kaplan-Meier and log-rank tests were applied for the determination of endurance rate and comparison, respectively $p<0.05$.

RESULTS

Online database analysis of the expression of PVT1 and miR-423-5p: In the online database "starBase", PVT1 was profoundly expressed in bladder cancer (Fig. 1a), colon cancer (Fig. 1b) and oesophageal cancer (Fig. 1c), while miR-423-5p is low in pancreatic cancer (Fig. 1d), lung cancer (Fig. 1e) and thyroid cancer (Fig. 1f).

Impact of PVT1 on GC cells: The outcomes of the MTT experiment described that the cell proliferation ability of the sh-PVT1 group at 96 hrs in SGC7901 cells was 1.07±0.05, which was higher than that of the si-PVT1 group and the lncRNA-NC group, while the 96 hrs cell proliferation ability of

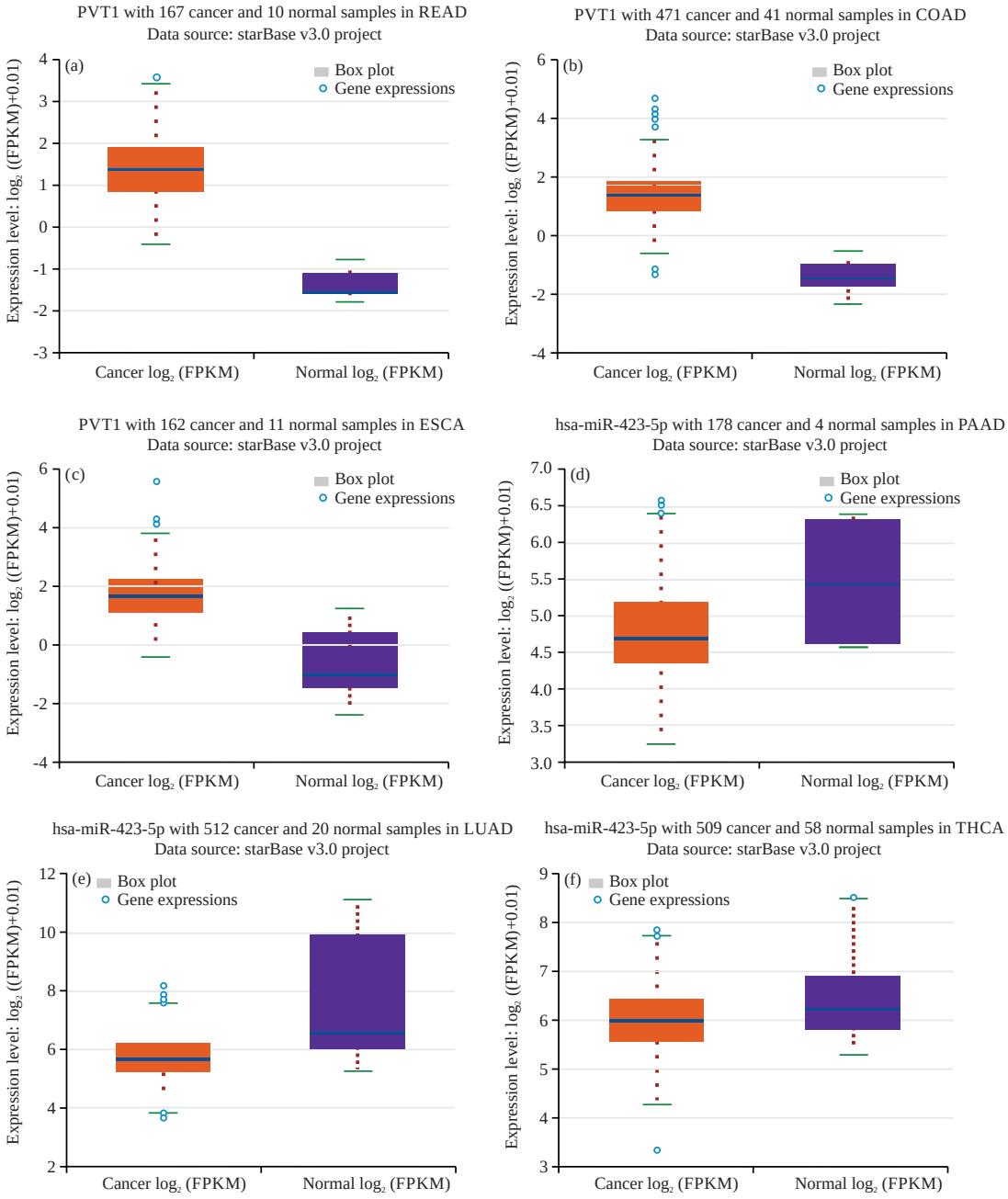

Fig. 1(a-f): Online database analysis of the expression of PVT1 and miR-423-5p

the si-PVT1 group was 0.53±0.04, lower than the lncRNA-NC group 0.76±0.04 ($p<0.05$, Fig. 2a). Similarly, the cell proliferation ability of the sh-PVT1 group in MGC803 cells after 96 hrs revealed the same results with different values Fig. 2b. Subsequently, the apoptosis rate of the cells through flow cytometry experiments was analyzed and the results were shown in Fig. 2c. The rate of apoptosis in SGC7901 and MGC803 cells treated with sh-PVT1 was 4.62±0.84 and 4.86±0.72%, respectively, which were lower than that of si-PVT1 and lncRNA-NC groups, while the apoptotic rate of the si-PVT1 group were 17.86±2.63 and 18.46±2.18%, which were higher than those in the lncRNA-NC group 10.57±1.03 and 9.86±1.15% ($p<0.05$, Fig. 2d). Transwell assay was used to measure the invasion ability of cells and the results were shown in Fig. 2e. In SGC7901 and MGC803 cells, the number of cell invasions in the sh-PVT1 group was 114.62±9.52 and 108.62±10.54, which were higher comparing the si-PVT1 group and lncRNA-NC group, while the number of cell invasions in the si-PVT1 group was 21.06±5.16 and 22.14±4.84, were lower than the lncRNA-NC group cell invasion number 61.22±7.26 and 58.42±7.59 ($p<0.05$, Fig. 2f). These results demonstrated that silencing PVT1 promotes apoptosis by inhibiting proliferation and invasion capacity of gastric cancer cells while over expressing PVTI has the opposite effect.

Impact of miR-423-5p on GC cells: MTT experiment results showed that the cell proliferation ability of the miR-423-5p-mimics group in SGC7901 cells was 0.69±0.04 at 96 hrs, which was lower than the miR-423-5p-inhibitor group and miR-NC group. The 96 hrs cell proliferation ability of the miR-423-5p inhibitor group was 1.16±0.04, which was higher than that of the miR-NC group at 0.89±0.04 ($p<0.05$, Fig. 3a). In MGC803 cells, the proliferation ability of the miR-423-5p-mimics group at 96 hrs was 0.71±0.04, which was lower than the miR-423-5p-inhibitor group and miR-NC group, while the value in the miR-423-5p-inhibitor group was 1.09±0.05, which was higher than the miR-NC group 0.84±0.04 ($p<0.05$, Fig. 3b). Subsequently, we analyzed the apoptosis rate of the cells through flow cytometry experiments and the results were shown in Fig. 3c. The apoptotic rates of the miR-423-5p-mimics group in SGC7901 and MGC803 cells were 16.52±1.86 and 15.62±1.08%, which were higher than the miR-423-5p-inhibitor group and miR-NC group and the apoptotic rates of the miR-423-5p-inhibitor group were 5.12±0.84 and 4.56±0.56%, respectively, which were lower than those of miR-NC group 9.42±1.15 and 9.94±1.24% ($p<0.05$, Fig. 3d). The Transwell experiment was used to analyze the invasion ability of the cells and the results were shown in Fig. 3e. The number of cell invasions in the miR-423-5p-mimics group in SGC7901 and MGC803 cells were 18.72±4.06 and 20.14±5.23, which were lower than those in the miR-423-5p-inhibitor group and miR-NC group, while miR-423 The cell invasion numbers in the miR-423-5p-inhibitor group were 118.62±8.96 and 115.62±9.54, which were higher than those in the miR-NC group 60.57±7.53 and 58.16±6.92 ($p<0.05$, Fig. 3f). It can be concluded that silencing miR-423-5p can promote the proliferation and invasion of gastric cancer cells and inhibit apoptosis while increasing miR-423-5p will have opposite effects.

Verification of the connection between PVT1 and miR-423-5p: First, the online target gene prediction website ENCORI showed that PVT1 and miR-423-5p have complementary sites that can bind (Fig. 4a). Subsequently, through the dual-luciferase reporter experiment, we got that the fluorescence activity of PVT1-WT after transfection with miR-423-5p-mimics was 0.49±0.04, lower than PVT1-WT transfected with miR-NC 1.12±0.06 ($p<0.05$, Fig. 4b). Afterwards, we detected the impact of PVT1 on the expression level of miR-423-5p by PCR. The results described that the expression levels of miR-423-5p in the sh-PVT1 group in SGC7901 and MGC803 cells were 0.42±0.02 and 0.35±0.06, accordingly. The expression levels of miR-423-5p in the si-PVT1 group were 1.94±0.08 and 2.04±0.07, which were higher than those in the lncRNA-NC group 1.06±0.15 and 1.12±0.12 ($p<0.05$, Fig. 4c) suggesting that PVT1 affects the biological behaviour of gastric cancer cells by targeting miR-423-5p.

Rescue experiment: Si-PVT1 and miR-423-5p-inhibitor were co-transfected into GC cells and set as group A, Group B was transfected with miR-423-5P-inhibitor alone and group C was transfected with lncRNA-NC alone. The results of the MTT experiment showed that the cell proliferation ability of SGC7901 cells in group A was 0.74±0.04 at 96 hrs, which was no different from the cell proliferation ability of group C at 0.75±0.04 ($p>0.05$) and was greater than that of group B 0.55±0.04 ($p<0.05$, Fig. 5a). In MGC803 cells, the cell proliferation ability of group A at 96 hrs was 0.75±0.05, which was no different from the cell proliferation ability of group C 0.76±0.04 ($p>0.05$) and was greater than that of group B 0.58±0.04 ($p<0.05$, Fig. 5b). Afterwards, we examined the apoptosis rate of the cells through flow cytometry experiments and the results were shown in Fig. 5c. The apoptotic rates of group A in SGC7901 and MGC803 cells were 8.94±1.51 and 9.04±1.08%, which were similar to those of group C 10.42±1.12 and 9.94±1.08% ($p>0.05$), lower than the

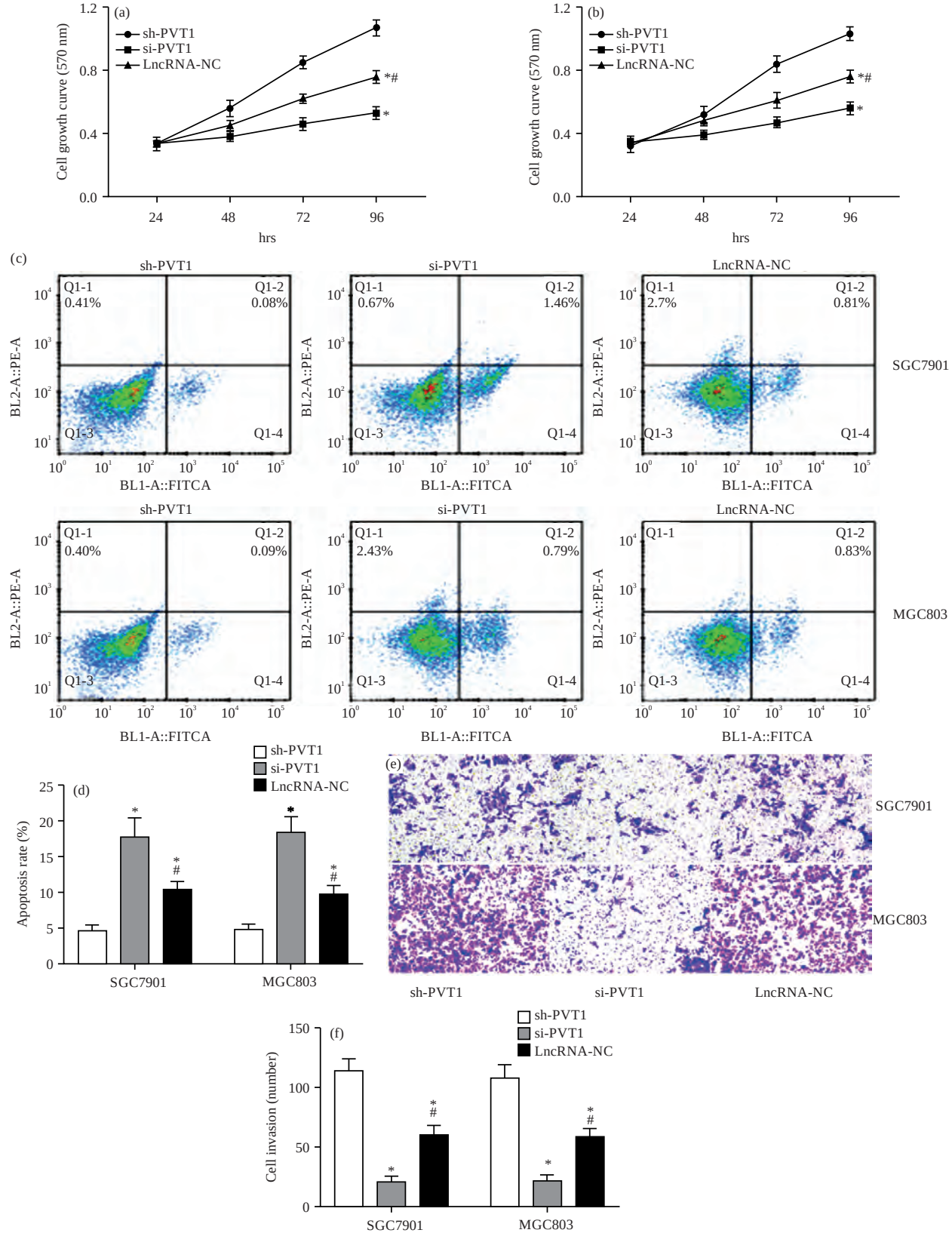

Fig. 2(a-f): Effect of PVT1 on GC cells, (a) SGC7901 growth curve, (b) MGC803 growth curve, (c) Flow cytometry, (d) Apoptosis rate, (e) Cell invasiveness and (f) Cell invasiveness number

*p<0.05 vs. sh-PVT1 group and #p<0.05 vs. si-PVT1 group

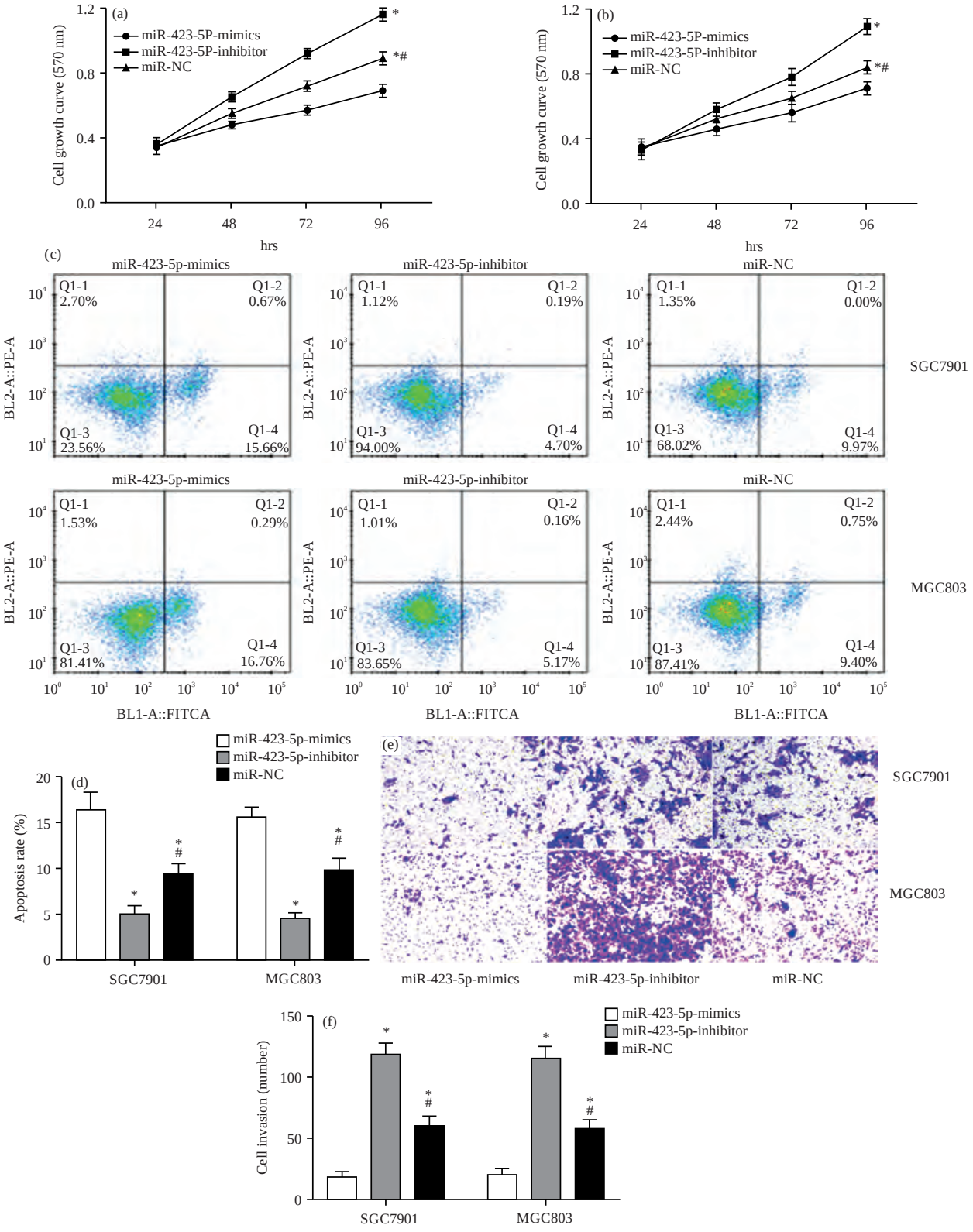

Fig. 3(a-f): Effect of miR-423-5p on GC cells, (a) SGC7901 growth curve (X-axis: Treatment time of miRNA mimics or inhibitor), (b) MGC803 growth curve (X-axis: Treatment time of miRNA mimics or inhibitor), (c) Flow cytometry, (d) Apoptosis rate (X-axis: Names of cell lines), (e) Cell invasiveness and (F) Cell invasiveness number (X-axis: names of cell lines)

*p<0.05 vs. miR-423-5p-mimics group and #p<0.05 vs. miR-423-5p-inhibitor group

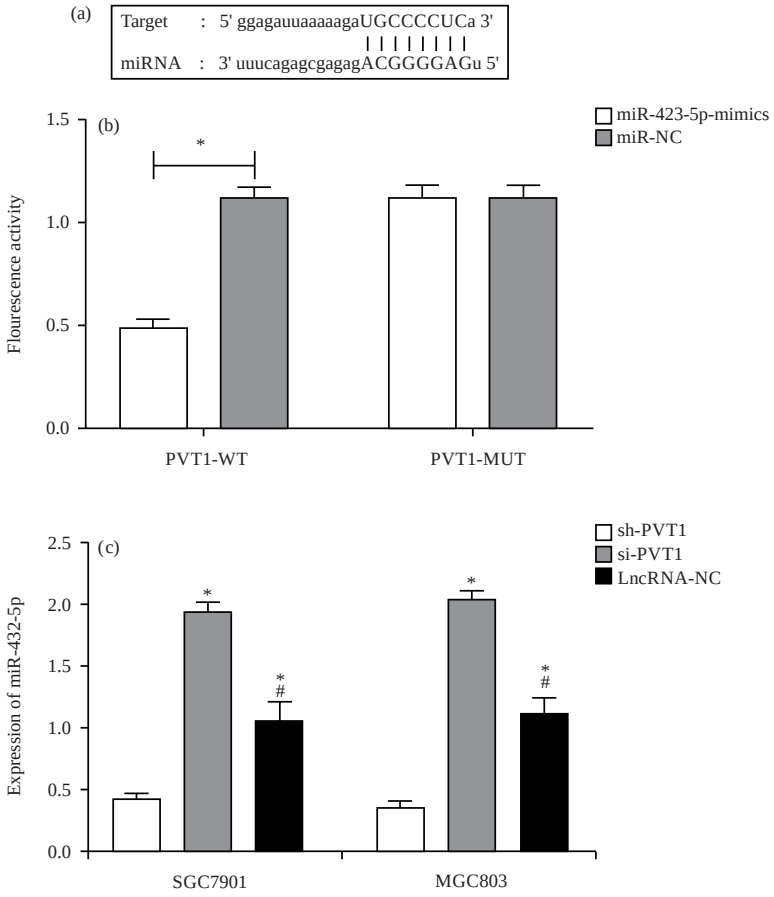

Fig. 4(a-c): Verification of the relationship between PVT1 and miR-423-5p, (a) Binding complementary site of PVT1 and miR-423-5p, (b) Dual-luciferase reporter assay (X-axis: Luciferase reporter plasmids containing wild type PVT1 or mutant PVT1 sequences that were complementary to miR-423-5p sequence) and (c) Effect of PVT1 on miR-423-5p (X-axis: Names of cell lines)

*p<0.05 vs. sh-PVT1 group and #p<0.05 vs. si-PVT1 group

apoptosis rate of group B 16.98±2.54 and 17.86±2.23% ($p<0.05$, Fig. 5d). The Transwell experiment was used to examine the invasion ability of cells and the results were shown in Fig. 5e. In SGC7901 and MGC803 cells, the number of cell invasions in group A was 114.62±9.52 and 108.62±10.54, respectively and there was no difference between the number of cell invasions in group C 60.57±7.62 and 59.13±7.24 ($p>0.05$), both the number of cell invasion was higher than that of group B 21.63±4.92 and 21.63±4.92, ($p<0.05$, Fig. 5f). The effect of silencing PVT1 on gastric cancer cells was completely reversed after silencing miR-423-5p.

DISCUSSION

This study indicated the oncogenic role of PVT1 on GC by promoting cancer cell line proliferation, invasion and suppressing apoptosis. Furthermore, miR-423-5p was found as the downstream target of PVT1. Given the ever-higher incidence of GC[16], a thorough understanding of its pathogenic mechanism is the basic to prevent and treat GC in the upcoming. In recent years, the role of lncRNA in the pathological mechanism has become increasingly popular. For example, Wei and Wang[17] proposed that lncRNA MEG3 inhibited GC progression, while Hu *et al.*[18] recommended that lncRNA SNHG1 endorsed GC cell multiplication via regulating the DNMT. This study, by exploring the influence mechanism of PVT1 on GC, carries huge implications for future clinical practice.

In previous studies, that PVT1 was profoundly expressed and miR-423-5p was low expressed in GC patients, suggesting that both may interfere with gastric carcinogenesis and progression[19,20]. And in the online database, we found that both of them have the same expression in multiple tumours, which can preliminarily confirm the significance of both.

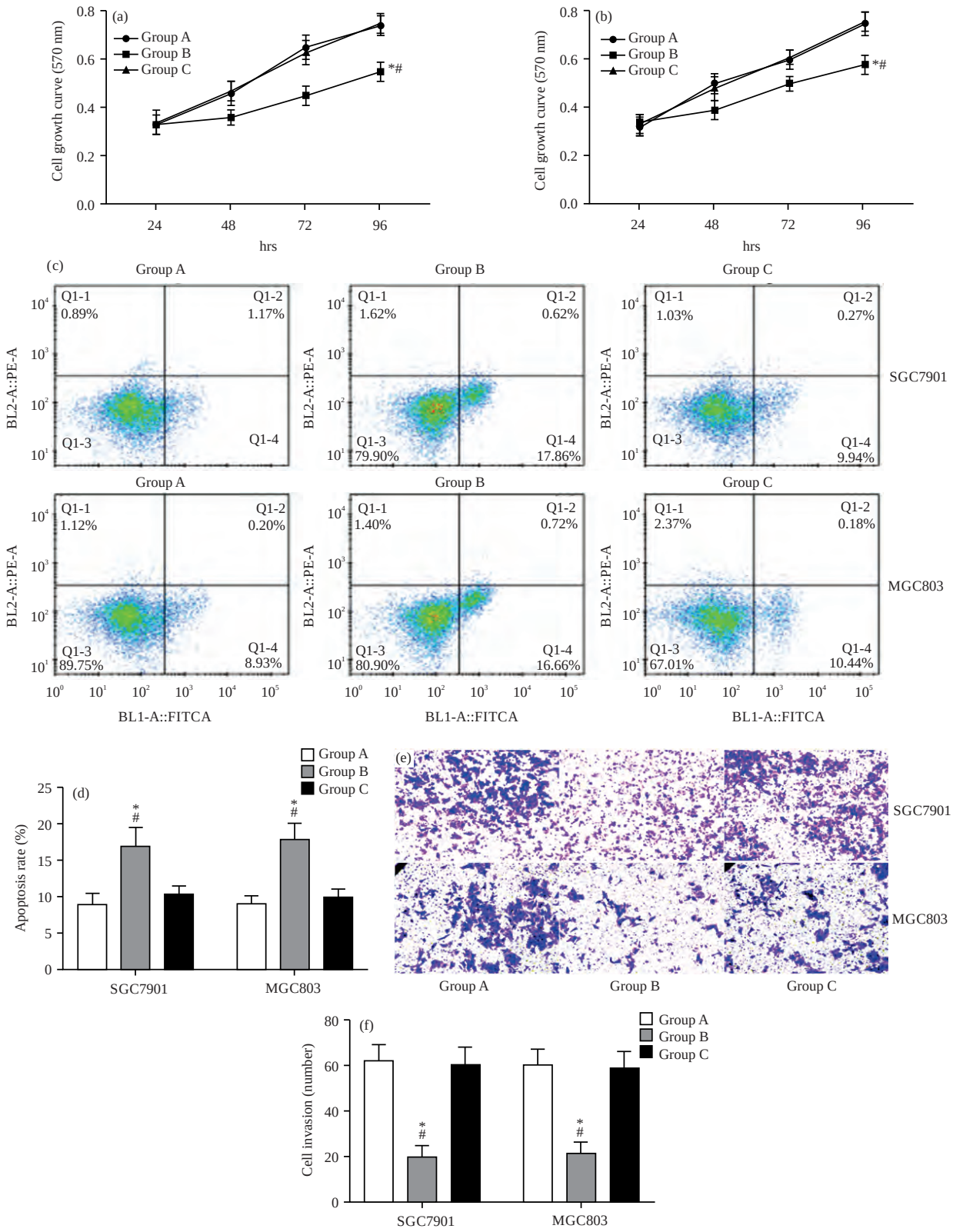

Fig. 5(a-f): Effect of co-transfection of PVT1 and miR-423-5p on GC cells, (a, b) Growth curve of SGC7901 and MGC803 cells (X-axis: Treatment time of miRNA mimics or inhibitor), (c) Results of flow cytometry experiments, (d) Apoptosis rate (X-axis: Names of cell lines), (e) Transwell experimental results and (f) Number of cell invasions (X-axis: Names of cell lines)

*Represents comparison with group A, $p<0.05$ and #Represents comparison with group C, $p<0.050$

PVT1 and miR-423-5p in GC were analyzed through the above experiments but the influencing mechanism remains uncharacterized. Therefore, GC cell strains SGC7901 and MGC803 were purchased for basic experiments. At first, it was found that after increasing PVT1, the multiplication and invasiveness ability of GC cells was boosted and the apoptosis rate reduced, while the inhibition of PVT1 produced the opposite effects, indicating that the highly expressed PVT1 played a role in an oncogene in GC. While the biological behaviour of GC cells after increasing miR-423-5p was opposite to that of PVT1, which agreed with previous studies[21,22]. Subsequently, through the online website, we found that PVT1 and miR-423-5p had complementary binding sites and DLRA identified that the fluorescence activity of PVT1-WT was inhibited after transfection of miR-423-5p-mimics, which confirmed our initial conjecture that PVT1 targeted and regulated miR-423-5p. However, miR-423-5p in GC cells was increased after PVT1 silencing and the reverse was observed after PVT1 elevation, indicating that PVT1 can inhibit miR-423-5p in a targeted manner, which was consistent with current results in detecting the correlation between the peripheral blood miR-423-5p and miR-423-5p of GC patients. Finally, the rescue experiment showed that the impact of silencing PVT1 on GC cells can be turned by simultaneously inhibiting miR-423-5p, which validated the targeted regulation relationship between the two. Therefore, we can get the preliminary mechanism of PVT1's involvement in GC, that is, it promotes GC cell multiplication and invasiveness and reduces apoptosis via targeted inhibition of miR-423-5p.

Of course, this experiment also has many shortcomings to be addressed. For example, the short time frame of this investigation prevented us from analyzing the connection between PVT1, miR-423-5p and the long-term prognosis of GC patients. Besides, since no tumorigenesis experiment has been conducted in nude mice, it is not known how these two factors affect specific tumorigenesis. Moreover, the mechanism by which PVT1-targeting miR-423-5p regulates GC cells may also be related to relevant target proteins and signalling pathways, which are worthy of further experimental analysis.

CONCLUSION

PVT1 participates in gastric carcinogenesis and progression via the targeted inhibition of miR-423-5p to promote GC cell activity and reduce apoptosis, which may be a breakthrough in the future diagnosis and treatment of GC.

SIGNIFICANCE STATEMENT

This study discovers the PVT1-miR-423-5p axis in GC and reveals the antiproliferative, anti-invasive and pro-apoptotic potentials of PVT1 silence that can be beneficial for GC patients. This study will help the researcher to uncover the critical areas of GC pathogenesis that many researchers were not able to explore. Thus, a new theory on the molecular targeted therapy of GC may be arrived at.

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