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Original Article

PABPC1 exerts carcinogenesis in gastric carcinoma by targeting miR-34c

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Abstract: As one of the common malignant tumors that threaten human health severely, gastric carcinoma is the second highest cause of cancer death and the fourth most common cancer globally. However, the mechanism underling gastric cancer is still not fully understood. PABPC1 plays an important role in translation, control the rate of mRNA deadenylation and participates in mRNA decay, which is involved in carcinogenesis. Here in present study, we reported that PABPC1 is an oncogenic protein in gastric carcinoma. The results showed that PABPC1 is upregulated in gastric carcinoma tissues, and high PABPC1 expression predicts poor survival. PABPC1 regulates proliferation and transformation of gastric cancer cells in vitro and in vivo. PABPC1 knockdown induces apoptosis by upregulating pro-apoptotic proteins and downregulating anti-apoptotic proteins. In addition, miR-34c is a target of PABPC1, and miR-34c is critically essential for the function of PABPC1. In summary, PABPC1 exerts carcinogenesis and promotes growth and survival of gastric cancer cells by regulating miR-34c.

Keywords: PABPC1, gastric carcinoma, carcinogenesis, miR-34c

Introduction

Gastric carcinoma is the second highest cause of cancer death and the fourth most common cancer globally [1]. So far, gastric carcinoma is still one of the common malignant tumors that threaten human health severely. Gastric carcinoma is difficult to cure unless it is found at an early stage and the treatment is dependent mainly on surgery, chemotherapy and radiation therapy [2]. Unfortunately, for there is little or even no peculiar symptom in early stage and the tumor has often metastasized plus the most elderly patients, the diagnosis is often delayed and the prognosis is generally poor with the five-year survival is less than 10% [3]. Given this, to improve the quality of life and survival of gastric cancer patients, expounding the underlying molecular mechanisms to find out novel effective therapeutic targets is urgently needed.

Polyadenylate binding proteins (PABPs) are a special type of proteins that interact in a sequence specific fashion with single-stranded poly (A) by RNA recognition motif (RRM). PABPs are classified into PABPC in the cytoplasm and PABPN1 in the nucleus. PABPCs play important roles in translation, control of the rate of mRNA deadenylation and participate in mRNA decay [4]. PABPC1 as the classical cytoplasmic polyadenylate binding protein expressed in most eukaryotes [5]. PABP3 expression had been reported to bypass PABP1 translational repression and to produce the amount of PABP needed for active mRNA translation in spermatids [6]. Described as iPABP, PABPC4 up-regulation is dependent on the status of cells, such as during T cell activation [7]. PABPC5 encoded on the X chromosome and expressed in fetal brain and in a range of adult tissues [8]. For mRNA degradation mechanism controls gene expression, numerous previous studies have been suggested that PABPs play an important role in carcinogenesis. PABPC4 expression regulates telomerase activity and cell growth in cervical cancer cell lines [9], and may have predictive value in the prognosis of patients with colorectal cancer [10]. The recent study shown knockdown of PABP decreased Paip2 level, this was not sufficient to support mRNA translation, but consequently leaded to apoptotic cell death in the Hela cell line [11]. It has been suggested that

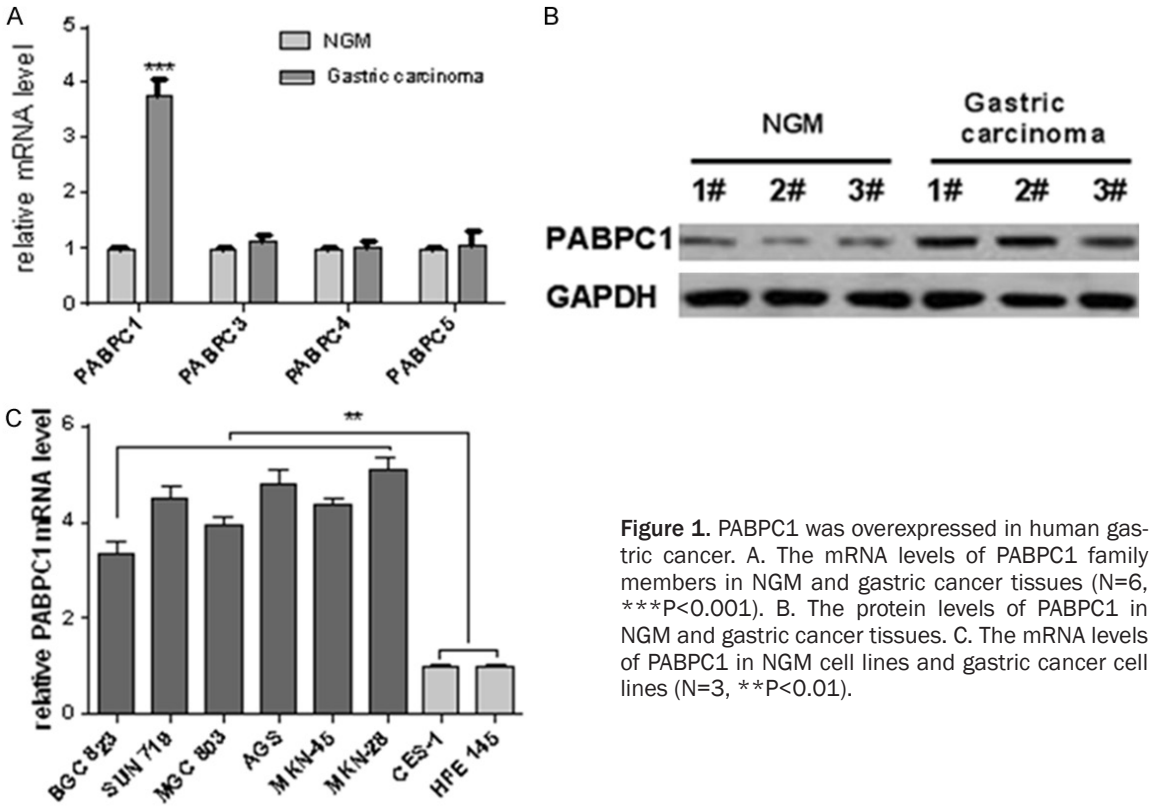

Figure 1. PABPC1 was overexpressed in human gastric cancer. A. The mRNA levels of PABPC1 family members in NGM and gastric cancer tissues (N=6, ***P<0.001). B. The protein levels of PABPC1 in NGM and gastric cancer tissues. C. The mRNA levels of PABPC1 in NGM cell lines and gastric cancer cell lines (N=3, **P<0.01).

PABPC1 also participants in breast cancer and esophageal cancer. PABPC1 was required for translation initiation through interaction with EIF4G1, as protein essential for the formation of emboli in inflammatory breast cancer [12]. Reduced expression of PABPC1 was correlated with local tumor progression and poor prognosis after surgery in esophageal cancer [13].

However, the functional role and mechanistic action of PABPCs in gastric carcinoma remains unknown. In view of the above mentioned reports, we make the proposal that PABPC1 is closely related to the occurrence and development of tumor in gastric carcinoma. Here in this study, we report the correlation between PABPC1 expression and the clinicopathological factors and prognosis of gastric carcinoma patients. We explored the effects of PABPC1 on gastric cancer cell growth in vitro and in vivo. We also investigated the action mechanism of PABPC1 on regulating apoptosis in gastric cancer. These results not only present the evidence that PABPC1 is overexpressed in human gastric carcinoma and provide PABPC1 facilitates gastric cancer growth and inhibits apoptosis by targeting miR-34c, but also provide the theoretical and experimental basis for clinical application and development of new drugs for patients with gastric cancer.

Patients and methods

Patients

One hundred and twenty six cases patients with gastric cancer were enrolled in this study, collected at Huadong Hospital (Shanghai). The fifteen patient-matched noncancerous tissues were obtained from the antrum and the body of the normal stomach separated by a distance of 5 cm. The diagnosis of breast cancer was established using World Health Organization (WHO) morphological criteria. A written form of informed consent was obtained from all patients participating in the study. The study was approved by Department of general surgery of Huadong hospital.

Cell culture

Gastric epithelial cell lines (GES-1 and HFE145) and gastric cancer cell lines (BGC823, SNU-719, MGC803, AGS, MKN-45 and MKN-28) were purchased from the American Type Culture Collection. All the cells were cultured in

Table 1. Characteristics of gastric cancer patients

Variable		Patients (126)	Expression of PABPC1		*P* value
			High PABPC1 (70)	Low PABPC1 (56)	
Age	≤65	69	38	31	0.9461
	>65	57	32	25	
Sex	Male	76	44	32	0.6152
	Female	50	26	24	
Tumor stage	T1	10	7	3	0.4711
	T2	51	33	18	
	T3	56	27	29	
	T4	9	3	6	
Nodal status	N0	39	31	8	<0.0001
	N1	41	22	19	
	N2	31	14	17	
	N3	15	3	12	
Stage of metastasis	M0	93	48	45	0.0248
	M1	33	22	11	
Lauren	Intestinal	60	36	24	0.5793
	Diffuse	66	34	32	

RPMI1640 medium supplemented with penicillin streptomycin, GlutaMAX-1 and 10% fetal bovine serum (Gibco) at 37°C with 5% CO_2.

Retrovirus package, transduction and transfection

Control shRNA and specific sh-RNAs targeting PABPC1 were purchased from Invitrogen, and the corresponding sequences were cloned into the pSIREN-RetroQ plasmid (Addgene) for retrovirus production with 293T cells. miR-34c was knocked down with a specific miR-34c sponge. For transduction, cells were incubated with virus-containing supernatant in the presence of 8 mg/ml polybrene. After 48 h, infected cells were selected for 72 h with 200 mg/ml hygromycin. For transfection, the locked nucleic acid-antimiR-34c or LAN-control were delivered at a final concentration of 50 nM using Lipofectamine 2000 reagent (Invitrogen).

Cell proliferation assay

Cell proliferation was monitored by a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) Cell Proliferation/Viability Assay kit (R&D SYSTEMS) in according to the guidelines.

Soft agar colony formation assay

Gastric cancer cells were suspended in 1.5 ml complete medium supplemented with 0.45% low melting point agarose (Invitrogen). The cells were placed in 35 mm tissue culture plates containing 1.5 ml complete medium and 0.75% agarose on the bottom layer. The plates were incubated at 37°C with 5% CO_2 for 2 weeks. Cell colonies were stained with 0.005% crystal violet and analyzed using a microscope.

Tumor xenograft experiments

Xenograft mice experiments were performed as described previously [14]. In brief, equal number gastric cancer cells stably with either control or PABPC1 knockdown or overexpression were implanted subcutaneously into the forelegs of 4 to 6 weeks old male nu/nu mice (Vital River). The mice were killed and the tumor weight was evaluated at the terminal of the experiment. This experiment was repeated for three times.

Western blot

Cells were lysed with RIPA buffer supplied with mixture of protease inhibitors (Thermo). Cells with equal amounts protein were resolved by 10% SDS-PAGE. After blotting on PVDF membranes, the membrane was blocked with 3% fat-free milk for 2 hours, which were probed with primary antibody for Bcl-2, Bax, p-casp3, casp3 and GAPDH (Santa Cruz Biotechnology) at 4°C overnight. Then the membranes were incubation with horseradish peroxidase-conjugated secondary antibodies for 2 hours at room temperature. Signals were detected using enhanced chemiluminescence reagents (Thermo).

Statistics

Student's t test was performed to compare the differences between two groups. The Kaplan-Meier method was used to estimate overall and disease-free survival. The log-rank test was performed to analyze the survival differences according to PABPC1 expression. Linear regression analysis was performed to analyze the relation between PABPC1 and miR-34c expres-

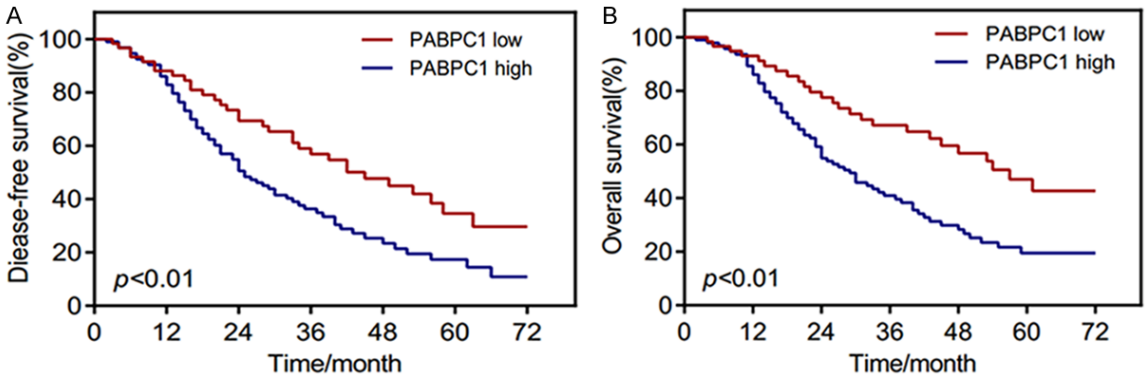

Figure 2. High PABPC1 predicted poor survival. A. High PABPC1 expression predicted poor overall survival. B. High PABPC1 expression predicted poor disease-free survival.

sion in human gastric cancers. *P* values of less than 0.05 were considered statistically significant.

Results

PABPC1 overexpressed in human gastric cancer

To understand the relation between PABPs and gastric cancer, we evaluated the mRNA levels of the members of PABPs in human normal gastric mucosa (NGM) and gastric carcinoma tissues. The results revealed remarkable PABPC1 up-regulated expression in tumor tissues compared to NGM, whereas the mRNA levels of other PABPs did not change obviously (**Figure 1A**). To examine the protein levels of PABPC1 in tumor tissues and NGM, we employed the western blot and the results revealed that PABPC1 protein level also increased in human gastric carcinoma tissues (**Figure 1B**). Next, we investigated the mRNA levels of PABPC1 in normal gastric epithelial cell lines (GES-1 and HFE145) and gastric cancer cell lines (BGC823, SNU-719, MGC803, AGS, MKN-45 and MKN-28). Conformity to the condition in human gastric cancer patients, the mRNA levels of PABPC1 was significantly increased in gastric cancer cell lines compared to normal gastric epithelial cell lines (**Figure 1C**). Based on findings from mRNA and protein array, we found that PABPC1 was overexpressed in human gastric carcinoma and gastric cancer cell lines.

PABPC1 predicted poor prognosis of gastric carcinoma

Given the report that esophageal cancer patients with low PABPC1 mRNA expression had a significantly shorter survival time than those with high expression [13], we put forward a proposal that PABPC1 may be a good molecular prognostic marker in cancer. The analysis of characteristics of gastric cancer patients showed that high miRNA expression level of PABPC1 was related with tumor stage, nodal status and stage of metastasis (**Table 1**). We performed Kaplan-Meier and log-rank test to analyze the difference in survival durations between PABPC1 low and high expression groups. Contrary to esophageal cancer, the results indicated that high expression of PABPC1 predicted poor overall survival (**Figure 2A**) and predicted poor disease-free survival (**Figure 2B**). This suggested that PABPC1 may serve as independent factor predicting gastric carcinoma patients' prognosis and PABPC1 expression was correlated with disease recurrence. In summary, PABPC1 was a significant prognostic factor for predicting poor survival in human gastric carcinoma.

PABPC1 regulated gastric cancer cell growth in vitro and in vivo

For the base of the above results, we deduced that PABPC1 may participate in gastric carcinoma development and investigated whether PABPC1 can regulate gastric cancer growth in vitro and in vivo. To knock down PABPC1 in gastric cancer cell line BGC823, MKN-45 and MGC803, we infected gastric cancer cells with retrovirus carrying sh-PABPC1 and evaluated the effects on cell growth by MTT. The results showed that PABPC1 depletion reduced the proliferation rate of BGC823, MKN-45 and MGC803 cells (**Figure 3A-C**). We next probed the potential contribution of PABPC1 in the

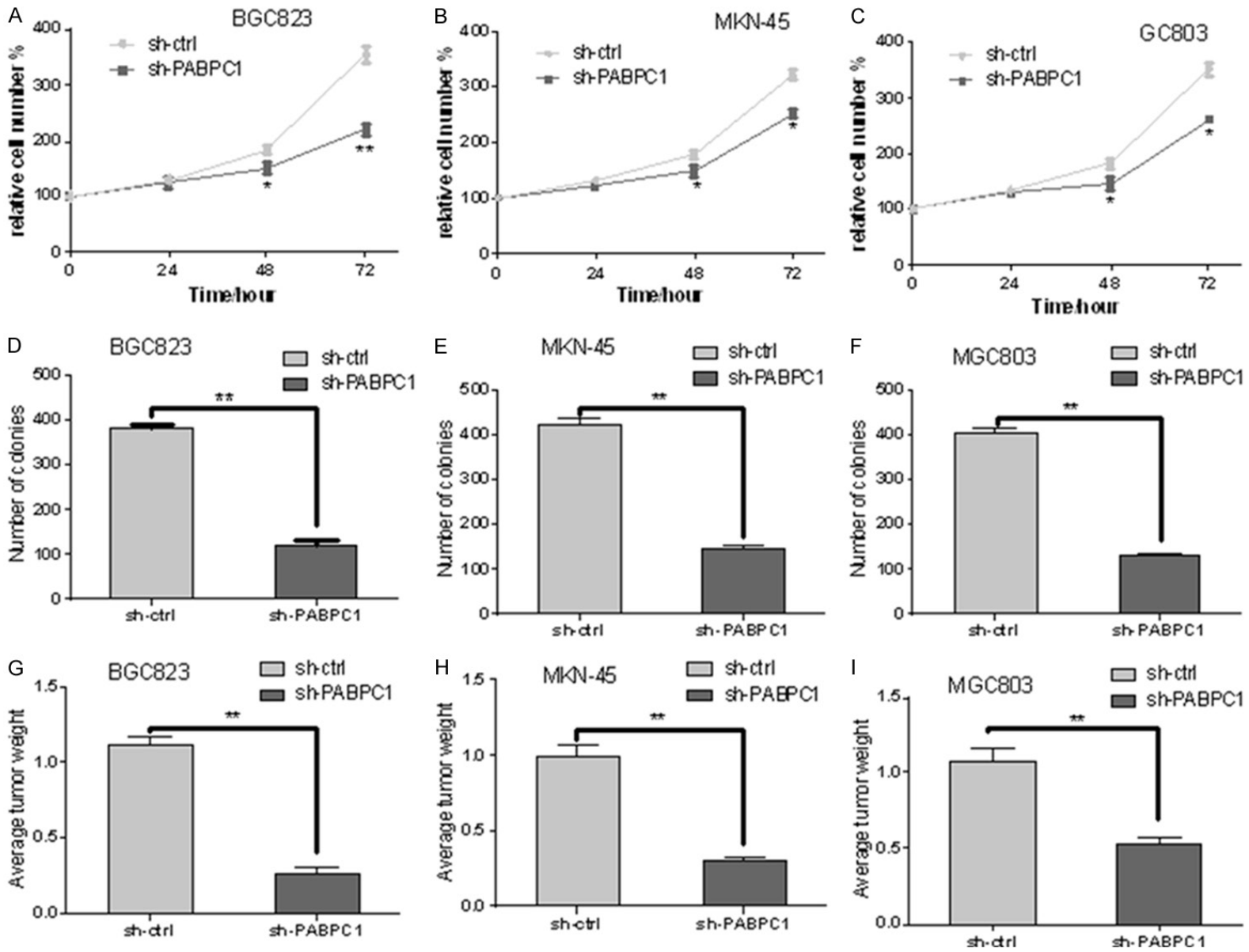

Figure 3. PABPC1 regulated gastric cancer growth in vitro and in vivo. A-C. Knockdown of PABPC1 suppressed proliferation in BGC823, MKN-45 or MGC803cells (N=3, *P<0.05, **P<0.01). D-F. Knockdown of PABPC1 suppressed colony formation in BGC823, MKN-45 or MGC803 cells (N=3, **P<0.01). G-I. Knockdown of PABPC1 suppressed gastric cancer growth in BGC823, MKN-45 or MGC803 cells (N=3, **P<0.01).

transformative properties of gastric cancer cells. We observed that PABPC1-depleted cells possessed reduced colony forming activity in BGC823, MKN-45 and MGC803 cells (**Figure 3D-F**). Then we explored whether PABPC1 could regulate gastric cancer growth in vivo, thus we performed tumor xenograft experiments. We evaluated the effects of PABPC1 on tumor weight at the terminal of the experiment, and we found PABPC1 knockdown significantly inhibited gastric cancer growth in vivo (**Figure 3G-I**). Taken together, these results demonstrated that PABPC1 promoted gastric cancer growth in vitro and in vivo.

PABPC1 regulated cell apoptosis and targeted miR-34c in gastric cancer

To uncover the underlying mechanisms of how PABPC1 affects gastric cancer growth, we knocked down PABPC1 in gastric cancer cells BGC823, MKN-45 and MGC803 and analyzed the cells apoptosis by FACS. The results showed that PABPC1 knockdown significantly increased the percentage of apoptotic cells in BGC823, MKN-45 and MGC803 cells (**Figure 4A**). We further performed western blot to analyze the effects of PABPC1 knockdown on apoptosis related protein expression. The results indicated that PABPC1 knockdown activated apoptotic and block anti-apoptotic. PABPC1 knockdown increased the levels of pro-apoptotic proteins Bax and cleaved Caspase 3), while the anti-apoptotic protein Bcl-2 was down-regulated (**Figure 4B**). These results suggested that knockdown of PABPC1 promoted apoptosis in gastric cancer cells.

One of the tumor suppressor microRNA, miR-34c, was previously reported that it exhibits tumor suppressing effects on proliferation, apoptosis and invasiveness in many cancers [15-17]. To study the mechanism how PABPC1 regulated the apoptosis of gastric cancer cells, RT-PCR was performed to evaluate the level of miR-34c. **Figure 4C** showed that miR-34c was down-regulated in human gastric carcinoma. Furthermore, we performed linear regression analysis to figure out whether PABPC1 is correlated with the level of miR-34c in human gastric carcinoma. The results showed that miR-34c level was significantly but negatively correlated with PABPC1 mRNA level (**Figure 4D**). To ascertain which one regulated another between PABPC1 and miR-34c, we knocked down PABPC1 and/or miR-34c in MGC803 cells. **Figure 4E** showed that PABPC1 knockdown enhanced the expression level of miR-34c. **Figure 4F** showed that inhibition of miR-34c abolished PABPC1 knockdown induced apoptosis in MGC803 cells. Significantly, **Figure 4G** showed that PABPC1 knockdown restored the expression of miR-34c in MGC803 cells, whereas miR-34c knockdown did not change the expression of PABPC1 obviously. In addition, inhibition of miR-34c abolished PABPC1 knockdown induced reduction of colony formation in MGC803 cells (**Figure 4H**). Taken together, these results indicate that PABPC1 may exert carcinogenesis via inhibiting miR-34c expression in gastric cancer cells.

Discussion

PABPC1 is a complex cytoplasmic protein containing four highly conserved repeats RNA-binding domains, which is important for protein translation initiation as well as RNA processing and stability [18]. PABPC1 shuttles between the nucleus and cytoplasm in some cases, and associates with intron containing pre-mRNAs undergoing polyadenylation and interacts with poly (A) polymerase to engage in nuclear RNA processing when it exists in the nucleus [19]. In eukaryotic cytoplasm, PABPC1 binds to the 3'poly (A) tail of mRNA by RRMs and interacts with the N-terminus of eukaryotic initiation factor 4G (eIF4G) [20]. In addition, PABPC1 is involved in nonsense mediated decay (NMD) through interaction with eukaryotic release factor 3 (eRF3) and an exon junction complex [21]. However, a recent study reported that PABPC1 does not require the interaction with eRF3a to retain its NMD suppressing activity, and a mutant of PABPC1 unable to bind eIF4G does not inhibit NMD [22]. Consider the ability to regulate protein expression of PABPC1 and the abnormal changes of PABPC1 expression in breast cancer and esophageal cancer [12, 13], we evaluated the mRNA levels of PABPC1 in human normal gastric mucosa (NGM) compared to gastric carcinoma tissues. We found that PABPC1 was overexpressed in human gastric carcinoma and gastric cancer cell lines. Furthermore, the analysis of Kaplan-Meier and log-rank test showed the difference in survival durations between PABPC1 low and high expression groups. The results showed that PABPC1 was a significant prognostic factor for

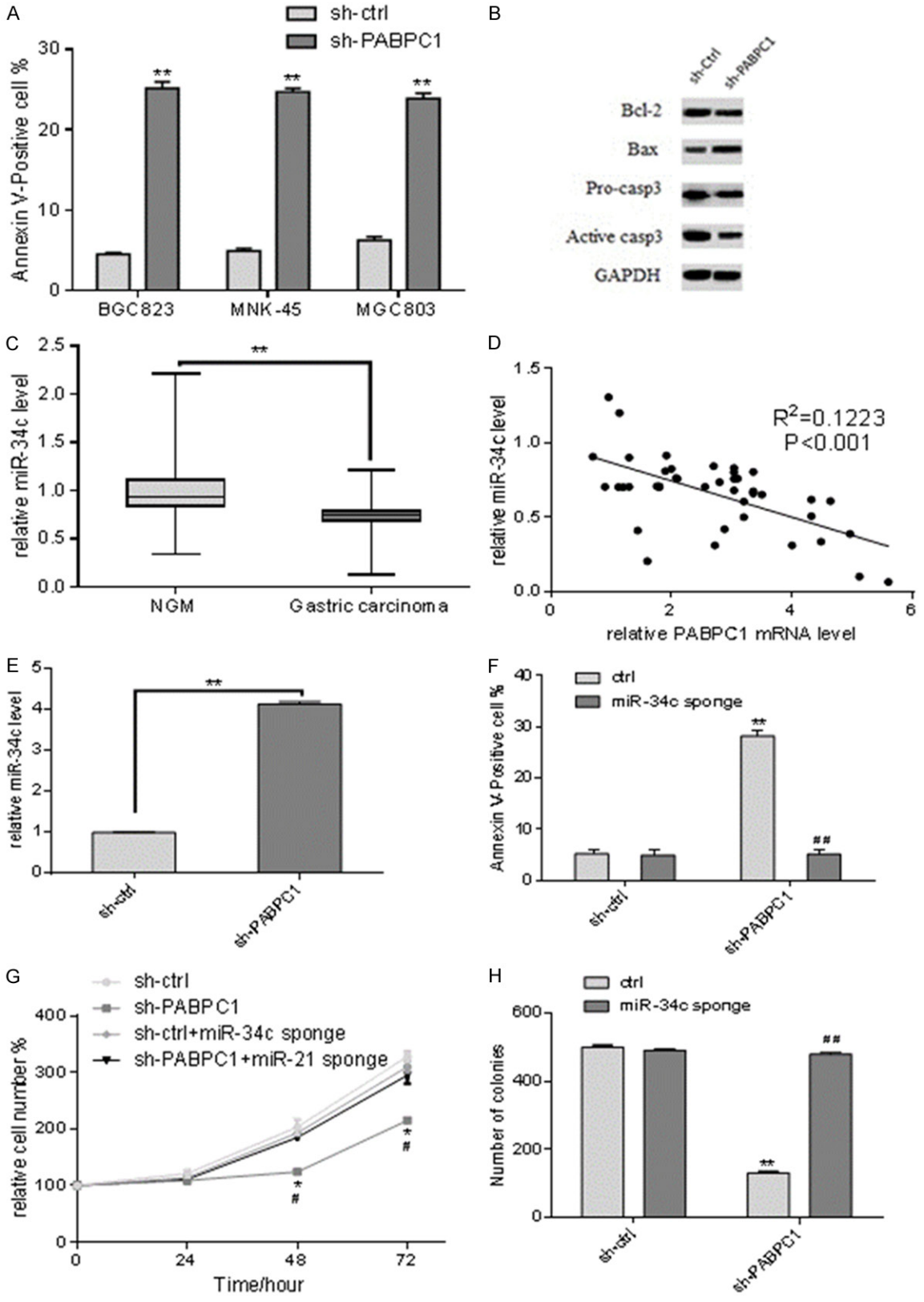

Figure 4. Knockdown of PABPC1 induced apoptosis of gastric cancer cells by targeting miR-34c. A. Knockdown of PABPC1 induced apoptosis in BGC823, MNK-45 and MGC803 (N=3, **P<0.01). B. The expression of pro-apoptotic

proteins (Bax, active caspase 3) and anti-apoptotic proteins (Bcl-2) in MGC803 cells. C. miR-34c level in gastric cancer tissues compared to NGM (**P<0.01). D. miR-34c was negatively correlate with PABPC1 in human gastric cancer. E. Knockdown of PABPC1 enhanced the expression of miR-34c in MGC803 cells (N=3, **P<0.01). F. Inhibition of miR-34c abolished PABPC1 knockdown induced apoptosis in MGC803 cells (N=3, **P<0.01, ##P<0.01). G. Inhibition of miR-34c abolished PABPC1 knockdown induced reduction of proliferation rate in MGC803 cells (N=3, *P<0.05, #P<0.05). H. Inhibition of miR-34c abolished PABPC1 knockdown induced reduction of colony formation in MGC803 cells (N=3, **P<0.01, ##P<0.01).

predicting poor survival in human gastric carcinoma. This suggested that PABPC1 may be added as a possible prognostic indicator in patients with gastric cancer.

Gastric carcinoma is a kind of disease that seriously imperil the health and lives of human beings. The basic feature of gastric carcinoma is the uncontrolled proliferation, invasion and metastasis of cancer cells. Abnormal expressions of PABPC1 in gastric carcinoma tissues revealed that PABPC1 may be a regulator of tumor development. To verify the hypothesis, we knocked down PABPC1 in gastric cancer cell line, and found PABPC1 depletion reduced the proliferation rate of cancer cells. Then we probed the transformative properties of the gastric cancer cells when PABPC1 depleted, and found PABPC1-depleted cells possessed reduced colony forming activity in BGC823, MKN-45 and MGC803 cells. Moreover, we showed that PABPC1 knockdown significantly attenuated the tumorigenicity of gastric cancer cells in vivo. In addition, PABPC1 knockdown induced apoptosis in gastric cancer cells by upregulating apoptotic protein Bax and casp3, and down-regulating anti-apototic protein Bcl-2. Together with the previous study, the evidence indicates that PABPC1 could regulate cellular proliferation, transformation and apoptotic of gastric cancer cells.

MicroRNAs are a kind of small noncoding single-stranded RNAs from the endogenous chromosome, mediating posttranslational regulation via base pairing with target messenger RNAs and playing an important role in cancer cell growth control [23]. We found PABPC1 may exert carcinogenesis via inhibiting miR-34c expression in gastric cancer cells. miR-34 is a conservative microRNA family, and miR-34c is one of this family acted as a tumor suppressor. Studies have been shown that genes encoding miR-34 family induced by DNA damage or oncogenic stress are directly targeted by transcription factor p53, which suppresses tumor formation [24, 25]. miR-34b and miR-34c were downregulated in p53-null human ovarian carcinoma cells, and they suppressed proliferation and soft agar colony formation of neoplastic epithelial ovarian cells [26]. However, the relation of miR-34c and p53 in gastric cancer has not yet been explicitly reported to date. Whether and how PABPC1-miR-34c-p53 effects on the development of gastric carcinoma needs to be explored in further researches.

In present study, we found that PABPC1 was overexpressed in gastric cancer cells in vivo and in vitro. The analysis of Kaplan-Meier and log-rank test indicates that PABPC1 may be a good molecular prognostic marker, and a molecular treatment target for gastric carcinoma. Then we identified that abnormal increased expression of PABPC1 played an important role in proliferation of gastric carcinoma. Interestingly, we proved PABPC1 regulated cell apoptosis, and miR-34c was a direct target of it. In conclusion, our study demonstrated that PABPC1 is upregulated and acts as a carcinogen factor by targeting miR-34c in gastric carcinoma.

Disclosure of conflict of interest

None.

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