CELL CYCLE
2020, VOL. 19, NO. 5, 601–609
https://doi.org/10.1080/15384101.2020.1728017

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RESEARCH PAPER

MAFG-AS1 is a novel clinical biomarker for clinical progression and unfavorable prognosis in gastric cancer

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ABSTRACT

MAFG antisense 1 (MAFG-AS1) is recently identified as a novel lncRNA and serves as a tumor promoter in several types of human tumor. However, no prior study has been performed to evaluate the role of MAFG-AS1 in gastric cancer. In our study, we found MAFG-AS1 expression was increased in gastric cancer tissue samples compared with normal gastric mucosa tissue samples, and associated with poor overall survival in gastric cancer patients at The Cancer Genome Atlas database. Furthermore, we confirmed the clinical and prognostic significance of MAFG-AS1 in gastric cancer. We found gastric cancer tissues and cell lines had remarkably increased MAFG-AS1 expression in comparison to normal gastric mucosa tissues and normal human gastric epithelial cell line, and high MAFG-AS1 expression was positively associated with diffuse type, advanced clinical stage, extensive depth of invasion, more lymph node metastasis, and present distant metastasis in gastric cancer patients. Moreover, high MAFG-AS1 expression acted as one of the independent poor prognostic factors for overall survival in gastric cancer patients. The loss-of-function study showed knocking down MAFG-AS1 expression inhibited gastric cancer cell proliferation, migration and invasion *in vitro*. In conclusion, MAFG-AS1 is probable to be a valuable prognostic biomarker, and a novel potential target for gastric cancer.

ARTICLE HISTORY
Received 17 January 2020
Revised 3 February 2020
Accepted 6 February 2020

KEYWORDS
MAFG-AS1; lncRNA; biomarker; gastric cancer

Introduction

Gastric cancer is one of the most prevalent malignancies of the digestive system [1]. According to Global Cancer Statistics 2018, gastric cancer ranks as the sixth most common cancer in the world and the second leading cause of cancer-related death [2]. In China, gastric cancer is the second frequently diagnosed cancer and the second leading cause of cancer-associated death accounting for 679,100 newly diagnosed cases and 498,000 deaths in 2015 [3]. Due to lack of symptoms during early stages, gastric cancer patients were often diagnosed at an advanced stage with obstruction and distant metastasis [4 5,]. Although Apatinib and Trastuzumab are applied to treat advanced gastric cancer patients in recent years, the prognosis of gastric cancer patients with advanced stage remains poor [6–9]. Therefore, searching for novel biomarkers or effective therapeutic targets will be helpful for improving the clinical outcome in gastric cancer patients.

Long non-coding RNA (lncRNA) is a classification of non-coding RNAs with lengths ranging from 200 to 100,000 nucleotides [10]. lncRNAs lack any detectable open reading frame, but can regulate gene expressions at the transcriptional and posttranscriptional stages [11 12,]. MAFG-AS1 is recently identified as a novel lncRNA and has been reported to serve as a tumor promoter in lung cancer [13 14,], hepatocellular carcinoma [15], colorectal cancer [16] and breast cancer [17]. The role of MAFG-AS1 in gastric cancer was still unknown. For estimating the expression and clinical significance of MAFG-AS1 in gastric cancer, we analyzed the online database, and found MAFG-AS1 was overexpressed in gastric cancer samples compared with normal gastric mucosa samples, and negatively associated with overall survival time of gastric cancer patients. So, we thought MAFG-AS1 also functions as oncogenic lncRNA in gastric cancer. For confirming our guess, we detected MAFG-AS1 expression in gastric cancer tissues and analyzed the association of MAFG-AS1 expression with clinicopathological characteristics and prognosis. Moreover, we performed loss-of-function study to assess the biological function of MAFG-AS1 in gastric cancer cells.

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Materials and methods

Ethical statement

The experimental protocols were approved by the Ethics Committee of Shandong University Hospital, Taishan Sanatorium and Jinan Central Hospital, and performed according to the guidelines of the 1975 Declaration of Helsinki. All participants involved in this study provided written informed consent.

Database analysis

The Starbase software (http://starbase.sysu.edu.cn/) including 375 gastric cancer samples and 32 normal gastric tissue samples from The Cancer Genome Atlas (TCGA) was used to analyze the difference of MAFG-AS1 between cancer and normal tissues. Survival analysis was conducted in Kaplan–Meier plotter (http://www.kmplot.com), which consists of 631 gastric cancer cases.

Specimen collection

Total 120 gastric cancer tissues and 45 adjacent normal gastric mucosa tissues were collected from Shandong University Hospital and Jinan Central Hospital. The pathologic diagnosis of each specimen was evaluated by a pathologist. None of the patients had received anti-tumor treatment before collecting specimens. The clinicopathological features including age, gender, Lauren's classification, differentiation degree, clinical stage, depth of invasion, lymph node metastasis, and distant metastasis were obtained from the medical records of gastric cancer patients. All tissue specimens were stored at −80°C until use.

Cell lines

The normal human gastric epithelial cell line GES-1 and human gastric cancer cell lines MKN-45, AGS, SGC7901 were cultured in Dulbecco modified Eagle's medium (DMEM, Gibco, Carlsbad, CA, USA) supplemented with 10% fetal bovine serum (FBS), 100 ug/ml streptomycin and 100 U/ml Penicillin in an incubator with 5% CO_2 at 37°C.

Reverse transcription quantitative polymerase chain reaction (RT-qPCR)

Total RNAs were extracted from gastric cancer tissue sample or cell lines by TRizol Reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. 1 μg of total RNA was used to synthesize first-strand complementary DNA through the PrimeScript RT reagent Kit (Promega, Madison, WI, USA). Then, the qPCR was conducted via Power SYBR Green PCR Master Mix (Thermo Fisher Scientific, Waltham, MA, USA) and specific primers at Applied Biosystems 7500 Real Time PCR System (Applied Biosystems, Foster City, CA, USA). The sequences of primers were forward 5′-GGGACGGAGACAAATGACGG-3′ and reverse 5′-GCAGGCTCCCTGACACGTA-3′ for MAFG-AS1; Forward 5′-CACCCACTCCTCCACCTTTG-3′ and Reverse 5′-CCACCACCCTGTTGCTGTAG-3′ for GAPDH. GAPDH was used as the endogenous control for measuring relative lncRNA expression.

Cell transfection

The small interfering RNAs (siRNAs) targeting MAFG-AS1 (si-MAFG-AS1, 5′-GCTGCAGTGA GCTGTGATCAT-3′) and negative control siRNAs (si-control, 5′-GTACGCTTTCGAAGGC TAGGT-3′) were purchased from GenePharma Co., Ltd. (Shanghai, China). The gastric cancer at logarithmic growth phase was selected to 6-well plates, and grown to about 50% confluence. Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA) and Opti-MEM (Gibco, Carlsbad, CA, USA) were utilized for siRNAs transfection based on the manufacturer's instructions.

Cell counting kit-8 assay

CCK-8 (Beyotime, Shanghai, China) was used to measure the cell viability. The cell viability was detected by cell counting kit-8 (CCK-8, Dojindo, Kumamoto, Japan). In brief, 4×10^3 gastric cancer cells were seeded into 96-well plate and incubated for 24, 48, 72 and 96 h. Subsequently, 10 μL CCK-8 reagent was added into each well and incubated for 2 h at 37°C. The optical density (OD) value of each well was detected under a wavelength of 450 nm at a microplate reader.

Transwell migration assay

Transwell migration assay was performed in Transwell chambers (Corning, NY, USA). Briefly, 1×10^5 gastric cancer cells in serum free medium were seeded onto the membrane of the top chamber, 10% FBS medium was added into the bottom chamber. After 24 h, the membranes were washed, fixed and stained with crystal violet, and migrated cells were quantified at five randomly selected areas under the microscope field.

Matrigel invasion assay

Matrigel (BD Biosciences, San Jose, CA, USA) was diluted in serum free medium at a volume ration of 1:6 and then, 100 μL of diluted Matrigel was placed in the upper chamber at 37°C overnight. The other protocols were similar to those in migration.

Statistical analysis

All of the data were representative of at least three independent experiments and are showed as the mean ± standard deviation. Comparisons among three or more than three groups were analyzed by one-way analysis of variance followed by Tukey post hoc test, and the differences between two groups were analyzed by student's t-test. The correction of MAFG-AS1 expression with clinicopathological characteristics was estimated by chi-square test. Survival curve was drawn by the Kaplan–Meier method, and differences were evaluated by the log rank test. The independent prognostic factors were identified through univariate and multivariate Cox regression analyses. SPSS 18.0 software was used for statistical analysis, and P value less than 0.05 was considered as significant difference.

Results

Database analysis

Initially, the gene-expressed profiles of 375 gastric cancer tissue samples and 32 normal gastric mucosa tissue samples from The Cancer Genome Atlas database were analyzed at Starbase software. We found that levels of MAFG-AS1 were increased in gastric cancer tissue samples compared with normal gastric mucosa tissue samples ($P < 0.001$, Figure 1a). In survival analysis of Kaplan–Meier method and log rank test, we observed gastric cancer patients with high MAFG-AS1 expression had shorter overall survival than patients with low MAFG-AS1 expression ($P < 0.001$, Figure 1b). Moreover, univariate Cox regression analysis indicated high MAFG-AS1 expression was an unfavorable prognostic factor for overall survival in gastric cancer patients (hazard ratio, 95% confidence interval: 1.49, 1.19–1.87; Figure 1b).

Increased MAFG-AS1 expression in gastric cancer tissues and cells

For further confirm the MAFG-AS1 expression in gastric cancer tissues, we performed RT-qPCR to detect MAFG-AS1 expression in 120 gastric cancer tissues and 45 adjacent normal gastric mucosa

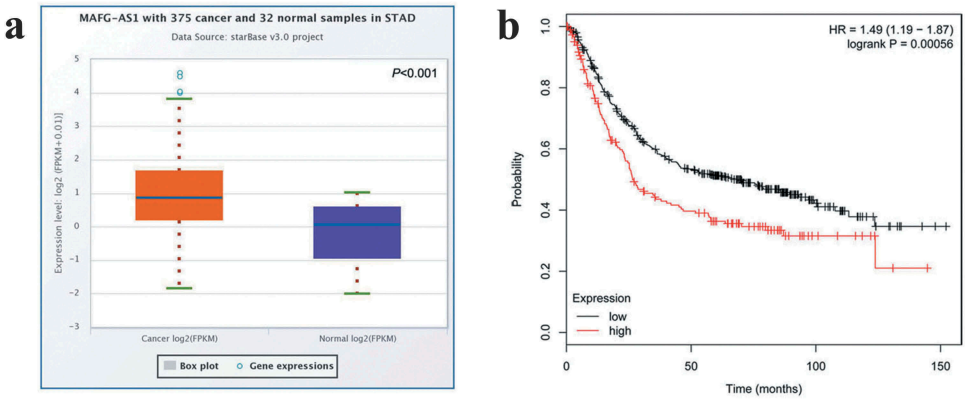

Figure 1. Database analysis of MAFG-AS1 expression in gastric cancer.

(a) MAFG-AS1 was increased in gastric cancer tissue samples compared with normal gastric mucosa tissue samples. (b) Gastric cancer patients with high MAFG-AS1 expression had shorter overall survival than patients with low MAFG-AS1 expression.

tissues, and found gastric cancer tissues had remarkably increased MAFG-AS1 expression in comparison to normal gastric mucosa tissues ($P < 0.001$, Figure 2a). Furthermore, we measured the MAFG-AS1 expression in normal human gastric epithelial cell line GES-1 and human gastric cancer cell lines MKN-45, AGS, SGC7901, and observed increased MAFG-AS1 expression in human gastric cancer cell lines compared to that in normal human gastric epithelial cell line ($P < 0.001$, Figure 2b).

The correlation between MAFG-AS1 expression and clinicopathological characteristics of gastric cancer

For evaluating the clinical value of MAFG-AS1 expression in gastric cancer patients, we divided all gastric cancer samples into two groups: high MAFG-AS1 expression group (n = 60, more than median value of MAFG-AS1 expression) and low MAFG-AS1 expression group (n = 60, less than median value of MAFG-AS1 expression). Then, the correlation between MAFG-AS1 expression and clinicopathological characteristics of gastric cancer was analyzed through chi-square test. As shown in Table 1, we found high MAFG-AS1 expression was associated with diffuse type ($P = 0.017$), advance clinical stage ($P = 0.040$), extensive depth of invasion ($P = 0.005$), more lymph node metastasis ($P = 0.044$), and present distant metastasis ($P = 0.001$) in gastric cancer patients. However, we did not find any association of MAFG-AS1 expression with age ($P = 0.133$), gender ($P = 0.090$) and differentiation degree ($P = 0.568$).

The correlation between MAFG-AS1 expression and overall survival of gastric cancer

For confirming the prognostic value of MAFG-AS1 expression in gastric cancer patients, we performed Kaplan–Meier method and log rank test to estimate the correlation between MAFG-AS1 expression and overall survival of gastric cancer patients. Similar to the result of database analysis, we also found high MAFG-AS1 expression was associated with short overall survival in gastric cancer patients ($P < 0.001$, Figure 3). Then, we conducted univariate Cox regression analyses and identified clinical stage ($P < 0.001$, Table2), depth of invasion ($P = 0.001$, Table2) Lymph node metastasis ($P < 0.001$, Table2), distant metastasis ($P < 0.001$, Table2), and MAFG-AS1 expression ($P < 0.001$, Table2) were prognostic factors for overall survival in gastric cancer patients. Furthermore, the results of multivariate Cox regression analyses suggested clinical stage ($P = 0.024$, Table2), M classification ($P < 0.001$, Table2) and MAFG-AS1 expression ($P = 0.043$, Table2) were the independent prognostic factors for overall survival with hazard ratio 1.756, 95% confidence interval: 1.018–3.028.

The biological function of MAFG-AS1 expression in gastric cancer

To disclose the influence of MAFG-AS1 expression on gastric cancer cell proliferation, migration and invasion, si-MAFG-AS1 was transfected into MKN-45 and AGS cells, which were relative high MAFG-AS1 expression among three cell lines. As shown in Figure 4a, MAFG-AS1 expression was definitely suppressed in MKN-45 and

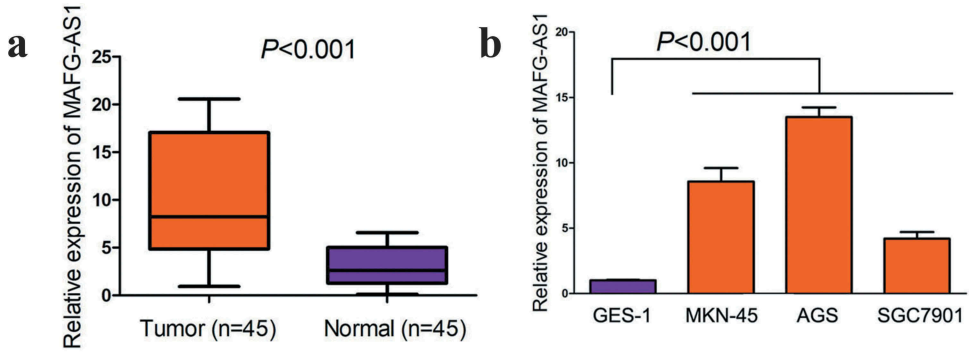

Figure 2. Increased MAFG-AS1 expression in gastric cancer tissues and cells.

(a) Gastric cancer tissues had increased MAFG-AS1 expression in comparison to normal gastric mucosa tissues. (b) MAFG-AS1 expression was increased in human gastric cancer cell lines compared with normal human gastric epithelial cell line.

Table 1. Correlations between MAFG-AS1 expression and clinicopathological characteristics of gastric cancer.

Characteristics	n	High MAFG-AS1 expression	Low MAFG-AS1 expression	*P*
Gender				
Female	45	27	18	0.090
Male	75	33	42	
Age(y)				
<50	46	27	19	0.133
≥50	74	33	41	
Lauren's classification				
Intestinal	63	25	38	0.017
Diffuse	57	35	22	
Differentiation degree				
High and moderate	77	37	40	0.568
Low and undiferentiated	43	23	20	
Clinical stage				
I-II	47	18	29	0.040
III-IV	73	42	31	
Depth of invasion				
T1-T2	49	17	32	0.005
T3-T4	71	43	28	
Lymph node metastasis (n)				
<3	55	22	33	0.044
≥3	65	38	27	
Distant metastasis				
Absent	110	50	60	0.001
Present	10	10	0	

AGS cells ($P < 0.001$). In addition, we conducted CCK-8 assay to appraise the effect of MAFG-AS1 expression on gastric cancer cell proliferation, and found knocking down MAFG-AS1 expression strikingly inhibited cell proliferation of MKN-45 and AGS cells ($P < 0.01$, Figure 4b). Meanwhile, the effect of MAFG-AS1 expression on gastric cancer cell migration and invasion was estimated by transwell migration and invasion assays. The results of transwell migration assay indicated knocking down MAFG-AS1 expression notably decreased migrated gastric cancer cells ($P < 0.001$, Figure 4c). Similar to the results of transwell migration assay, Matrigel invasion assay also showed knocking down MAFG-AS1 expression obviously reduced invasive gastric cancer cells ($P < 0.001$, Figure 4d).

Discussion

MAFG-AS1 is a novel lncRNA transcribed from 17q25 and shares a head-to-head promoter with MAF bZIP transcription factor G (MAFG), which induced the CpG island methylator phenotype and tumorigenesis of colorectal cancer [18]. Originally, Cui Shanshan et al. found MAFG-AS1 expression was significantly higher in colorectal cancer tissues and cell lines compared with adjacent corresponding non-tumor tissues and normal colon epithelial cell line, respectively [16]. Meanwhile, they showed high MAFG-AS1 expression was associated with advanced TNM stage of colorectal cancer patients [16]. Subsequently, Jia You-Chao et al. and Sui Yuan et al. consistently reported that non-small cell lung cancer tissues and cells exhibited remarkably higher levels of MAFG-AS1 expression than corresponding normal lung tissues and bronchial epithelial cell line [13 14,]. Moreover, Ouyang Hui et al. reported that levels of MAFG-AS1 expression were elevated in hepatocellular carcinoma tissue sample and cell lines compared with normal liver tissue samples and human liver cell line [15]. Similarly, higher expression of MAFG-AS1 was observed in breast cancer tissues and cells than that in normal mammary tissues and normal epithelial breast cell line [17]. The expression pattern of MAFG-AS1 was still unknown in gastric cancer patients. We firstly analyzed the MAFG-AS1 expression in 375 gastric cancer tissue samples and 32 normal gastric mucosa tissue samples from The Cancer Genome Atlas database, and found levels of MAFG-AS1 were increased in gastric cancer tissue samples compared with normal gastric mucosa tissue

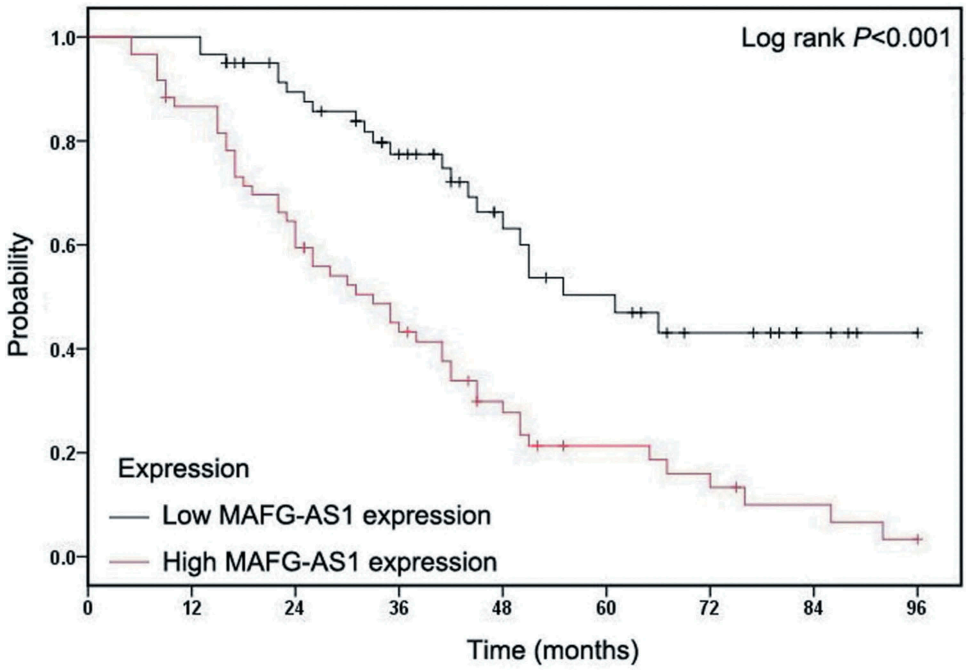

Figure 3. The survival analysis of MAFG-AS1 expression in gastric cancer.
Kaplan–Meier method with log rank test suggested high MAFG-AS1 expression was associated with short overall survival in gastric cancer patients.

Table 2. Univariate and multivariate Cox regression analyses for overall survival in gastric cancer.

	Univariate analysis			Multivariate analysis		
Parameter	HR	95%CI	*P*	HR	95%CI	*P*
Gender (Female vs. Male)	1.125	0.693–1.828	0.633			
Age (y) (<50 vs. ≥50)	1.131	0.707–1.809	0.609			
Lauren's classification (Intestinal vs. Diffuse)	1.209	0.763–1.916	0.420			
Differentiation degree (High and moderate vs. Low and undiferentiated)	1.319	0.824–2.109	0.248			
Clinical stage (I-IIvs. III-IV)	4.478	2.551–7.860	<0.001	3.401	1.171–9.879	0.024
Tumor depth (T1-T2 vs. T3-T4)	2.331	1.424–3.817	0.001	1.661	0.972–2.837	0.064
Lymph node metastasis (n) (<3 vs. ≥3)	3.650	2.144–6.213	<0.001	0.985	0.352–2.758	0.978
Distant metastasis (Absent vs. Present)	14.458	6.205–33.688	<0.001	6.333	2.593–15.465	<0.001
MAFG-AS1 expression (Low vs. High)	2.903	1.769–4.765	<0.001	1.756	1.018–3.028	0.043

HR, hazard ratio; 95% CI, 95% confidence interval;

samples. Then, we performed RT-qPCR to confirm the MAFG-AS1 expression in gastric cancer tissues and cells, and also found gastric cancer tissues and cell lines had remarkably increased MAFG-AS1 expression in comparison to normal gastric mucosa tissues and normal human gastric epithelial cell line. Furthermore, we analyzed correlations between MAFG-AS1 expression and clinicopathological characteristics of gastric cancer and observed high MAFG-AS1 expression was positively associated with diffuse type, advance clinical stage, extensive depth of invasion, more lymph node metastasis, and present distant metastasis in gastric cancer patients.

The correlation between MAFG-AS1 expression and clinical outcome was still unknown in most

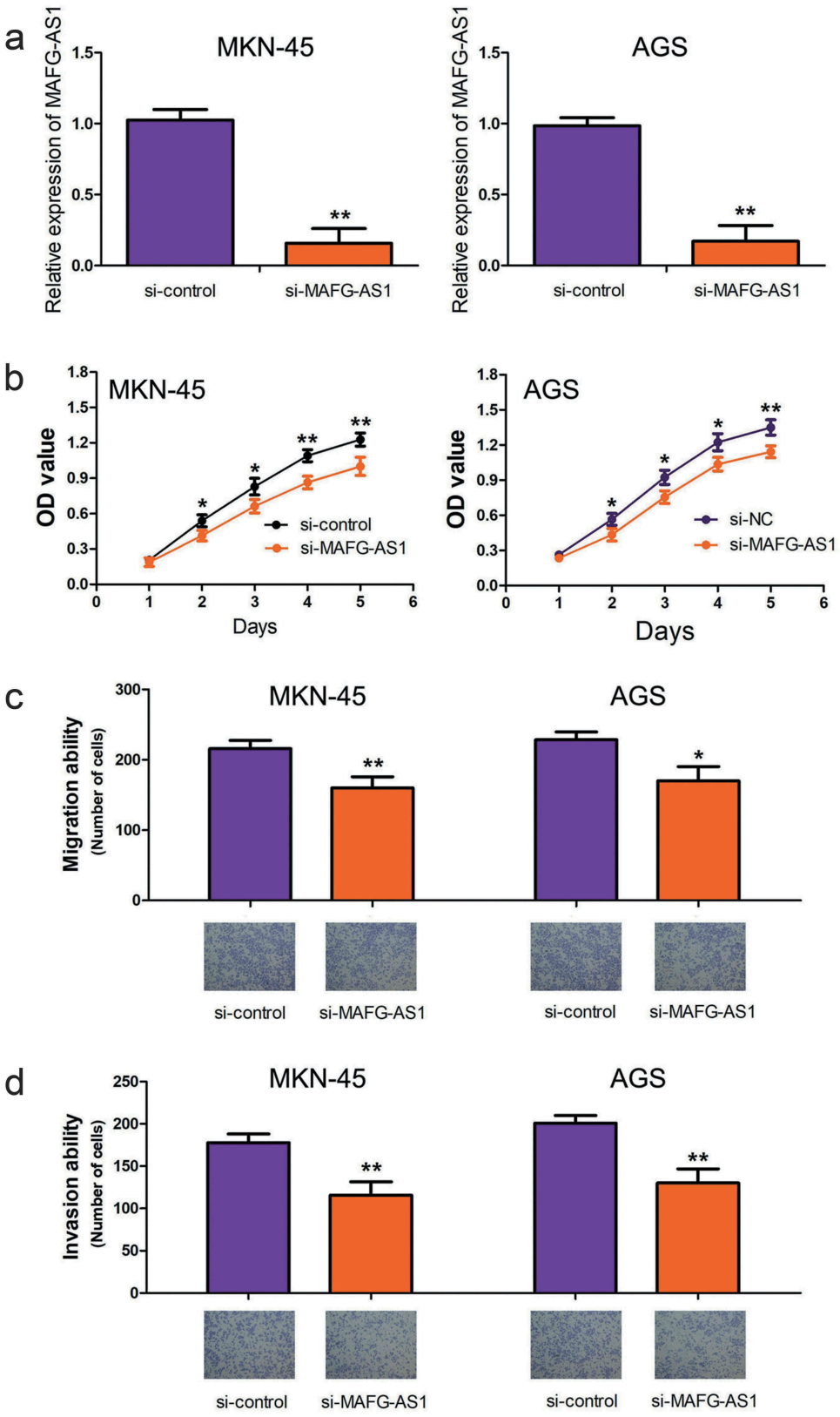

Figure 4. The biological function of MAFG-AS1 expression in gastric cancer.

(a) The si-MAFG-AS1 definitely suppressed MAFG-AS1 expression in MKN-45 and AGS cells. (b) Knocking down MAFG-AS1 expression strikingly inhibited cell proliferation of MKN-45 and AGS cells. (c) Knocking down MAFG-AS1 expression notably decreased migrated gastric cancer cells. (d) Knocking down MAFG-AS1 expression obviously reduced invasive gastric cancer cells. (*: $P < 0.01$; **: $P < 0.001$)

types of human cancer. In non-small cell lung cancer patients, Jia You-Chao et al. and Sui Yuan et al. analyzed non-small cell lung cancer cohort from The Cancer Genome Atlas database and found patients with high MAFG-AS1 expression had markedly short overall survival compared to patients with low MAFG-AS1 expression [13 14,]. However, Cui Shanshan et al. reported that there was no statistical correlation between MAFG-AS1 expression and overall survival time in colorectal cancer patients [16]. In our study, we tried to analyze the relationship between MAFG-AS1 expression and overall survival time in gastric cancer cohort from The Cancer Genome Atlas database, and observed gastric cancer patients with high MAFG-AS1 expression had shorter overall survival than patients with low MAFG-AS1 expression. Similar to the result of database analysis, we also found high MAFG-AS1 expression was associated with short overall survival in gastric cancer patients from our study. Furthermore, we conducted univariate and multivariate Cox regression analyses for identifying the independent prognostic factor, and found high MAFG-AS1 expression acted as one of the independent poor prognostic factors for overall survival in gastric cancer patients.

MAFG-AS1 has been shown to play tumor promoter in tumorigenesis. In lung cancer cells, Jia You-Chao et al. showed MAFG-AS1 overexpression promoted cell metastasis *in vitro* and *in vivo* through miR-339-5p-MMP15 axis [13]. In addition, Sui Yuan et al. suggested the up-regulation of MAFG-AS1 enhanced cell proliferation and inhibited apoptosis in lung adenocarcinoma via miR-744-5p/MAFG axis [14]. Moreover, Ouyang Hui et al. reported knockdown of MAFG-AS1 suppressed the proliferation, migration and invasion of hepatocellular carcinoma cells [15]. In colorectal cancer, Cui Shanshan et al. demonstrated the up-regulation of MAFG-AS1 enhanced cell proliferation, cell cycle progression and cell invasion, and repressed apoptosis through modulating miR-147b/NDUFA4 [16]. In breast cancer cells, MAFG-AS1 overexpression accelerated cell migration and invasion *in vitro* and promoted tumor metastasis *in vivo* by regulating miR-339-5p/MMP15 [17]. In our study, we found knocking down MAFG-AS1 expression inhibited gastric cancer cell proliferation, migration and invasion. However, the molecular mechanism of MAFG-AS1 in gastric cancer was still unclear. Based on the above studies, the main molecular mechanism of MAFG-AS1 is to sever as a "sponge" to sequester microRNAs for regulating functional gene expression. In addition, we tried to predict the potential target of MAFG-AS1 at starBase (http://starbase.sysu.edu.cn/index.php), and screened out the top 10 potential targets including hsa-miR-331-3p, hsa-miR-6816-5p, hsa-miR-3180, hsa-miR-3605-5p, hsa-miR-3612, hsa-miR-650, hsa-miR-5586-5p, hsa-miR-620, hsa-miR-4770 and hsa-miR-143-3p. In future studies, we will identify the functional target of MAFG-AS1, and investigate its effects on gastric cancer cell proliferation, migration and invasion.

In conclusion, MAFG-AS1 is overexpressed in gastric cancer tissues and cells. High MAFG-AS1 expression is associated with clinical progression and poor prognosis in patients with gastric cancer. Knocking down MAFG-AS1 expression inhibits gastric cancer cell proliferation, migration and invasion *in vitro*.

Disclosure statement

No potential conflict of interest was reported by the authors.

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