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Integrin subunit alpha V promotes growth, migration, and invasion of gastric cancer cells

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ABSTRACT

Integrin subunit alpha V (ITGAV), a member of integrin family of extracellular matrix receptors, is involved in many types of cancer. In this study, the expression levels, clinical features and prognosis of ITGAV in gastric cancer (GC) patients were investigated, and the functional roles of ITGAV were also investigated. Cell Counting Kit-8 (CCK-8) assay was performed to examine the proliferation of GC cells. Transwell assays and wound-healing assays were conducted to explore the effect of ITGAV expression on GC cell migration and invasion. We found that ITGAV was overexpressed in both GC tissues and GC cells. ITGAV expression was positively correlated with lymph node metastasis and TNM stage of GC. High expression of ITGAV was associated with shorter overall survival (OS) and disease-free survival (DFS). Interestingly, the downregulation of ITGAV resulted in suppression of proliferation, migration, and invasion in GC cells. In conclusion, ITGAV is overexpressed in gastric cancer and is associated with poorer prognostic outcomes. ITGAV may serve as an important prognostic marker for GC staging and progression.

1. Introduction

The incidence of and mortality from gastric cancer (GC) have been increasing in China [1]. Current treatment options for gastric cancer include surgery, radiotherapy, and chemotherapy [2]. Despite improvements in theses therapies, patients with GC still have poor prognosis [3]. Consequently, it has become very important to elucidate the molecular mechanism of GC and identify novel diagnostic or therapeutic biomarkers for GC to improve prognosis.

Integrins are a large family of extracellular matrix (ECM) receptors comprising 8 beta and 18 alpha subunits, which are involved in adhesion of cells and control cell proliferation, motility, and differentiation [4]. Integrin subunit alpha V (ITGAV) is a member of the integrin alpha chain family, which could associate with up to 5 beta subunits to form αvβ1, αvβ3, αvβ5, αvβ6, and αvβ8 integrin receptors [5]. ITGAV interacts with transforming growth factor-beta 1 to better suppress E-Cadherin expression, an important factor for epithelial-to-mesenchymal transition (EMT) [6]. It is likely that the downregulation of ITGAV would suppress these biological functions by interfering with the combination of ITGAV and beta subunits, which would inhibit tumour progression [7]. Indeed, in previous studies, ITGAV was shown to influence the progression of angiogenesis, cell proliferation, migration, and invasion in several cancers, such as colorectal cancer, skin carcinogenesis, laryngeal, and hypopharyngeal squamous cell carcinoma [8–12]. Furthermore, research has demonstrated that the loss of ITGAV and epithelial tumour protein p53 could induce squamous cell carcinoma through Akt activation, but prevent the remodelling of tumour microenvironment and suppress tumour growth [13]. Thus, ITGAV may be act as a regulator of tumour progression. However, ITGAV expression levels in GC and its clinical and prognostic significance have not been clarified.

Therefore, the present study was conducted to evaluate the expression level of ITGAV and its clinicopathological and prognostic significance in GC patients, and to investigate the role of ITGAV in cell proliferation, migration, and invasion.

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Table 1
Correlations of ITGAV expression with clinicopathological characteristics in patients with GC.

Clinical features	TMA			
	Case	Low, n (%)	High, n (%)	*P*
Tissue type				
Cancer	70	37(0.529)	33(0.471)	0.013
Non-cancer	10	10(1.000)	0(0.000)	
Age				
≤65	65	37(0.569)	28(0.431)	0.689
>65	15	10(0.667)	5(0.333)	
Gender				
Male	62	35(0.565)	27(0.435)	0.615
Female	18	12(0.667)	6(0.333)	
Histological differentiated				
Well/moderate	26	17(0.654)	9(0.346)	0.115
Poorly/other	38	16(0.421)	22(0.579)	
Depth of invasion				
T1-T2	19	13(0.684)	6(0.316)	0.189
T3-T4	51	24(0.471)	27(0.529)	
Lymph node metastasis				
N0-N1	49	30(0.612)	19(0.388)	0.021
N2-N4	19	5(0.263)	14(0.737)	
Distant metastasis				
M0	69	37(0.536)	32(0.464)	0.954
M1	1	0(0.000)	1(1.000)	
TNM				
Stage I-Stage II	32	22(0.688)	10(0.313)	0.028
Stage III-Stage IV	38	15(0.395)	23(0.605)	

TNM, tumor node metastasis stage.*:

2. Methods

2.1. Bioinformatics prediction

We analysed the expression levels and prognostic value of the ITGAV gene from TCGA database using GEPIA (http://gepia.cancer-pku.cn/) [14].The differences in ITGAV expression between GC and normal tissues were compared. According to the ITGAV expression levels, the patients were divided into two groups. The survival analysis was analysed via the Kaplan-Meier plotter method with the log rank test.

2.2. Tissue samples and clinicopathological data

Tissue microarray (TMA, No. ST8014) with 70 GC tissues and 10 normal gastric tissues were obtained from US Biomax, Inc. (MD, US), containing relevant clinical records for all patients. The clinical data are presented in Table 1.

2.3. Immunohistochemistry (IHC) analysis

Dako EnVision Systems (Dako Diagnostics, Switzerland) were used to stain the TMA specimens based on the manufacturer's instructions [15]. TMA specimens were incubated with rabbit monoclonal antibody against ITGAV (ab179475, Abcam, the United States) at a dilution of 1: 600 at 4℃ overnight. Then the slide was washed by phosphate buffered saline (PBS) and substrate-chromogen and peroxidase labelled polymer were added for the visualization of the stained protein. TMA specimens were analysed by Image Scope v11 Software (Vista, CA, US). Visual immunoreactive score (IRS) was used to calculate the expression levels of ITGAV. The staining intensity was scored according to the following criteria: no staining (score 0), mild staining (score 1), moderate staining (score 2), and strong staining (score 3). The percentage of staining was defined as follows: Negative (score 0), 1–10% (score 1), 11–50% (score 2), 51–75% (score 3), and > 76% (score 4). IRS was calculated by staining intensity (SI) x number of stained cells. Samples were classified as low (IRS < 4) or high (IRS ≥ 4) groups according to ITGAV expression.

2.4. Cancer cell lines and culture

Human gastric epithelial cell line GES-1, human gastric cancer cell line HGC-27, and SGC-7901 were cultured in RPMI-1640 medium with penicillin (100 units/ml) and streptomycin (100 μg/ml) and 10% foetal bovine serum (FBS), in 5% CO_2 at 37℃. After being cultured for 24 h, the cells were divided into two groups.

2.5. siRNA construction and cells transfection

An siRNA targeting ITGAV (ITGAV-siRNA) was designed and the sequence was as follows: forward 5′−CCACAUUGGUUACCACUA ATT-3′, reverse 5′-UUAGUGGUAACCAAUGUGGTT-3′ (Genepharma, Suzhou, China). A scrambled siRNA (NC-siRNA) was constructed as the control treatment. The transfection was performed by using a GP-siRNA-Mate plus transfection kit (Shanghai Genechem Co., Ltd.). In brief, the diluted GP-siRNA-Mate plus reagent was mixed with siRNA for 15 min and then transfected GC cell lines. Cells were harvested for use in the following assays: quantitative real-time polymerase chain reaction (RT-qPCR), western blot analysis, CCK-8 assay, cell apoptosis assay, transwell invasion assay, and wound-healing assay. Knockdown efficiency of ITGAV was evaluated by qRT-PCR and western blot analysis 48 h after transfection.

2.6. qRT-PCR

We used RNA isolation kit (No. RP1201, BIOTEKE, China) to extract total RNA from the cells. The ITGAV mRNA expression levels were determined through qPCR by the one-step PCR kit (Takara Bio, Inc., Japan) based on the manufacturer's protocol. The primers used were as follows: ITGAV forward (TAGCGTATCTGCGGGATGAA), ITGAV reverse (GTTAGCAGGCGTGAACTGGT), β-actin forward (AGATCAAGATCATT GCTCCTCCT), β-actin reverse (ACGCAGCTCAGTAACAGTCC). The mRNA expression levels of ITGAV gene were normalized to the mRNA expression levels of β-actin by using the $2^{-\Delta\Delta CT}$ method. All samples were examined in triplicate.

2.7. Western blotting analysis

As previously study described, western blotting analysis was performed to analyse protein expressions [16]. Briefly, GC cells were collected and lysed in ice-cold lysis buffer [2% sodium dodecyl sulphate (SDS),5% glycerinum, 100 mM NaCl, 50 mM Tris, 1 mM ethylene diamine tetra acetic acid, pH 6.8]. BCA Protein Assay Kit (Pierce, US) was used to measure the protein concentrations of the lysate. A total of 50 μg protein in each lane was electrophoresed on 10% SDS-polyacrylamide gel electrophoresis to separate the total protein and then transferred onto polyvinylidene fluoride membranes and incubated with rabbit monoclonal anti-ITGAV primary antibody (1:100; No. ab179475, Abcam, Taiwan), and anti-GAPDH primary antibody (1:500, BOSTER Biological Technology Co., Ltd, China) overnight at 4 ℃. Membranes were then incubated with anti-Rabbit IgG (1:5000; HRP-conjugated Donkey, BOSTER Biological Technology Co., Ltd, China). According to the manufacturer's protocol, signals were detected using ECL luminescence reagent (Sangon Biotech, China). GAPDH was used as the internal standard.

2.8. CCK-8 assay

The viability of GC cells was evaluated by using the CCK-8 assay kit (Beyotime, China) [17]. After 48 h of siRNA infection, 5×10^3 GC cells were seeded in each well of 96-well plates and cultured for 24 h, 48 h, or 72 h. All samples were set in triplicates. Then 20 μL CCK8 solution was added into each well and cultured for additional 2 h. Thereafter,

spectrophotometery (Multiskoun GO, Thermo, US) was conducted to determine the absorbance at 450 nm.

2.9. Transwell invasion assay

Following the instruction of the transwell invasion assay kit, the effect of ITGAV on cell invasion was evaluated [18]. The upper chamber was seeded with 4×10^4 GC cells and RPMI-1640 medium with 10% FBS was filled in the lower chamber. All samples were set in triplicate. After incubation for 24 h in an incubator, 1% paraformaldehyde was used to fix the cells in the lower chamber. Then the cells were stained by hematoxylin and counted.

2.10. Wound-healing assay

The migratory ability of GC cells was accessed using a wound-healing assay [19]. GC cells (1×10^6 cells/well) were seeded and cultured in a 6-well plate. A scratch line was made by a pipette tip (10 μl) in the well and then washed twice with PBS. To inhibit cell division, serum-free medium with 4 μg/mL mitomycin was used to culture the cells. Cells that migrated from the wound edge were imaged and counted at the time point of 0, 6, 24, 30, 48, and 72 h, respectively.

2.11. Statistical analysis

Data from the experiments were presented as mean ± standard deviation (SD) and analysed using the SPSS 21.0 software (SPSS Inc, IL, US). The difference between groups were analysed by using student's t-test. The relationship between expression of ITGAV gene and clinicopathological characters was accessed by Chi-squared tests. Overall survival rate was calculated using Kaplan-Meier method with log-rank test. The independent prognostic factors were identified by using the Cox proportional hazards regression model. $P < 0.05$ was defined as statistically significant.

3. Results

3.1. ITGAV mRNA was overexpressed and predicted poor prognosis in GC

We examined and analysed the expression level of ITGAV in GC tissues by mining the TCGA database in GEPIA. ITGAV expression increased in 408 GC tissues compared with 36 normal tissues (Fig. 1). The median ITGAV expression level was 27.34 in GC tissues, while the median ITGAV expression level in normal tissues was much lower (10.81). Next, we analysed the correlation between ITGAV mRNA expression levels and overall survival (OS) and disease-free survival (DFS) in GC patients using TCGA database by GEPIA. We found that the OS and DFS of patients with high expression of ITGAV were remarkably shorter than in patients with low expression (HR = 1.28, 95% CI = 1.06–1.54, P = 0.0093, Fig. 2A&B).

3.2. ITGAV was overexpressed in GC tissues samples

To verify the above predictions, IHC analysis was applied to evaluate the expression pattern of ITGAV using the TMA that contained 70 GC tissues and 10 normal gastric tissues (Fig. 3A). ITGAV was significantly overexpressed in GC tissues (IRS: tumour = 6.56 ± 3.66 vs. normal = 3.90 ± 1.3, P = 0.026) than that of the normal tissues (Fig. 3B). Additionally, IHC staining showed that ITGAV expression was mainly localized to the membranous regions of GC cells (Fig. 3C). The high expression rate of ITGAV in GC samples was significantly higher than that of normal gastric mucosa specimens (P = 0.013; Table 1). ITGAV expression was positively associated with lymph node metastasis and TNM ($P < 0.05$). Taken together, our findings indicate that ITGAV may play a key role in GC development.

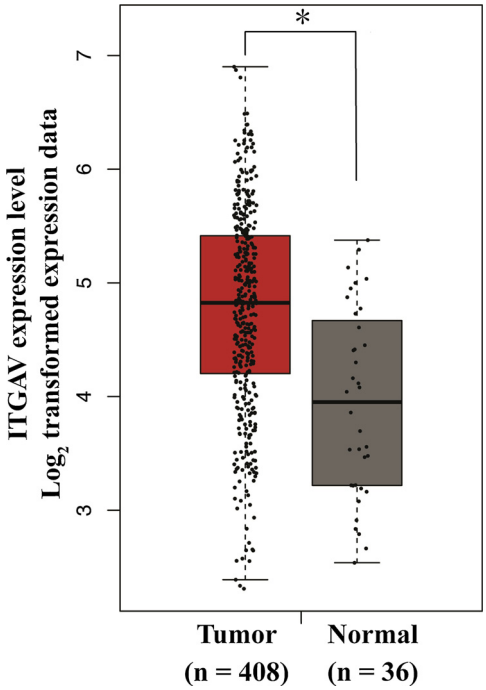

Fig. 1. Analysis of ITGAV mRNA expression in human GC using the GEPIA database. ITGAV gene was overexpression in gastric adenocarcinoma tissues than in normal gastric mucosa tissues. (* : $P < 0.05$).

3.3. ITGAV expression is reduced in siRNA-transduced GC cells

ITGAV mRNA levels were decreased in ITGAV-siRNA group compared to NC-siRNA group. The knockdown efficacy of ITGAV by ITGAV-siRNA was 81.4% in HGC-27 cells and 83.2% in SGC-7901 cells, suggesting that siRNA knockdown was specific and the loss-of-function outcome was not possibly caused by an off-target effect (Fig. 4A). In addition, ITGAV protein was reduced following the ITGAV knockdown in western blot analysis (Fig. 4 B). These results suggest that ITGAV-siRNA could significantly downregulate ITGAV in GC cells.

3.4. Knockdown of ITGAV suppressed cell proliferation and migration and invasion in GC cells

The effect of ITGAV on cell proliferation was evaluated by CCK-8 assay, with obvious inhibitory effects on cell proliferation observed in ITGAV-siRNA group (Both in HGC-27 and SGC-7901), see Fig. 4C.

As shown in Fig. 4D, ITGAV-siRNA group contained less migratory and invasive cells than did the control group in both HGC-27 and SGC-7901 cells. Similarly, the results of wound-healing assays indicated that the downregulation of ITGAV could significantly suppress the healing of GC cells compared with the control group (Fig. 4E). Based on these results, ITGAV likely plays an important role in GC progression.

4. Discussion

GEPIA is a useful database that is publicly available to predict the expression and prognostic potential of cancer genes from the Cancer Genome Atlas (TCGA) Consortium project [15]. In the present study, by mining data from this database, we demonstrated the expression of ITGAV in GC. Online Kaplan-Meier plotter analysis found that overexpression of ITGAV predicts a poorer prognosis in GC patients. Similar correlation has also been reported between ITGAV expression and other types of cancers, such as colorectal cancer [8]. Our results showed that ITGAV protein was significantly overexpressed in human GC samples. ITGAV expression was positively associated with lymph node metastasis

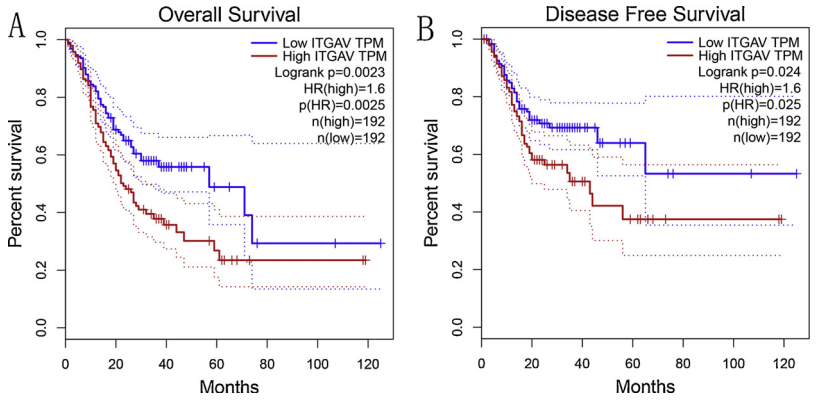

Fig. 2. Correlation of RECQL4 mRNA expression with overall survival and disease free survival in GC patients using GEPIA database. HR: hazard ratio; CI: confidence interval; p value: log-rank test.

and TNM. These results imply that ITGAV plays a potential role in carcinogenesis and ITGAV may serve as a novel biomarker for predicting the prognosis of GC.

It has been demonstrated that ITGAV is associated with cell differentiation and metastasis and may be a potential prognostic marker in laryngeal and hypopharyngeal carcinomas. ITGAV downregulation is shown to suppress cell proliferation and induce apoptosis in laryngeal and hypopharyngeal carcinomas [20,21]. In a retrospective study, increased ITGAV expression was observed in colorectal carcinoma and was correlated with epidermal-derived growth factor receptor (EGFR) expression [8,22,23]. Additionally, ITGAV was regarded as the target of a series of micro ribonucleic acids (miRNAs) which inhibited tumour progression, such as miR-217-5p in colorectal cancer cells, miR-548c-3p in osteosarcoma, miR-122 in hepatocellular carcinoma, miR-9-3p in nasopharyngeal carcinoma, and miR-142-3p in breast cancer [11,24–27]. Particularly, miR-217-5p may negatively regulate the MAP

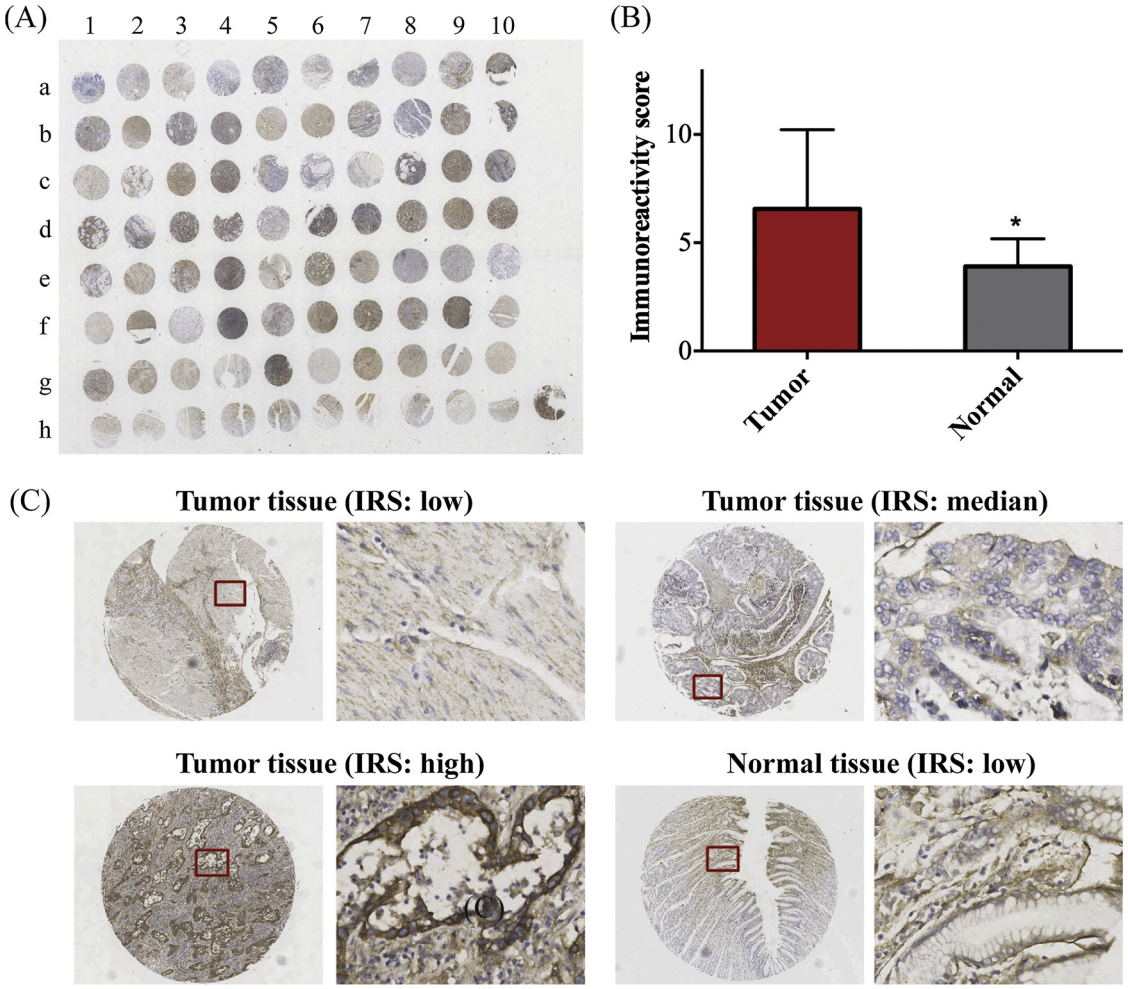

Fig. 3. Immunohistochemical examination. Immunohistochemical staining of ITGAV in the (a) Tissue microarray (TMA, No. ST8014) with 70 GC tissues and 10 normal gastric tissues; (b) ITGAV was significantly overexpression in GC tissues than that of the normal gastric tissues using the IRS method; (c) Gastric cancer with low expression of ITGAV in GC tissues and normal gastric mucosa tissues 200 × .

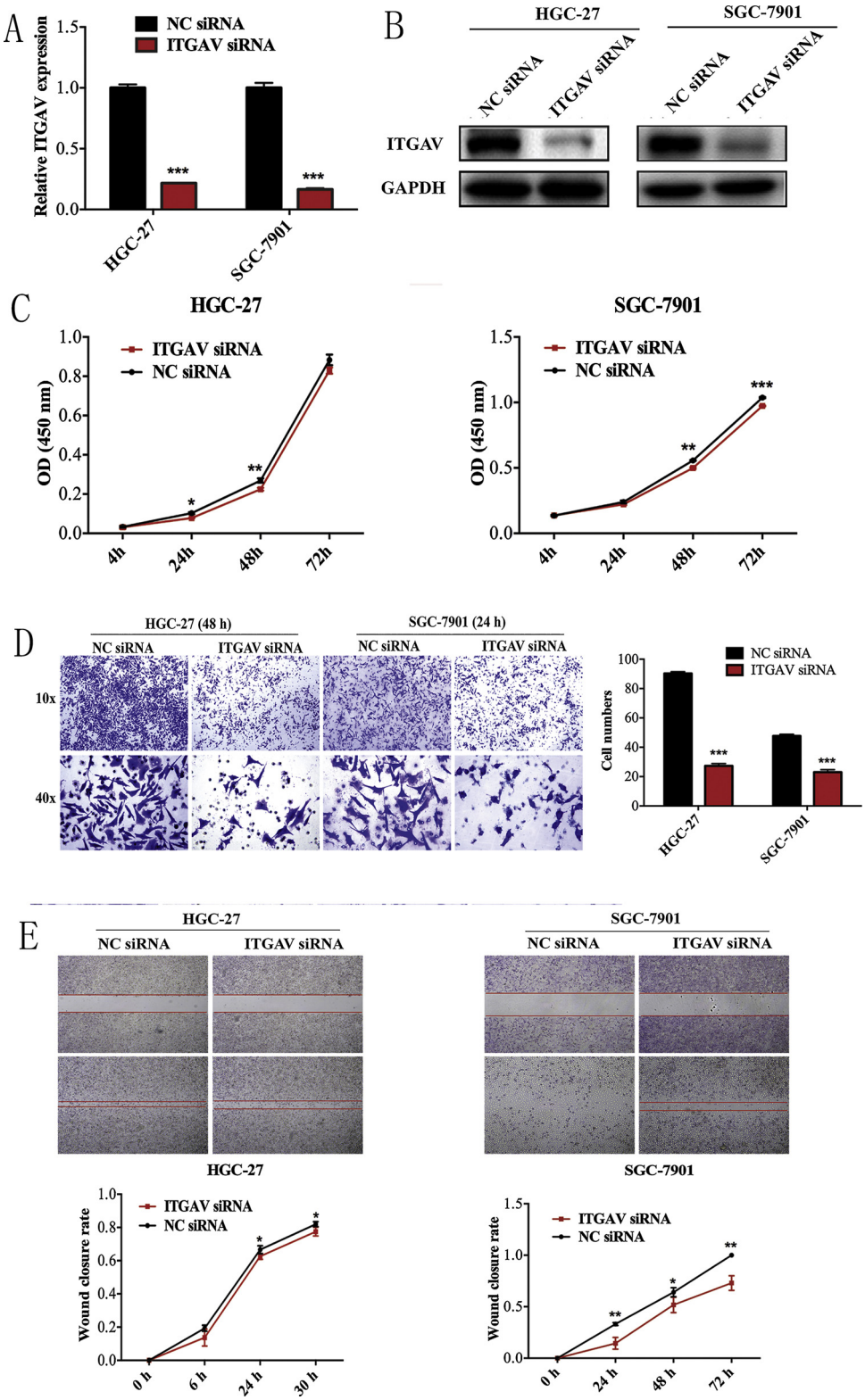

Fig. 4. Knockdown of ITGAV inhibited the number of colonies formed and induced cell cycle arrest in AGS cells and SGC-7901 cells. (A) qRT-PCR analysis of ITGAV mRNA levels in HCG-27 and SGC-7901 cells after siRNA infection ; (B) Western blot analysis of ITGAV protein levels in HCG-27 and SGC-7901 cells after siRNA infection. (C) Growth curve of HCG-27 and SGC-7901 cells assessed by MTT assay. (D) Number of colonies formed in HCG-27 and SGC-7901 cells treated with siRNA. *:P < 0.001.(E) Downregulated of ITGAV could significantly suppress the healing of GC cells using wound-healing assays.

kinase signalling pathway by targeting it to ITGAV, resulting in suppression of cell survival and proliferation in colorectal cancer cells [24]. ITGAV and tissue inhibitor of metalloproteinase-1 were downregulated by interleukin (IL)-32γ through the inactivation of the NF-κB signalling pathway, resulting in the suppression of inflammation in the tumour microenvironment in skin carcinogenesis [10]. In this study, using siRNA technology, we demonstrated sufficient downregulation of ITGAV, which effectively suppressed cell proliferation, migration, and

invasion of GC cells. These findings, together with the ones reported by others, suggest that ITGAV might play an important role in GC progression.

In summary, the findings of the present study demonstrated overexpression ITGAV in GC samples and cells compared to normal tissues and cells. ITGAV might act as a tumour promotor in GC. More studies are warranted to further clarify these observations and to test the clinical utility of ITGAV as a potential therapeutic target against GC.

Declarations

The study was approved by the Ethics Committee of the Sixth Affiliated Hospital, Sun Yat-sen University and have been performed in accordance with the Declaration of Helsinki.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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