Menin represses the proliferation of gastric cancer cells by interacting with IQGAP1

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Abstract. The multiple endocrine neoplasia type 1 gene coding the protein menin was originally identified in patients with multiple endocrine tumors, and is mainly expressed in the cell nucleus. Multiple lines of evidence have indicated that menin acts as a tumor suppressor protein interacting with other various proteins. The mechanism of menin inhibiting tumorigenesis remains unclear. The present study analyzed the expression of menin and IQ motif-containing GTPase-activating protein 1 (IQGAP1) proteins in gastric cancer tissues and cell lines, and investigated the association between these two molecules. Western blotting was used to determine the quantity of target proteins. Cell proliferation was measured using MTT assay. It was found that the protein expression of menin was lower in gastric cancer tissues and AGS cells, while the protein expression of IQGAP1 was higher, compared with the levels observed in normal tissues and GES-1 cells. Ectopic expression of IQGAP1 stimulated the proliferation of gastric cancer cells, but did not affect the expression of menin. However, overexpression of menin inhibited the proliferation of gastric cancer cells. The inhibition was partly achieved through inhibiting the expression of IQGAP1, which was accompanied by inhibition of PI3K and NF-κB expression. Taken together, the present results suggest a novel function for menin and IQGAP1 contributing to suppress the proliferation of gastric cancer cells.

Introduction

The multiple endocrine neoplasia type 1 gene was identified in 1997, and consists of 10 exons encoding a 610-amino acid protein referred to as menin (1). Menin is predominantly localized in the cell nucleus, although it is also found in the cytosol and membrane (2). The distribution of menin is gene-related, and it is associated with the two nuclear localization signals present in its carboxy-terminal region. Menin, as a critical tumor suppressor protein, has been proposed to play important roles in transcriptional regulation, genome stability, cell division, proliferation and apoptosis, and its emerging roles in cancer development have attracted large attention (3-6).

IQ motif-containing GTPase-activating protein 1 (IQGAP1) is a scaffold protein that participates in several cellular functions, including cell-cell adhesion (7), migration (8), transcription (9) and signal transduction (10). IQGAP1 has been implicated in the tumorigenesis and progression of a variety of human cancer types, including aggressive lung (11), breast (12) and pancreatic (9) cancer, as well as colorectal carcinoma (13) and gastric cancer (14).

Yan *et al* (15) revealed that menin reduced the interaction of GTP-Rac1 with IQGAP1 and enhanced the intercellular adhesion of β cells. The roles of IQGAP1 and menin in tumor progression have been confirmed in previous research (15). However, the mechanisms by which menin inhibits tumor occurrence, and the association of menin with IQGAP1 remain elusive. In the present study, the expression of menin and IQGAP1 was examined in gastric cancer tissues and cells, and the association between these two molecules and the proliferation of gastric cancer cells was investigated.

Materials and methods

Tissue samples. A total of 108 samples of tumor and adjacent tissue specimens from patients with gastric cancer who were diagnosed and received surgery at the Department of Surgery, Affiliated Hospital of Jiangnan University (Wuxi, China) were obtained between June 2012 and July 2014. None of the patients received preoperative chemotherapy or radiotherapy. Cases were excluded if they had been diagnosed with previous, recurrent or metastasized cancer from another origin. The samples were ground for protein extraction. The corresponding non-neoplasia mucosa tissues, which were resected ≥5 cm away from the tumor margin, served as controls. Clinicopathological data were obtained from a retrospectively constructed medical database, which had been reviewed and confirmed by two pathologists. The present study was approved by the Research Ethics Committee of Jiangnan University (approval no. JDFY20220801-1), and all

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patients provided written informed consent for the use of their data in research.

Reagents and antibodies. The adenoviral vectors pAd-LacZ (encoding β-galactosidase), pAd-IQGAP1 and pAd-Menin were kindly gifted by Dr Yong-Chang Chen (Jiangsu University, Zhenjiang, China). Mouse anti-menin antibody (EPR3986; product code ab92443) was obtained from Abcam, while mouse anti-IQGAP1 (cat. no. sc-376021), mouse anti-phosphorylated (p)-Akt (cat. no. sc-377556), mouse anti-Akt (cat. no. sc-5298), mouse anti-NF-κB (cat. no. sc-8414) and goat anti-β-actin antibodies (cat. no. sc-8432), as well as short-interfering RNAs (siRNAs) for IQGAP1 (5'-AAGTTCTACGGGAAG TAATTG-3') and menin (5'-CCACCUUUCUUGUGCAGU CCCUA-3'), and negative control siRNAs (RNA sequence, 5'-AUGAACGUGAAUUGCUCAA-3') were purchased from Santa Cruz Biotechnology, Inc. The horseradish peroxidase (HRP)-conjugated secondary antibody (cat. no. KCB002) was purchased from Rockland Immunochemicals Inc. Immunohistochemical and ECL reagents were acquired from EMD Millipore. All other reagents were of analytical grade.

Cell culture, transfection and plasmid construction. The AGS cell line (cat. no. TCHu232) was purchased from the Institute of Cell Biology of the Chinese Academy of Sciences. The human gastric epithelial cell line GES-1 was a kind gift from Dr Yong-Chang Chen (Jiangsu University, Zhenjiang, China). The cells were cultured in DMEM (Gibco; Thermo Fisher Scientific, Inc.) with 10% new-born calf serum (NBCS; Lanzhou Minhai Bio-Engineering Co., Ltd.) in an incubator with 5% CO_2 at 37˚C. The culture medium was changed every 2 days, and the cells were sub-cultured until reaching confluence.

Adenovirus encoding menin or IQGAP1 gene at an MOI of 100 pfu/cell was used to infect human gastric cancer AGS cells. The expression level of target protein in AGS cells infected with the above recombinant adenovirus was detected by western blotting. For transfection, a complex of Lipofectamine® 2000 (Invitrogen; Thermo Fisher Scientific, Inc.) and siRNA was prepared according to the manufacturer's instructions. Briefly, cells were seeded to 80% confluence and infected at 37˚C for 6 h using 100 pmol siRNA. After 6 h, the siRNA/lipid complexes were removed, and the cells were maintained in complete medium for an additional 48 h. The protein expression was then determined by western blotting.

Western blot analysis. The target proteins were extracted and detected by western blotting. Frozen tissue samples and cells were homogenized in RIPA buffer (Sigma-Aldrich; Merck KGAa). The homogenates were heated in boiling water for 5 min, and the proteins in the supernatant were quantified by Bio-Rad Protein Assay (Bio-Rad Laboratories, Inc.). In total, 20 μg protein extracts were separated using 10% SDS PAGE and transferred onto a PVDF membrane. After blocking with 10% non-fat milk in TBS with 0.1% Tween-20 for 1 h at room temperature (RT), the membrane was incubated with specific antibodies against menin (1:500), IQGAP1 (1:1,000), p-Akt (1:1,000), Akt (1:1,000), NF-κB (1:1,000) and β-actin (1:1,000 as a loading control) overnight at 4˚C. Subsequently, the membrane was incubated with the corresponding HRP-conjugated secondary antibodies (1:1,000) for 1 h at room temperature, followed by three washes. The proteins bands were visualized using ECL. Images were analyzed using the imaging system (iBright™ CL750 Imaging System; Thermo Fisher Scientific Inc.).

MTT assay. AGS cells were infected with pAd-IQGAP1 or pAd-Menin to overexpress IQGAP1 or menin, respectively, whereas siRNAs were transfected into AGS cells to knock down the expression of menin or IQGAP1. The cells were serum-starved for 12 h and then trypsinized, washed, counted and re-suspended in 96-well plates (10,000 cells in 100 μl DMEM) for various time periods (12, 24, 48 and 72 h). Cell proliferation was measured using MTT assay. Briefly, 20 μl of MTT dye (5 mg/ml) was added to each well, and the plate was incubated for 4 h. Dimethylsulfoxide (DMSO; 150 μl) was added to the wells to dissolve the formazan crystals. The absorbance value at 450 nm was measured for each sample, and all the experiments were repeated three times with ≥3 replicates.

Statistical analysis. Data are expressed as the mean ± standard deviation. Unpaired two-tailed Student's t-test followed by Bonferroni's post hoc test were used to analyze differences among the variables. One-way ANOVA followed by Dunnett's post hoc test was employed to analyze differences between multiple sets of data. The association between each independent clinicopathological variable and menin or IQGAP1 was examined by χ^2 test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Expression of menin and IQGAP1 in gastric cancer tissues and cell lines. Total proteins were extracted from 108 gastric cancer and paired normal tissues. Western blotting was used to detect the expression of menin and IQGAP1 proteins. According to the relative intensity of the protein bands (calculated as the ratio of the median of the gray scale bands of target proteins to β-actin), the samples were separated into an expression group (≥0.467 for menin and ≥0.57 for IQGAP1) and a no-expression group (<0.467 for menin and <0.57 for IQGAP1). The median of the gray scale bands of menin protein/β-actin was 0.315 in 108 gastric cancer tissues and 0.800 in paired normal tissues. The median of the gray scale bands of IQGAP1 protein/β-actin was 0.852 in 108 gastric cancer tissues and 0.371 in paired normal tissues (Fig. S1). As shown in Fig. 1, and Table I, menin expression was significantly lower in 23.1% (25 out of 108) gastric cancer tissues than in 76.9% (83 out of 108) paired non-neoplastic mucosa tissues ($P<0.001$). However, IQGAP1 was positively expressed in 66.7% (72 out of 108) gastric cancer tissues and 33.3% (36 out of 108) paired normal tissues ($P<0.001$). A negative association was identified between menin and IQGAP1 expression in gastric cancer tissues.

The protein expression of menin in AGS cells was significantly lower than that in GES-1 cells. However, the expression of IQGAP1 in AGS cells was significantly higher than that in GES-1 cells (Fig. 1B). The expression of menin and IQGAP1 was overexpressed in AGS cells infected with pAd-IQGAP1

Table I. Expression of menin and IQGAP1 in 108 gastric cancer tissues and paired normal tissues.

		Menin[a]			IQGAP1[b]		
Gastric tissues	No.	>0.467	≤0.467	P-value	>0.57	≤0.57	P-value
Gastric cancer tissues	108	25	83	<0.001	72	36	<0.001
Paired normal tissues	108	83	25		36	72	

[a]Amount of menin protein relative to β-actin protein in 108 samples of tumor and adjacent tissue specimens from patients with gastric cancer; [b]Amount of IQGAP1 protein relative to β-actin protein in 108 samples of tumor and adjacent tissue specimens from patients with gastric cancer. IQGAP1, IQ motif-containing GTPase-activating protein 1.

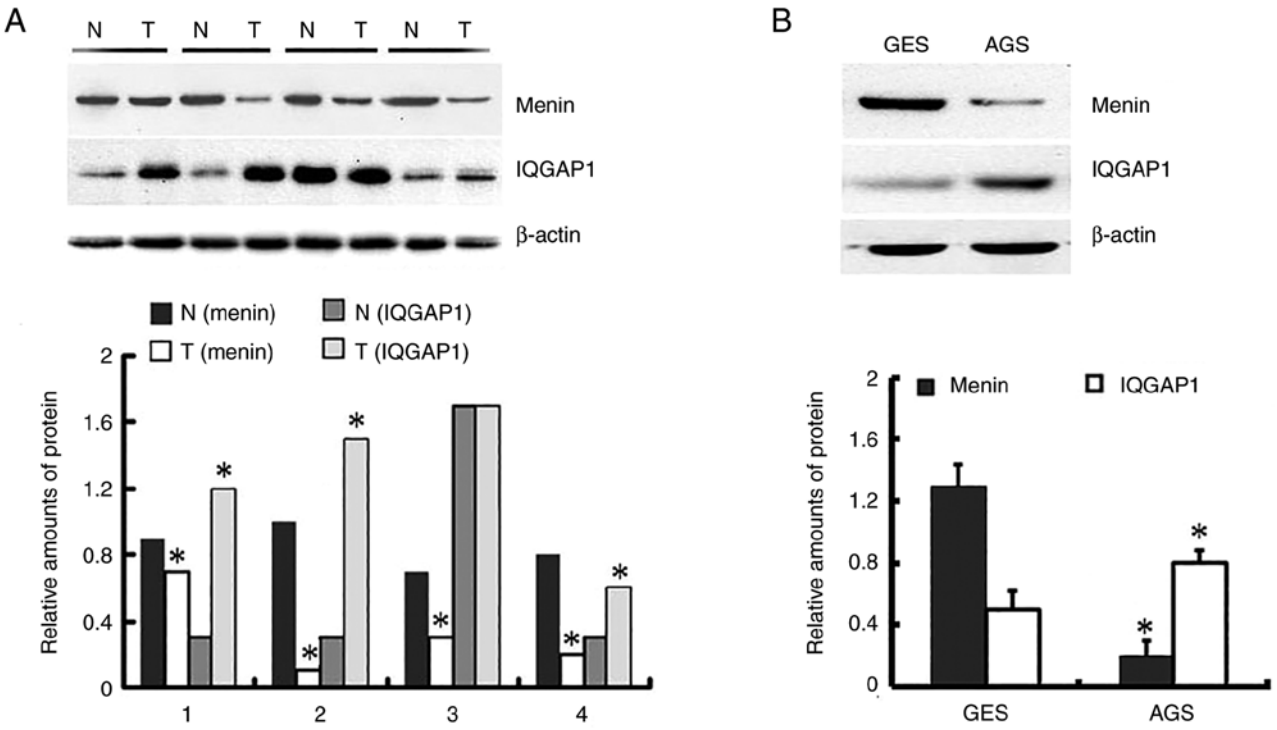

Figure 1. Western blotting was used to detect the expression of the target proteins. (A) Lane N, paired normal tissues; lane T, gastric cancer tissues. The graph is a representation of panel A. Samples 1, 2, 3 and 4 correspond to gastric cancer and adjacent tissue samples from 4 patients with gastric cancer. (B) Menin and IQ motif-containing GTPase-activating protein 1 expression in AGS and GES-1 cells. The graph is a representation of panel B. Values are presented as the mean ± standard deviation from triplicate samples. *P<0.05 vs. the corresponding GES cell group. IQGAP1, IQ motif-containing GTPase-activating protein 1.

and pAd-Menin, while the expression of IQGAP1 was knocked down in AGS cells transfected with IQGAP1 siRNAs (Fig. 2). The expression of menin and IQGAP1 in cells infected with pAd-IQGAP1 and pAd-Menin or transfected with IQGAP1 siRNAs for 12, 24, 48 and 72 h was also detected, and the expression of menin and IQGAP1 was observed to be increased or decreased in a time-dependent manner. The expression reached the highest or lowest level at 48 h post-infection, and remained at a stable level thereafter; thus, 48 h was used in subsequent experiments (Fig. 3). Of note, the expression levels of menin were not significantly altered over the period of time assessed in the menin siRNA groups compared with those in the control group. (Figs. 2 and 3).

Menin and IQGAP1 expression levels are associated with clinicopathological characteristics in 108 patients with gastric cancer. The association between menin and IQGAP1 expression levels and clinicopathological parameters is summarized in Table II. The results showed that menin and IQGAP1 expression were associated with histological grade (P=0.047 and P=0.044, respectively), distant metastasis (P=0.033 and P=0.028, respectively), lymph node (LN) metastasis (P=0.006 and P=0.04, respectively) and TNM stage (P=0.014 and P=0.038, respectively). However, no significant associations were observed with patient sex (P=0.662 and P=0.561, respectively) or age (P=0.349 and P=0.395, respectively).

Menin influences IQGAP1 expression. To determine whether the increase or decrease in one protein would affect the expression of the other protein, menin and IQGAP1 were overexpressed with pAd-Menin and pAd-IQGAP1, respectively. siRNAs targeting menin and IQGAP1 were transfected into AGS cells to knock down the expression of menin and IQGAP1. Western blotting was used to detect the expression

Table II. Association of menin and IQGAP1 expression with clinicopathological parameters in 108 gastric cancer patients.

		Menin			IQGAP1		
Clinicopathological parameters	No.	≥0.467	<0.467	P-value	≥0.57	<0.57	P-value
Sex							
Male	73	16	57	0.662	50	23	0.561
Female	35	9	26		22	13	
Age (years)							
<60	39	11	28	0.349	24	15	0.395
≥60	69	14	55		48	21	
Histological grade							
WD and MD	59	18	41	0.047	35	24	0.044
PD	49	7	42		38	11	
Distant metastasis							
Absence	47	17	30	0.033	28	19	0.028
Presence	61	11	50		44	17	
LN metastasis							
Absence	34	15	19	0.006	18	16	0.040
Presence	74	14	60		54	20	
TNM stage							
I and II	48	18	30	0.014	26	22	0.038
III and IV	60	10	50		44	16	

IQGAP1, IQ motif-containing GTPase-activating protein 1; WD, well-differentiated; MD, moderately differentiated; PD, poorly differentiated LN, lymph node.

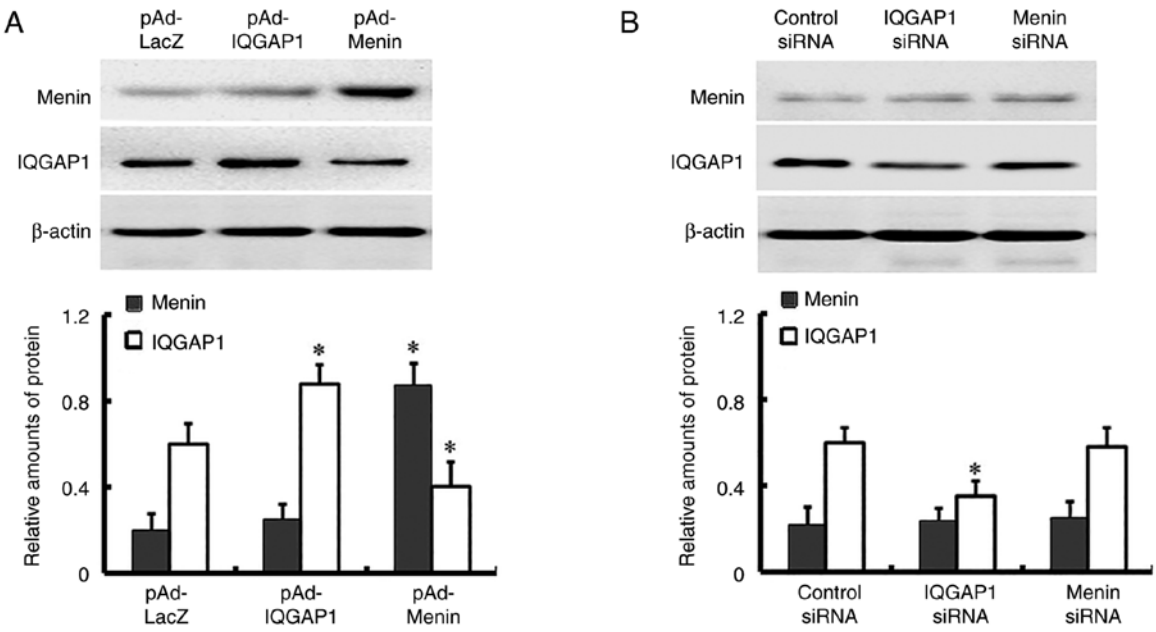

Figure 2. Protein expression levels of menin and IQGAP1 in AGS cells determined using western blotting. (A) AGS cells were infected with recombinant adenovirus pAd-LacZ (an empty vector, used as a negative control), pAd-IQGAP1 and pAd-Menin. The graph is a representation of panel A. (B) AGS cells were transfected with control, IQGAP1 and menin small interfering RNAs. The graph is a representation of panel B. Menin markedly inhibited IQGAP1 expression; however, IQGAP1 did not affect the expression of menin. *P<0.05 vs. the respective control groups. IQGAP1, IQ motif-containing GTPase-activating protein 1; siRNA, small interfering RNA.

of menin and IQGAP1. The results revealed that exogenous expression of menin repressed IQGAP1 expression. However, increased or knocked down expression of IQGAP1 did not affect the expression of menin. There was no change in menin

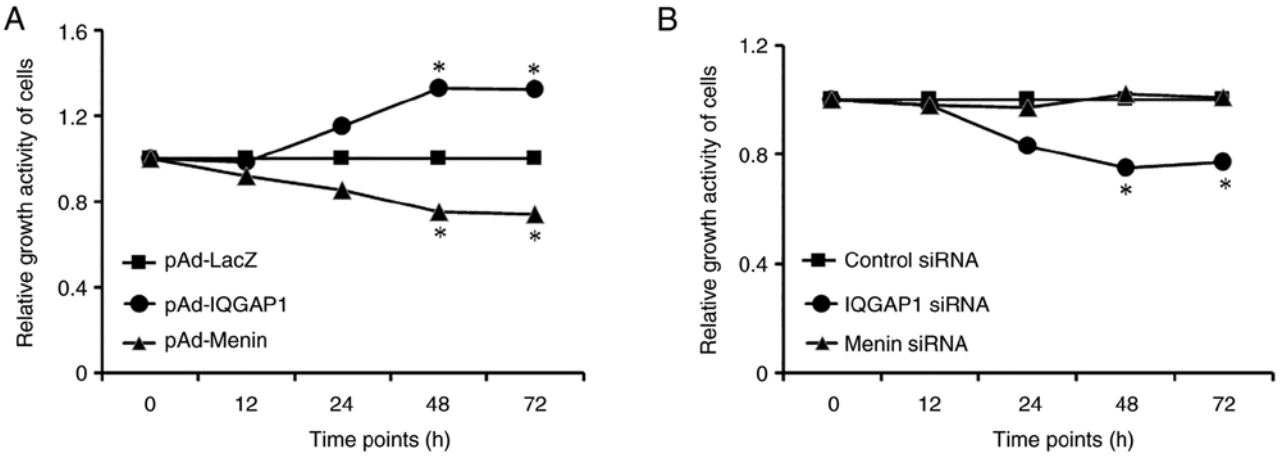

Figure 3. Proliferation of AGS cells evaluated using MTT assay. (A) AGS cells infected with pAd-LacZ, pAd-IQGAP1 and pAd-Menin. (B) AGS cells transfected with control, IQGAP1 and menin siRNAs for various time periods (12, 24, 48 and 72 h). In a time-dependent manner, menin inhibited, whereas IQGAP1 stimulated, gastric cancer cell proliferation. Data are expressed as the mean ± SD standard deviation of three independent experiments. *P<0.05 vs. the pAd-LacZ group or the control siRNA group. IQGAP1, IQ motif-containing GTPase-activating protein 1; siRNA, small interfering RNA.

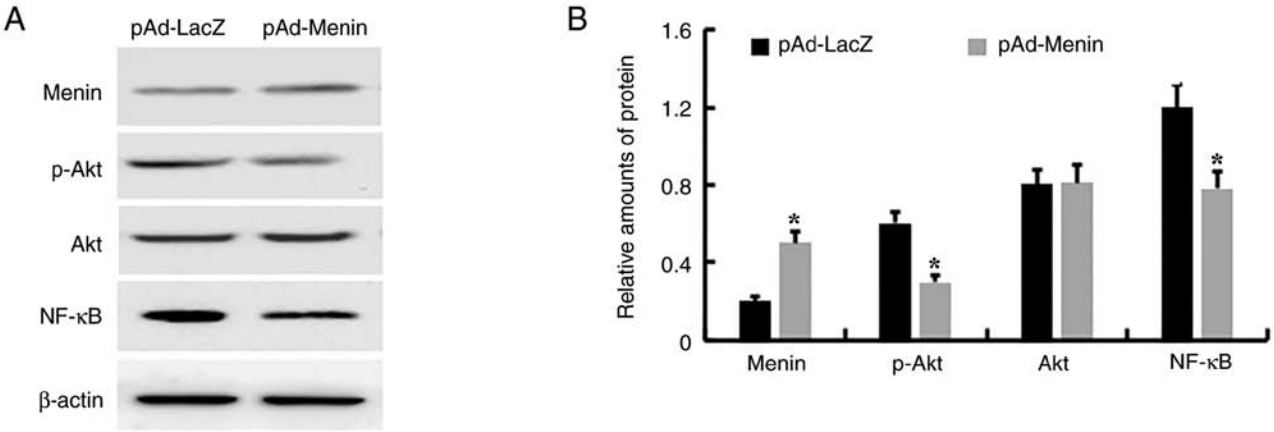

Figure 4. Protein expression levels of phosphorylated Akt, Akt and NF-κB in AGS cells determined using western blotting. Data are representative of three independent experiments. *P<0.05 vs. the respective control groups. p-, phoshorylated.

or IQGAP1 expression levels in the menin siRNA group compared with those in the control group (Fig. 2).

Effects of menin and IQGAP1 on the proliferation of gastric cancer cells. The effects of menin and IQGAP1 on cell proliferation were evaluated by MTT assay. AGS cells were transfected with siRNAs, which interfered with the expression of menin and IQGAP1. In addition, AGS cells were infected with an adenovirus vector encoding IQGAP1 or menin for overexpression. The results revealed that ectopic expression of IQGAP1 promoted, whereas silencing of IQGAP1 expression inhibited, gastric cancer cell proliferation. On the other hand, increased expression of menin suppressed cell proliferation. Because menin protein is less expressed in AGS cells, menin siRNA could further reduce menin expression in AGS cells (Fig. 3). The results revealed that menin suppressed, whereas IQGAP1 stimulated, the proliferation of gastric cancer cells.

Menin inhibits the PI3K/Akt and NF-κB signaling pathways. To explore the potential mechanism by which menin suppressed the proliferation of gastric cancer cells, the effects of menin on the expression of crucial proteins of the PI3K and NF-κB signaling pathways were examined. The levels of p-Akt and NF-κB were notably downregulated in menin-overexpressing AGS cells, while no changes in Akt were observed (Fig. 4).

Discussion

In gastric cancer, the role of the expression of IQGAP1 is well understood; however, less is known about the expression of menin or the association between menin and IQGAP1 in this cancer type. The present study analyzed the protein expression of menin and IQGAP1 in gastric cancer tissues and AGS cell lines, since these proteins appeared to be implicated in the development and progression of gastric cancer according to previous studies (2,14). The present results revealed that menin expression was significantly lower in gastric cancer tissues than in paired non-neoplastic mucosa tissues. However, IQGAP1 was highly expressed in gastric cancer tissues compared with its expression in paired non-neoplastic mucosa tissues. The protein expression of IQGAP1 in AGS cells was significantly higher than that in GES-1 cells. However, the expression of

menin in AGS cells was significantly lower than that in GES cells.

In the present study, various clinicopathological factors were analyzed for their potential association with menin and IQGAP1 protein expression in gastric cancer tissues. Low menin expression in gastric cancer was found to be significantly associated with poor clinicopathological factors, including poor differentiation, distant metastasis, LN metastasis and advanced clinicopathological stage, while high expression of IQGAP1 was associated with these poor clinicopathological characteristics. No significant associations of menin or IQGAP1 expression with sex or age were observed.

Menin has been identified as a tumor suppressor in a variety of endocrine neoplasia, including pituitary adenomas (16) and parathyroid tumors (17), as well as adrenal (18) and islet (19) tumors. Menin is predominantly expressed in the cell nucleus, and may act as a scaffold protein to regulate gene transcription through the coordination of various chromatin-associating proteins (20). Menin also interacts with cytoskeletal proteins such as glial fibrillary acid protein, vimentin and IQGAP1 (15,21). A previous study confirmed the co-localization of menin and IQGAP1 in β cell lines (15). Therefore, it could be speculated that menin may interact with IQGAP1 to affect the proliferation of gastric cancer cells.

To study the effects of menin and IQGAP1 on the proliferation of gastric cancer cells, menin and IQGAP1 were overexpressed with pAd-Menin and pAd-IQGAP1, respectively. siRNAs targeting IQGAP1 and menin were transfected into gastric cancer cells to knock down the expression of these proteins. The effects of menin and IQGAP1 on the proliferation of gastric cancer cells were studied using MTT assay. The results revealed that ectopic expression of IQGAP1 promoted, whereas silencing of IQGAP1 expression inhibited, the proliferation of gastric cancer cells. However, increased expression of menin inhibited cell proliferation. Notably, exogenous menin inhibited the expression of IQGAP1, while increasing or interfering with the expression of IQGAP1 did not inhibit the expression of menin. In the present study, no significant changes in menin expression were observed in the menin knockout group, possibly because menin is poorly expressed in AGS cells.

Menin inhibits cell proliferation via various mechanisms. For example, menin interacts with NF-κB and suppresses NF-κB-mediated cyclin D1 transcription, thus inhibiting cell proliferation (22). Through interacting with Akt1, menin suppressed both Akt1-induced proliferation and anti-apoptosis in non-endocrine and endocrine cells (23). Further studies should be carried out to detect the expression of transcription factors such as PI3K and NF-κB, which are involved in regulating cell proliferation and repressing IQGAP1-mediated transcription (24). It was observed that the level of p-AKT and NF-κB were significantly downregulated in menin-overexpressing AGS cells. However, Akt levels were not altered in menin-overexpressing AGS cells. The pre-experimental results revealed that menin siRNA could not further reduce the expression of menin in gastric cancer cells. Thus, the altered effect on phosphorylated protein (p-AKT) and NF-κB expression by reducing menin was not determined in the present study. This suggested that the function of menin was partly accomplished by the regulation of PI3K/Akt and NF-κB. However, the detailed mechanism by which menin inhibits PI3K/Akt and NF-κB in gastric cancer needs to be investigated in future studies.

In conclusion, the present study confirmed that the protein levels of menin in gastric cancer tissues and AGS cells was lower than those in paired normal tissues and GES-1 cells. To the best of our knowledge, the present study has demonstrated for the first time that menin significantly inhibits the proliferation of gastric cancer cells. The inhibition is partly achieved by suppressing the expression of IQGAP1, which is accompanied by reduced expression of PI3K and NF-κB. How menin inhibits the expression of IQGAP1 will be investigated in a future study. The results of the present study indicated that menin may be a potential molecular marker and target in gastric cancer therapy.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

FR and HZ conceived the study, wrote the manuscript and generated the figures. FR and QG conducted the experiments and analyzed the data. All authors examined and verified all the raw data. FR and HZ confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved (approval no. JDFY20220801-1) by the Research Ethics Committee of Jiangnan University (Wuxi, China), and written informed consent was obtained from all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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