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PRINT: ISSN 0972-3757 ONLINE: ISSN 2456-6330
Int J Hum Genet, 26(1): 37-45 (2026)
DOI: 10.31901/24566330.2026/25.01.910

FAM117B Modulates the EGFR/ERK Signalling Pathway to Affect Gastric Cancer Cell Proliferation and Invasion

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KEYWORDS Cell Proliferation. Epidermal Growth Factor Receptor. FAM117B. Neoplasm Invasiveness. Stomach Neoplasms

ABSTRACT This study aimed to elucidate the role of family with sequence similarity 117 member B (FAM117B) in regulating gastric cancer (GC) cell proliferation, invasion, and apoptosis through the epidermal growth factor receptor (EGFR)/extracellular signal-regulated kinase (ERK) signalling pathway. GC cells with FAM117B knockdown were treated with the EGFR pathway activator NSC228155, and cellular behaviours and pathway activation were evaluated using proliferation, colony formation, invasion, apoptosis assays, and Western blot analysis. FAM117B silencing significantly suppressed cell proliferation and invasion while promoting apoptosis, accompanied by reduced phosphorylation of EGFR, Raf1, MEK, and ERK. These effects were partially reversed by NSC228155 treatment. Collectively, the findings indicate that FAM117B promotes malignant phenotypes of GC cells by activating the EGFR/Raf/MEK/ERK signalling pathway and may represent a potential therapeutic target.

INTRODUCTION

Gastric cancer (GC) is a malignant tumour of the digestive tract characterised by high morbidity and mortality and currently ranks fifth among malignant tumours globally (Yang et al. 2024; Uchikoshi et al. 2024). Approximately one million new cases of GC are diagnosed globally each year, and in China alone, about 670,000 new cases GC are reported annually, with nearly 80 percent of patients already presenting with advanced disease at the time of diagnosis (Kimura et al. 2024). Despite advances in surgical techniques, chemotherapy and targeted therapies, the overall prognosis of advanced GC remains unsatisfactory, largely due to aggressive tumour biology and the rapid development of therapeutic resistance. GC progression is driven by complex and heterogeneous molecular mechanisms, underscoring the urgent need to further elucidate key oncogenic signalling pathways and their regulatory networks to identify more effective therapeutic targets.

Epidermal growth factor receptor (EGFR) is a membrane receptor extensively expressed in various mammalian cells, and belongs to the receptor tyrosine kinase family (Li et al. 2023). Upon ligand binding, EGFR undergoes receptor dimerisation followed by tyrosine autophosphorylation, leading to activation of its intrinsic kinase activity. This process subsequently recruits and phosphorylates downstream signalling molecules, including proto-oncogene serine/threonine-protein kinase (Raf), mitogen-activated protein kinase (MEK), and extracellular-signal-regulated kinase (ERK) (Shalaby et al. 2024). Recent study has highlighted that aberrant EGFR activation in GC is not limited to genetic mutations but also involves dysregulated upstream regulators and sustained pathway signalling, contributing to tumour aggressiveness and treatment failure (Piper et al. 2024). Clinically, elevat-

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ed EGFR expression has been associated with lymph node metastasis and poor prognosis in GC patients, and experimental silencing of EGFR has been shown to suppress GC cell proliferation and invasion while inducing cell cycle arrest (Yu et al. 2023). Although EGFR has been recognised as a key therapeutic target, the limited efficacy of EGFR-targeted therapies in GC suggests that additional regulatory mechanisms governing EGFR signalling remain incompletely understood.

Family with sequence similarity 117 member B (FAM117B) is encoded by a highly conserved gene in animal cells, which contains 589 amino acids. Recent literature has increasingly reported that members of the family with sequence similarity (FAM) proteins participate in tumour initiation and progression by modulating key oncogenic signaling pathways and cellular behaviours (Zhao et al. 2024). However, to date, direct evidence regarding the biological function of FAM117B in cancer, particularly in GC, remains scarce, and its potential involvement in EGFR-mediated signalling has not been explored.

Objectives

Based on these gaps in current knowledge, the present study critically investigates whether FAM117B functions as a regulatory factor of the EGFR/ERK signalling pathway and thereby influences gastric cancer cell proliferation, invasion, and apoptosis.

MATERIAL AND METHODS

Cell Lines, Reagents and Apparatus

The immortalised human gastric epithelial cell line (GES-1) and the human GC cell line (AGS) were obtained from the Cell Bank of Chinese Academy of Sciences. NSC228155 (catalog no. HY-101084), an activator of EGFR, was purchased from MedChemExpress (MCE). Short hairpin RNA targeting FAM117B (sh-FAM117B) and the corresponding negative control plasmid (sh-NC) was provided by Hedgehog (China). Dulbecco's modified Eagle medium (DMEM) and Roswell Park Memorial Institute (RPMI)-1640 medium were obtained from Gibco (USA). Primary antibodies against MEK, ERK1/2, phosphorylated (p)-ERK1/2, EGFR, Raf1, and p-Raf1 were purchased from Proteintech (USA), while antibodies against p-MEK and p-EGFR were obtained from Abcam (USA). Goat anti-rabbit IgG antibody and β-actin were purchased from Cell Signalling Technology (CST, USA). Polymerase chain reaction (PCR) kits were obtained from TaKaRa (Japan). An ultra-high-speed cryogenic centrifuge (L-90K) was purchased from Beckman Coulter. A fluorescence microscope (Olympus BX53) was purchased from Olympus. A multifunctional gel imaging system was provided by BIO-RAD (USA).

Cell Culture and Grouping

AGS and GES-1 cells were cultured at 37°C in a humidified incubator containing 5 percent CO_2 in RPMI-1640 medium supplemented with 10 percent foetal bovine serum and 1 percent penicillin-streptomycin. After seeding, cells adhered to the culture surface within 4 hours. When cell confluency reached approximately 80 percent, the medium was replaced with serum-free RPMI-1640 for 6 hours prior to transfection. Plasmid transfection was then performed using Lipofectamine 3000 according to the manufacturer's instructions. Cells were divided into four experimental groups of a sh-FAM117B group (cells were transfected with the sh-FAM117B plasmid), a sh-NC group (cells were transfected with the negative control plasmid), a sh-FAM117B+ NSC228155 group (AGS cells were transfected with the sh-FAM117B plasmid and subsequently treated with 2 μmol/L NSC228155, an EGFR activator), and a control group (AGS cells without plasmid transfection).

Reverse Transcription (RT)-PCR for Measurement of Relative Expression of FAM117B

Total RNA was extracted from cells in each group using TRIzol reagent according to the manufacturer's instructions. Then, concentration and purity of ribonucleic acid (RNA) were determined, and equal amounts of RNA were reverse-transcribed into complementary deoxyribonucleic acid (cDNA). Quantitative PCR was subsequently performed using a SYBR Green-based detection system. Each 10-μL PCR reac-

tion mixture consisted of 5 μL 2×SYBR mix, 0.4 μL of cDNA template, 0.4 μL of forward primer, 0.4 μL of reverse primers, 0.4 μL of ROX reference dye, and 3.4 μL of diethyl pyrocarbonate (DEPC)-treated water. Amplification was carried out under the conditions including initial denaturation at 95°C for 30 seconds, followed by 40 cycles of denaturation at 95°C for 5 seconds, and annealing/extension at 60°C for 60 seconds. Relative gene expression levels were calculated using the $2^{-\Delta\Delta ct}$ method, with the corresponding internal control gene used for normalisation.

Methyl Thiazolyl Tetrazolium (MTT) Assay for Detection of Cell Proliferation

AGS cells from each group were digested into single-cell suspensions and seeded into 96-well plates at a density of 2.5×10^4 cells/mL. After cell attachment, the culture medium was carefully removed, and each well was supplemented with MTT solution (200 ìL per well). Following incubation, the supernatant was discarded, and dimethyl sulfoxide (DMSO; 150 ìL per well) was added to dissolve the formazan crystals. The plates were gently shaken to ensure complete solubilisation. When the crystals were fully dissolved, the optical density (OD) of each well was measured at 490 nm using a microplate reader. The OD values were used to evaluate cell proliferative activity.

Colony Formation Assay for Determination of Proliferation of Cells

AGS cells from each group were harvested, digested into single-cell suspensions and seeded into a 6-well plate at a density of 2.5×10^4 cells/mL after removal of the original culture medium. Once cells had adhered to the culture surface, F12 medium containing 12 μM DT-3 was added, and the cells were allowed to grow continuously for 2 weeks to enable colony formation. At the end of the incubation period, the culture medium was discarded, and the cells were gently washed with phosphate-buffered saline (PBS), fixed with formaldehyde solution, and stained with crystal violet. were carried out on the cells. The plates were then rinsed and air-dried at room temperature. Colonies were photographed, and colony formation efficiency was calculated to evaluate long-term proliferative capacity.

Transwell Assay for Detection of Invasion Ability of Cells

AGS cells from each group were harvested, digested into single-cell suspensions, and resuspended in DMEM containing 0.1 percent foetal bovine serum. A total of 200 μL of the suspension was seeded into the upper chamber of Transwell inserts pre-coated with Matrigel, while the lower chamber was filled with DMEM supplemented with 10 percent foetal bovine serum as a chemoattractant. The cells were then incubated for 24 hours. After incubation, non-invaded cells on the upper surface of the membrane were gently removed. The invaded cells on the lower surface were fixed with formaldehyde solution for 10 minutes and stained with 0.1 percent crystal violet for an additional 10 minutes. Invaded cells were observed and photographed under a light microscope, and the number of invaded cells was quantified to assess invasive capacity.

Flow Cytometry for Detection of Apoptosis

AGS cells from each group were harvested after removal of the culture medium and digested into single-cell suspensions. The cell density was adjusted to 2.5×10^4 cells/mL, and the cells were seeded into 6-well plates. After cell attachment, the culture medium was removed, and the cells were fixed with 70 percent cold ethanol at 4°C for 12 hours. Following fixation, the cells were centrifuged and washed to remove residual ethanol. The cell pellets were then resuspended and incubated with propidium iodide (PI) staining solution containing 0.01 percent RNase in the dark according to the manufacturer's instructions. Apoptotic cells were subsequently analysed by flow cytometry.

Western Blotting for Measurement of Cellular Expressions of ERK1/2, MEK, p-MEK, p-ERK1/2, EGFR, p-EGFR, Raf1 and p-Raf1 Proteins

AGS cells were lysed in 100 μL of lysis buffer using a homogeniser and centrifuged at 15,000 rpm for 15 minutes at 4°C. The supernatant was collected, and total protein concentration was determined using bicinchoninic acid (BCA) assay. Protein samples were denatured by boiling

and subsequently separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). The separated proteins were then transferred onto a polyvinylidene difluoride (PVDF) membrane. The membranes were inhibited by 5 percent non-fat milk for 1 hour and then incubated with primary antibodies (1:500 dilution) at 4°C overnight. Following washing, the membranes were incubated with horseradish peroxidase (HRP)-conjugated secondary antibodies (1:1000 dilution) for 2 hours at room temperature. Protein bands were visualized using enhanced chemiluminescence (ECL) reagents, and images were captured using a gel imaging system. Band intensities were quantified using Image Lab software.

Statistical Analysis

All experimental data were analysed using GraphPad Prism 8.0 software. Quantitative data are presented as mean ± standard deviation (SD). For comparisons among multiple groups, data with a normal distribution were analysed using one-way analysis of variance (ANOVA), followed by the least significant difference (LSD) post hoc test for pairwise comparisons. $P<0.05$ indicated statistical significance.

RESULTS

Relative Expression of FAM117B in Cells

As shown in Figure 1A, the relative expression of FAM117B was significantly higher in AGS gastric cancer cells than in normal gastric epithelial GES-1 cells ($P<0.05$), indicating that FAM117B is upregulated in gastric cancer and may be associated with malignant transformation. To further verify the efficiency of FAM117B knockdown and its regulation, AGS cells were transfected with sh-FAM117B. As illustrated in Figure 1B, FAM117B expression was markedly reduced in the sh-FAM117B group compared

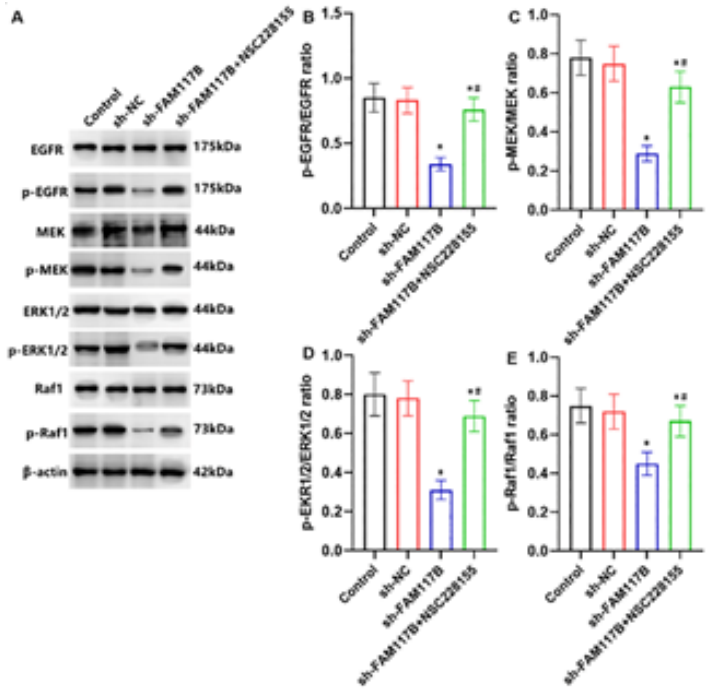

Fig. 1. Relative expression of FAM117B in cells. A: Comparison of relative expression of FAM117B between GES-1 cells and AGS cells. B: Comparison of FAM117B relative expression among different groups of AGS cells. $^{*}P<0.05$ *vs.* GES-1 cells/Control Group, $^{\#}P<0.05$ *vs.* sh-FAM117B Group

with the sh-NC group (P<0.0001), confirming effective gene silencing. Notably, treatment with the EGFR pathway activator NSC228155 significantly increased FAM117B expression in the sh-FAM117B+NSC228155 group relative to the sh-FAM117B group (P<0.0001). This partial restoration suggests that EGFR pathway activation positively regulates FAM117B expression, supporting a functional link between FAM117B and EGFR-mediated signalling in gastric cancer cells.

Proliferative Capability of Cells

As shown in Figure 2A, there was no significant difference in cell survival rate between the control group and the sh-NC group (P>0.05). In contrast, FAM117B knockdown resulted in a marked reduction in cell survival rate in the sh-FAM117B group compared with the sh-NC group (P<0.0001), demonstrating that FAM117B plays an important role in maintaining gastric cancer cell proliferation. Treatment with the EGFR pathway activator NSC228155 significantly increased cell survival in the sh-FAM117B+NSC228155 group compared with the sh-FAM117B group (P<0.0001). Consistent with these findings, the colony formation assay (Fig. 2B and 2C) showed a pronounced decrease in the number of colonies following FAM117B silencing. Quantitatively, the number of colonies in the sh-FAM117B group was significantly lower than that in the sh-NC group (P<0.0001). Notably, NSC228155 treatment partially restored colony formation ability, further supporting that FAM117B promotes gastric cancer cell proliferation at least in part through EGFR-mediated signalling.

Invasive Capacity of Cells

As shown in Figure 3A, the number of invaded cells was comparable between the control group and the sh-NC group (P>0.05), indicating that negative control transfection did not influence the invasive behaviour of gastric cancer cells. In contrast, FAM117B knockdown resulted in a pronounced reduction in cell invasion, as evidenced by a markedly lower number of cells penetrating the Matrigel-coated mem-

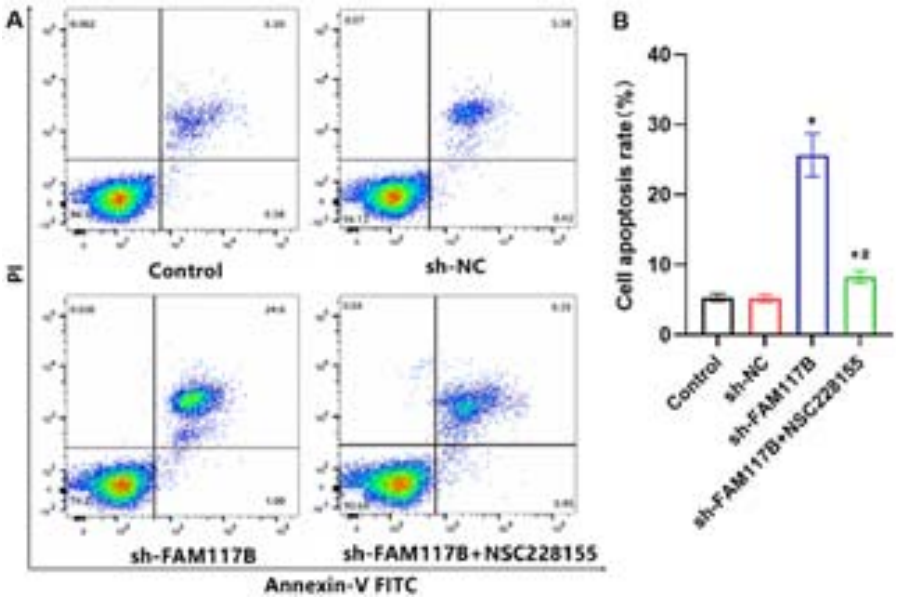

Fig. 2. Proliferation ability of cells. A: Cell survival rate examined using MTT assay. B: Cell proliferation determined by colony formation assay. C: Comparison of number of colonies. *P<0.05 *vs.* Control Group, #P<0.05 *vs.* sh-FAM117B Group

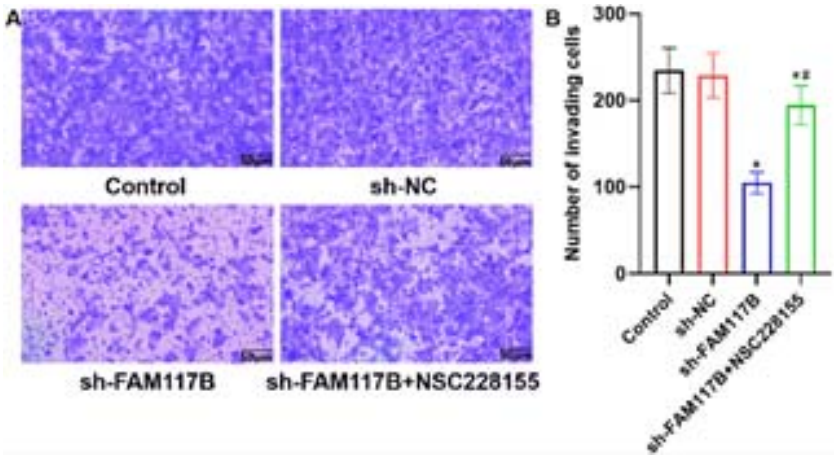

Fig. 3. Invasion ability of cells. A: Cell invasion ability examined by Transwell assay. B: Comparison of number of invaded cells among groups. *P<0.05 *vs.* Control Group, #P<0.05 *vs.* sh-FAM117B Group

brane in the sh-FAM117B group compared with the sh-NC group (P<0.0001). Quantitative analysis further confirmed these observations (Fig. 3B), showing a significant decrease in the number of invaded cells following FAM117B silencing. Importantly, treatment with the EGFR pathway activator NSC228155 significantly increased the number of invaded cells in the sh-FAM117B+ NSC228155 group compared with the sh-FAM117B group (P<0.0001). These findings suggest that FAM117B contributes to gastric cancer cell invasion, at least in part, through EGFR-mediated signaling.

Apoptosis Rate

As shown in Figure 4A, flow cytometric analysis revealed no significant difference in apoptosis rate between the control group and the sh-NC group (P>0.05). In contrast, silencing FAM117B markedly increased apoptosis, as evidenced by an obvious expansion of Annexin V-positive cell populations in the sh-FAM117B group compared with the sh-NC group (P<0.0001). Quantitative analysis further confirmed these observations (Fig. 4B), showing a significant elevation in total apoptotic cells following FAM117B knockdown.

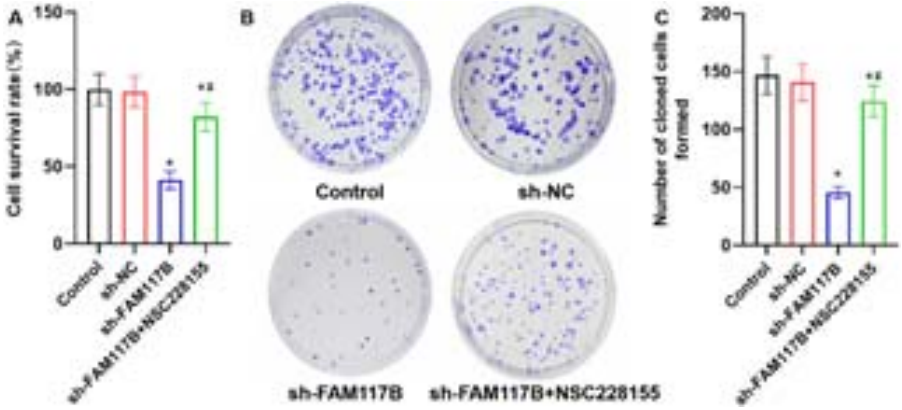

Fig. 4. Apoptosis rate. A: Apoptosis rate detected by flow cytometry. B: Intergroup contrast of apoptosis rate. *P<0.05 *vs.* Control Group, #P<0.05 *vs.* sh-FAM117B Group

The activation of the EGFR pathway by NSC228155 significantly reduced the apoptosis rate in the sh-FAM117B+NSC228155 group compared with the sh-FAM117B group ($P<0.0001$), although apoptosis levels remained higher than those in control cells. These results suggest that FAM117B suppresses apoptosis in gastric cancer cells, at least in part through EGFR-mediated signalling.

Expressions of MEK, EGFR, ERK1/2, p-MEK, p-ERK1/2, p-EGFR, Raf1 and p-Raf1 Proteins

Western blot analysis demonstrated that the total protein levels of EGFR, Raf1, MEK, and ERK1/2 were comparable between the control group and the sh-NC group, indicating that negative control transfection did not affect basal expression of these signaling molecules (Fig. 5A). Consistently, the ratios of phosphorylated to total proteins (p-EGFR/EGFR, p-Raf1/Raf1, p-MEK/MEK, and p-ERK1/2/ERK1/2) showed no significant differences between these two groups ($P>0.05$; Fig. 5B-E). In contrast, FAM117B knockdown markedly suppressed EGFR/ERK pathway activation, as evidenced by significant reductions in the phosphorylation ratios of EGFR, Raf1, MEK, and ERK1/2 in the sh-FAM117B group compared with the sh-NC group ($P<0.0001$). However, following the treatment of NSC228155, the decreased ratios of p-ERK1/2/ERK1/2, p-EGFR/EGFR, p-MEK/MEK, and p-Raf1/Raf1 were significantly restored in sh-FAM117B+NSC228155 group ($P<0.0001$). These findings indicate that FAM117B positively regulates the EGFR/Raf/MEK/ERK signalling cascade and provides mechanistic support for its role in promoting gastric cancer cell proliferation and invasion while inhibiting apoptosis.

DISCUSSION

As a malignant tumour of the digestive system, GC remains one of the leading causes of cancer-related morbidity and mortality, particularly in developing countries. Recent epidemiological study indicates that the global burden of GC continues to increase, which has been attributed not only to lifestyle factors such as dietary habits and irregular schedules (Ma et al. 2023). China bears a disproportionate share of this burden, accounting for approximately 40 percent of newly diagnosed GC cases world-

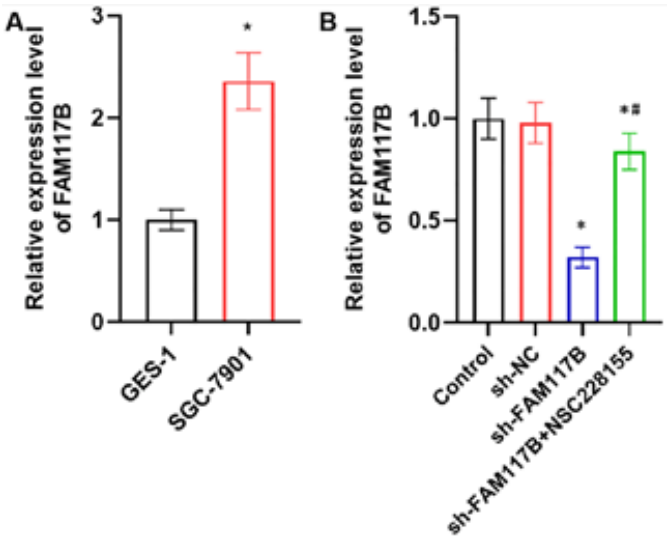

Fig. 5. Expressions of MEK, EGFR, ERK1/2, p-MEK, p-ERK1/2, p-EGFR, Raf1 and p-Raf1 proteins. A: Protein bands of MEK, EGFR, ERK1/2, p-ERK1/2, p-EGFR, Raf1, p-MEK, and p-Raf1 obtained through Western blotting. B: Comparison of p-EGFR/EGFR ratio in cells. C: Comparison of cellular p-MEK/MEK ratio. D: Comparison of cellular p-ERK1/2/ERK1/2 ratio. E: Comparison of cellular p-Raf1/Raf1 ratio. *P<0.05 *vs.* Control Group, #P<0.05 *vs.* sh-FAM117B Group

wide each year, and GC-related mortality is largely driven by aggressive invasion and distant metastasis (Jiang et al. 2024). Despite advances in surgical techniques and systemic therapies, the clinical outcomes of patients with advanced GC remain poor, highlighting the urgent need to identify novel molecular targets and to better understand the mechanisms underlying tumour progression and therapeutic resistance (Jiao et al. 2023).

FAM117B has been implicated in various biological processes, including DNA replication, chromosome segregation, cell cycle regulation, and p53-mediated signalling. Emerging evidence from recent study suggests that dysregulation of FAM family proteins contributes to tumorigenesis by modulating cell cycle checkpoints and apoptotic pathways (Deng et al. 2025). In lung adenocarcinoma, FAM117B has been reported to attenuate the proliferation, migration, and invasion of colorectal cancer cells via the modulation of DYRK1A/PLK2 signalling pathway (Yu et al. 2026). However, the role of FAM117B in gastric cancer has remained insufficiently characterised, and existing studies are limited in number and mechanistic depth. In the present study, the researchers demonstrated that FAM117B expression was significantly upregulated in AGS gastric cancer cells compared with normal gastric epithelial cells, and that FAM117B knockdown markedly suppressed cell proliferation and invasion while promoting apoptosis. These findings are consistent with, and extend, recent observations by Zhou *et al.* (2023), who reported a role for FAM117B in GC growth and drug resistance, thereby supporting its potential as an oncogenic driver and therapeutic target.

As a member of the ErbB receptor family, EGFR is a type I receptor tyrosine kinase that is widely expressed in epidermal cells and stromal cells and plays a central role in regulating cell proliferation, survival, and differentiation (Chen et al. 2016). Upon ligand binding, EGFR undergoes dimerisation and autophosphorylation, leading to activation of downstream signalling cascades (Purba et al. 2017). Recent studies have emphasised that aberrant EGFR activation in cancer is not restricted to gene mutations but also involves sustained signalling driven by upstream regulatory dysregulation, which contributes to tumour aggressiveness and resistance to targeted therapies (Boretto et al. 2024; Gamez-Belmonte et al. 2023). Among EGFR downstream pathways, the Ras/Raf/MEK/ERK signalling cascade, also known as the mitogen-activated protein kinase (MAPK) pathway, is one of the most extensively studied and is critically involved in cell cycle progression and apoptosis inhibition (Song et al. 2022). Raf, a key component of this pathway, phosphorylates and activates MEK1/2, which in turn activates ERK1/2. Activated ERK regulates transcription factors associated with proliferation and survival. Persistent activation of this pathway has been repeatedly associated with enhanced tumour growth, metastatic potential, and poor prognosis in multiple malignancies, including GC (Pandian and Ganesan 2022). In the present study, the researchers observed that FAM117B knockdown significantly reduced the phosphorylation ratios of EGFR, Raf1, MEK, and ERK without markedly affecting total protein levels, indicating that FAM117B primarily regulates pathway activation rather than basal protein expression. These results suggest that FAM117B functions upstream of, or in concert with, EGFR signalling to sustain MAPK pathway activation.

Importantly, activation of EGFR signalling using the EGFR pathway activator NSC228155 partially reversed the inhibitory effects of FAM117B knockdown on gastric cancer cell proliferation and invasion. This pharmacological rescue experiment provides functional evidence supporting a mechanistic link between FAM117B and EGFR/Raf/MEK/ERK signalling. Taken together, the findings critically expand current understanding by positioning FAM117B as a novel modulator of EGFR-driven signalling in gastric cancer, thereby offering new insights into the molecular basis of GC progression and potential therapeutic intervention strategies.

CONCLUSION

In summary, FAM117B is highly expressed in gastric cancer cells and plays a critical role in regulating malignant cellular behaviours. Silencing FAM117B markedly inhibits cell proliferation and invasion while promoting apoptosis, an effect that is associated with suppression of the EGFR/Raf/MEK/ERK signalling pathway. These findings highlight the functional importance of FAM117B in gastric cancer progression and underscore

its potential relevance as a molecular target in gastric cancer.

RECOMMENDATIONS

Future studies are recommended to further elucidate the upstream regulatory mechanisms and downstream effectors of FAM117B in gastric cancer. Validation of these findings in additional gastric cancer cell lines, animal models, and clinical samples would strengthen their translational relevance. Moreover, exploring the interaction between FAM117B and other oncogenic signalling pathways may provide a more comprehensive understanding of its role in gastric cancer progression. Such efforts may facilitate the development of more effective therapeutic strategies targeting FAM117B-associated signaling networks.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

FUNDING

This work was supported by the Xiamen Science and Technology Plan Project (No. 3502Z 20209060, No. 3502Z20224ZD1069 and No. 3502Z 20227278).

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Paper received for publication in January, 2025
Paper accepted for publication in February, 2026