European Review for Medical and Pharmacological Sciences 2021; 25: 1330-1338

HMGN5 promotes invasion and migration of colorectal cancer through activating FGF/FGFR pathway

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Abstract. – OBJECTIVE: To detect the expression of high-mobility group nucleosome-binding domain 5 (HMGN5) in colorectal cancer tissues, to explore the function of HMGN5 on the proliferation and metastasis of colorectal cancer cells, and to further study the molecular mechanism of HMGN5 in the malignant progression of colorectal cancer (CRC).

PATIENTS AND METHODS: The cancer tissues and para-carcinoma tissues were harvested from 40 patients with CRC. The expression of HMGN5 was detected via quantitative real-time polymerase chain reaction (qRT-PCR), and the relation between HMGN5 and clinical indexes of CRC patients was further analyzed. The CRC HT29 and HCT116 cell lines with high expression levels of HMGN5 were selected, and the HMGN5 knockdown model was established. The functions of HMGN5 on CRC cells were stated by cell counting kit-8 (CCK-8) assay and transwell migration assay. Then, the association between HMGN5 and fibroblast growth factor 12 (FGF12) was further explored via Dual-Luciferase reporter assay and reverse assay.

RESULTS: The qRT-PCR showed that HMGN5 expression was significantly rising in cancer tissues compared to the control group. The incidence rate of lymph node metastasis and distant metastasis was higher in higher expression HMGN5 group than the lower expression HMGN5 group. The results of cell function experiments revealed that silence of HMGN5 could suppress the proliferation and migration of HT29 and HCT116. In addition, it was found using qRT-PCR that knockdown of HMGN5 could significantly down-regulate the expressions of FGF12, FGFR, PI3K and AKT in HT29 and HCT116 cells. The targeted binding relation between HMGN5 and FGF12 was also indicated by the dual-luciferase reporter assay. The consequence of qRT-PCR manifested that FGF12 expression markedly rose in CRC tissues, which had a positive correlation with HMGN5. Moreover, reverse assay indicated that the inhibitory effect of HMGN5 knockdown on the malignant progression of CRC could be reversed by recombinant FGF12, indicating once again that there is a mutual regulatory effect between HMGN5 and FGF12.

CONCLUSIONS: HMGN5 can increase the proliferative and migrative capacity of CRC cells via targeted binding to FGF12. In addition, clinical data analyses demonstrate that HMGN5 is intimately related to the incidence rate of lymph node metastasis and distant metastasis in patients with CRC.

Key Words:
HMGN5, FGF12, Colorectal cancer, Invasion, Migration.

Introduction

Colorectal cancer (CRC) is a hackneyed cancer in China, and it has become the third major cancer and a common cancer-related death in China[1-4]. Although the survival rate of CRC patients has been improved currently, the prognosis of patients remains poor due to tumor recurrence[5,6]. The 5-year survival rate is 71% in early stage, and 14% in advanced stage[7,8]. Similarly, systemic chemotherapy causes severe side effects. For example, oxaliplatin can result in neuropathy, and has a bad impact on the patients' life quality, especially after colostomy[9,10]. To sum up, studying the pathogenesis of CRC can bring a positive effect on the treatment of CRC and increase the prognosis of CRC[11,12].

High-mobility group nucleosome-binding domain (HMGN) protein family is a group of nucleosome-binding proteins widely present in the nuclei of almost all mammals and most vertebrates[13,14]. They can alter the structure of chromatin, thereby regulating its activity, and af-

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fecting gene transcription, histone modification, and deoxyribonucleic acid (DNA) replication, repair and regeneration[14,15]. HMGN5, located on human chromosome Xq13.3, is a new and typical member of the HMGN family, which contains a functional nucleotide-binding domain structure and a negatively charged C-terminus[16,17]. HMGN5 protein can quickly move into the nucleus and interact with nucleosomes, thereby affecting the transcriptional process[17]. Previous studies[18,19] have indicated that the HMGN5 gene is up regulated in many human tumors, and exhibits tumor activity in tumor models.

However, there are very few studies on the role of HMGN5 in CRC, and its specific biological functions and related pathways in CRC remain unclear. In this study, therefore, the role of HMGN5 in the occurrence and development of CRC and its related mechanism were further explored, so as to seek effective molecular targets for individualized treatment of CRC.

Patients and Methods

Patients and CRC Samples

The carcinoma tissue and para-carcinoma tissue specimens were collected from 40 patients undergoing radical operation of CRC. Neither of patients received radiotherapy and chemotherapy before operation. The pathological typing and staging of CRC were based on the staging criteria for CRC of the International Union Against Cancer (UICC). In this study, the patients and their families had been informed and approved the informed consent. The basic information of the patients was shown in Table I. This research was approved by the Ethics Committee of Children's Hospital of Soochow University and conformed to the clinical practice guidelines of the Declaration of Helsinki. All candidates were followed up *via* telephone and outpatient service after discharge, and the follow-up content included general conditions, clinical symptoms and imaging examination.

Cell Lines and Reagents

The CRC cell (HT29, HCT8, HT116 and SW480) and normal human intestinal epithelial cell line (FHC) were bought from the American Type Culture Collection (ATCC) (Manassas, VA, USA). HT29 and SW480 cell lines were maintained with high-glucose Dulbecco's Modified Eagle Medium (DMEM) (Gibco, Rockville, MD, USA) with 10% fetal bovine serum (FBS) (Gibco, Rockville, MD, USA), penicillin (100 U/mL) and streptomycin (100 μg/mL). HCT8 and HT116 cells were maintained under Roswell Park Memorial Institute-1640 (RPMI-1640) medium (HyClone, South Logan, UT, USA) containing 10% FBS and antibiotics. All cells were cultured in an incubator with 5% CO_2 at 37°C. The cells were digested and passaged with an 80-90% confluence.

Transfection

HT29 and HT116 cells were seeded into 6-well plates and cultured until the cell density reached about 30-50%. Blank control vectors (sh-NC)

Table I. Association of HMGN5 expression with clinicopathologic characteristics of colorectal cancer.

Parameters	Number of cases	HMGN5 expression		*p*-value
		Low (%)	High (%)	
Age (years)				0.608
< 60	15	9	6	
≥ 60	25	17	8	
Gender				0.273
Male	21	12	9	
Female	19	14	5	
T stage				0.524
T1-T2	23	14	9	
T3-T4	17	12	5	
Lymph node metastasis				0.010
No	25	20	5	
Yes	15	6	9	
Distance metastasis				0.031
No	26	20	6	
Yes	14	6	8	

and HMGN5 knockdown sequence-containing vectors (sh-HMGN5) were purchased from GenePharma (Shanghai, China). About 48 h later, the cells were harvested for phenotype and mechanism assay.

Cell Proliferation Assay

The cells were collected and inoculated into 96-well plates (2000 cells/well) at 48h post-transfection. After cultured, cell counting kit-8 (CCK-8) reagent (Dojindo Molecular Technologies, Kumamoto, Japan) was added, and the cells continued to be cultured for 2 h. Finally, the optical density (OD) value was detected and analyzed at an absorption wavelength of 490 nm with a microplate reader.

Transwell Migration Assay

The cells were resuspended in serum-free medium at 48 h post-transfection. Then, about 3×10^4 cells with 200 μL media were seeded into the upper chamber, while 400 μL of medium containing 10% FBS was added into the lower chamber, followed by culture in the incubator at 37ºC. After 48 h, the chamber was taken out, and the cells were fixed, stained and washed with phosphate-buffered saline (PBS). The stained transmembrane cells on the outer surface observed with a microscope and counted in 5 randomly-selected fields of view.

Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR)

The RNA expressions level of HMGN5, FGF12, FGFR, PI3K, AKT and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) were detected *via* qRT-PCR. Total RNA was extracted from tissues by a one-step method using TRIzol reagent (Invitrogen, Carlsbad, CA, USA), and then reversely transcribed into first-strand complementary deoxyribose nucleic acid (cDNA) using PrimeScript RT Reagent Kit (TaKaRa, Otsu, Shiga, Japan). Then qRT-PCR was performed using StepOne Plus Real-time PCR system (Applied Biosystems, Foster City, CA, USA). The primers used for qRT-PCR are as follows. HMGN5: F: 5'-GCCAGGTTGTCTGCTATGCT-3', R: 5'-TGCTTCTTGCTTGGTTTCAGC-3'. FGF12: F: 5'-GGAAGGAAGTACGGGCGAAA-3', R: 5'-GGAATTAGATTGAAGAGAGCTTTGC-3'. FGFR: F: 5'-CGACTGCCTGTGAAGCCTAT-3', R: 5'-CGACCCATCGTTGCTGTAGA-3'. PI3K: F: 5'-CGTGCTGTGCAGACGAAAAA-3', R: 5'-CTCAGGTCCAACTCGCTGTT-3'. AKT: F: 5'-AAGTCATCGTGGCCAAGGAC-3', R: 5'-ACAGGTGGAAGAACAGCTCG-3'. GAPDH: F: 5'-CCTGGCACCCAGCACAAT-3', R: 5'-TGCCGTAGGTGTCCCTTTG-3'. The assay was conducted for 3 times with 3 replicates for each sample. The data were analyzed and processed using the in-built software of Bio-Rad PCR instrument (Bio-Rad, Hercules, CA, USA). The gene expression was calculated by the $2^{-\Delta\Delta Ct}$ method, with GAPDH as an internal control.

Western Blotting

The cells were lysed, shaken on ice for 30 min, and then centrifuged at 14,000 × g for 15 min at 4°C. The protein concentration was detected by the bicinchoninic acid (BCA) kit (Pierce, Rockford, IL, USA). HMGN5 antibody was purchased from Proteintech (Rosemont, IL, USA), and the secondary antibody was provided by Proteintech (Rosemont, IL, USA). The GAPDH was enrolled as an internal control. Subsequently, the samples were separated by the sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and then transferred onto membranes. At last, membranes were sealed, and incubated with primary antibody and secondary antibody, followed by color development with enhanced chemiluminescence (ECL) reagent.

Dual-Luciferase Reporter Assay

The pcDNA-NC and pcDNA-FGF12 vectors were constructed, and vectors including wild-type and mutant type 3′-untranslated region (3′-UTR) sequence of HMGN5 were co-transfected into cells by Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA). The Luciferase activity was normalized to the firefly luciferase activity by the Dual-Luciferase reporter assay system at 48 h post-transfection.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 22.0 software (IBM, Armonk, NY, USA) was applied for statistical analysis. Measurement data were compared using *t*-test, and categorical variables were analyzed by χ^2 -test or Fisher's exact probability test. Besides, data were expressed as mean ± standard deviation ($\bar{x} \pm s$). $p<0.05$ was considered to be statistically significant.

Results

HMGN5 was Highly Increased in CRC Tissues and Cell Lines

The consequence of qRT-PCR indicated that HMGN5 was significantly higher in CRC than that control group (Figure 1A). Compared with that in FHC cells, HMGN5 had a significantly higher expression level in CRC cell lines, especially in HT29 and HT116 cells, so these two cell lines were enrolled for the following assays (Figure 1B). Based on HMGN5 level in CRC tissues, the 40 patients were classified into higher expression group and lower expression group. Then, the association between HMGN5 level and clinicopathological parameters of CRC patients was analyzed. As shown in Table I, the incidence rate of lymph node metastasis and distant metastasis significantly rose in CRC patients with high expression of HMGN5 (Figure 1C). The above results indicated that HMGN5 may serve as a novel biological index for the diagnosis and treatment of CRC.

Knocking Down of HMGN5 Suppressed Proliferative and Migrative Capacity of CRC Cell Lines

To detect the function of HMGN5, the HMGN5 knockdown model was first established. The Western blotting assay indicated that the HMGN5 expression declined after transfection with sh-HMGN5 compared with blank vectors, confirming that the model was successfully established (Figure 2A). Besides, the consequences of CCK-8 results manifested that the proliferative activity of HT29 and HT116 prominently declined in sh-HMGN5 group than sh-NC group (Figure 2B). Transwell migration assay showed that the cells passing through the membrane in the transwell chamber were markedly less in sh-HMGN5 group than sh-NC group, suggesting that the cell migration ability was inhibited (Figure 2C).

Knocking Down of HMGN5 Suppressed FGF/FGFR Pathway in CRC Cell Lines

The interaction between HMGN5 and related pathways in HT29 and HT116 cell lines was further explored. It was found using qRT-PCR that knockdown of HMGN5 could markedly down-regulate the expressions of FGF12, FGFR, PI3K and AKT (Figure 3A). Dual-Luciferase reporter experiment revealed that overexpression of FGF12 could apparently reduce the Luciferase activity in cells containing wild-type HMGN5 vectors, but not lower that in cells containing mutant HMGN5 vectors, further proving that HMGN5 can be targeted by FGF12 *via* specific binding sites (Figure 3B). Besides, qRT-PCR consequences exhibited that FGF12 level in CRC tissues was distinctly higher than the control tissues (Figure 3C). Moreover, it was found that there was a positive relation between the levels of HMGN5 and FGF12 in CRC tissues (Figure 3D).

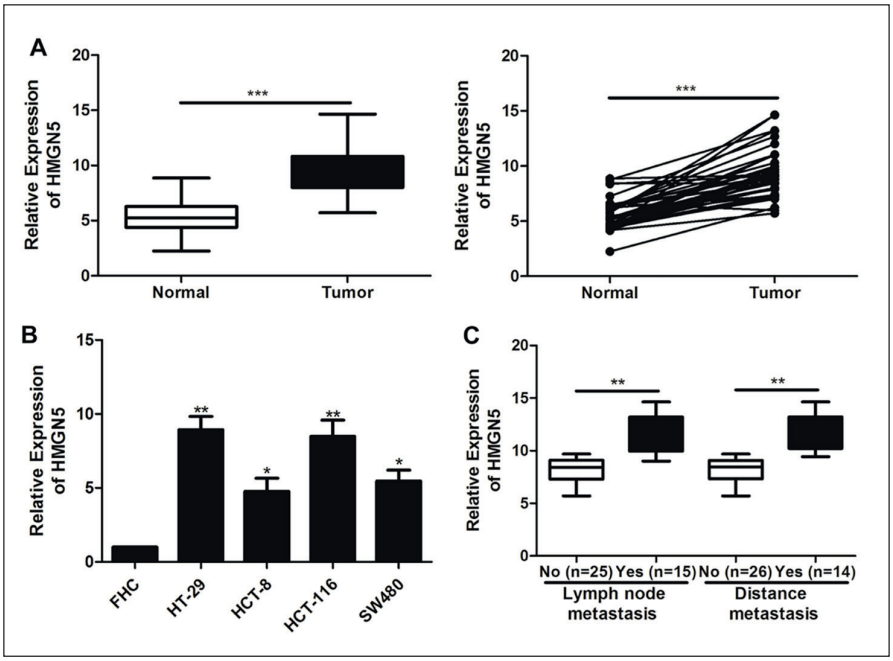

Figure 1. HMGN5 is highly expressed in CRC tissues and cell lines. **A,** Differences in HMGN5 expression in CRC tissues and para-carcinoma tissues were detected. **B,** Expression level of HMGN5 in CRC cell lines detected using qRT-PCR. **C,** Difference in HMGN5 level in CRC tissues with and without lymph node metastasis and distant metastasis detected using qRT-PCR. *p<0.05, **p<0.01, ***p<0.001.

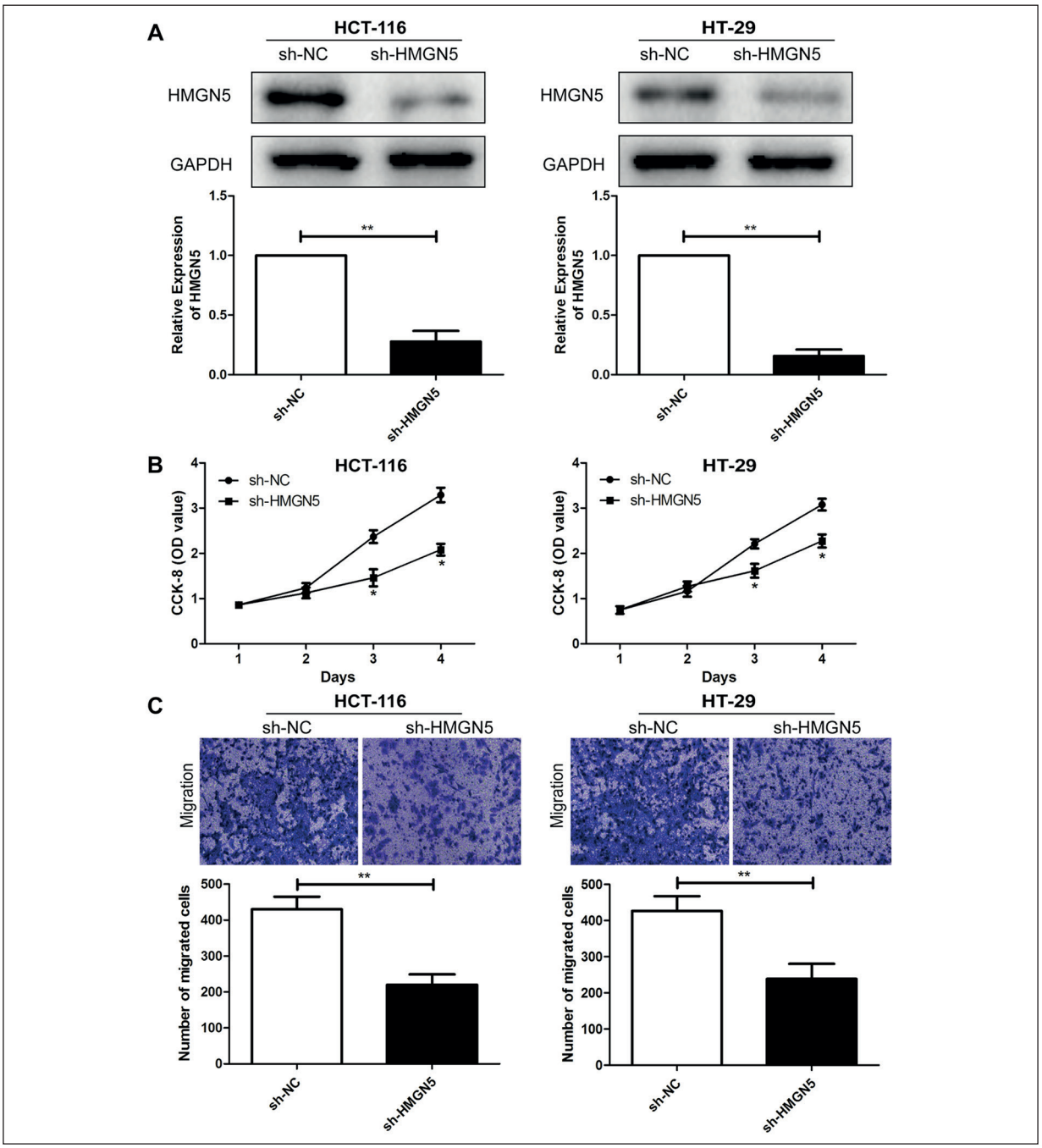

Figure 2. Silencing of HMGN5 can reduce the proliferative and migrative ability of CRC cells. **A,** Expression of HMGN5 in HT29 and HT116 cell lines transfected with sh-HMGN5 and sh-NC. **B,** Proliferative activity of HT29 and HT116 cell lines transfected with sh-HMGN5 and sh-NC determined using CCK-8 assay. **C,** Migration ability of HT29 and HT116 cell lines transfected with HMGN5 knockdown vectors determined using transwell migration assay (magnification: 40×). *p<0.05, **p<0.01.

Recombinant FGF12 Modulated HMGN5 Expression in CRC Cell Lines

To further explore the way through which HMGN5 and FGF12 promote the malignant progression of CRC, HT29 and HT116 cell lines were treated with recombinant FGF12 based on the knockdown of HMGN5 to investigate the mechanism in CRC. The results of Western blotting manifested that after knockdown of HMGN5, recombinant FGF12 could remarkably raise HMGN5 expression in CRC cells (Figure 4A). Further, it was observed *via* CCK-8 that the

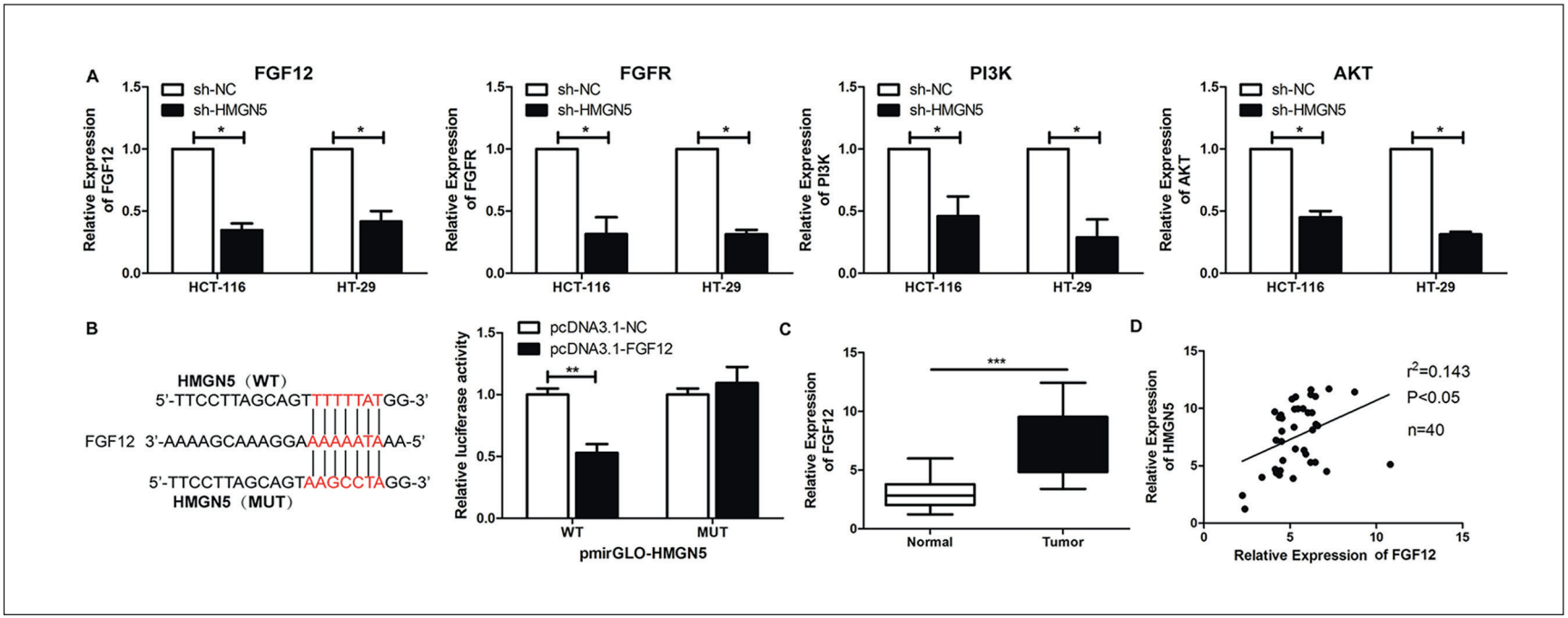

Figure 3. Relation between HMGN5 and FGF/FGFR in CRC cell lines. **A**, Expressions of FGF12, FGFR, PI3K and AKT in HT29 and HT116 cell lines transfected with sh-HMGN5 and sh-NC detected *via* qRT-PCR. **B,** Direct targeting relation between HMGN5 and FGF12 detected via dual-luciferase reporter assay. **C,** Difference in FGF12 expression in CRC tissues and para-carcinoma tissues detected via qRT-PCR. **D,** There is a significant positive correlation between the expressions of HMGN5 and FGF12 in CRC tissues detected *via* qRT-PCR. *p<0.05, **p<0.01, ***p<0.001.

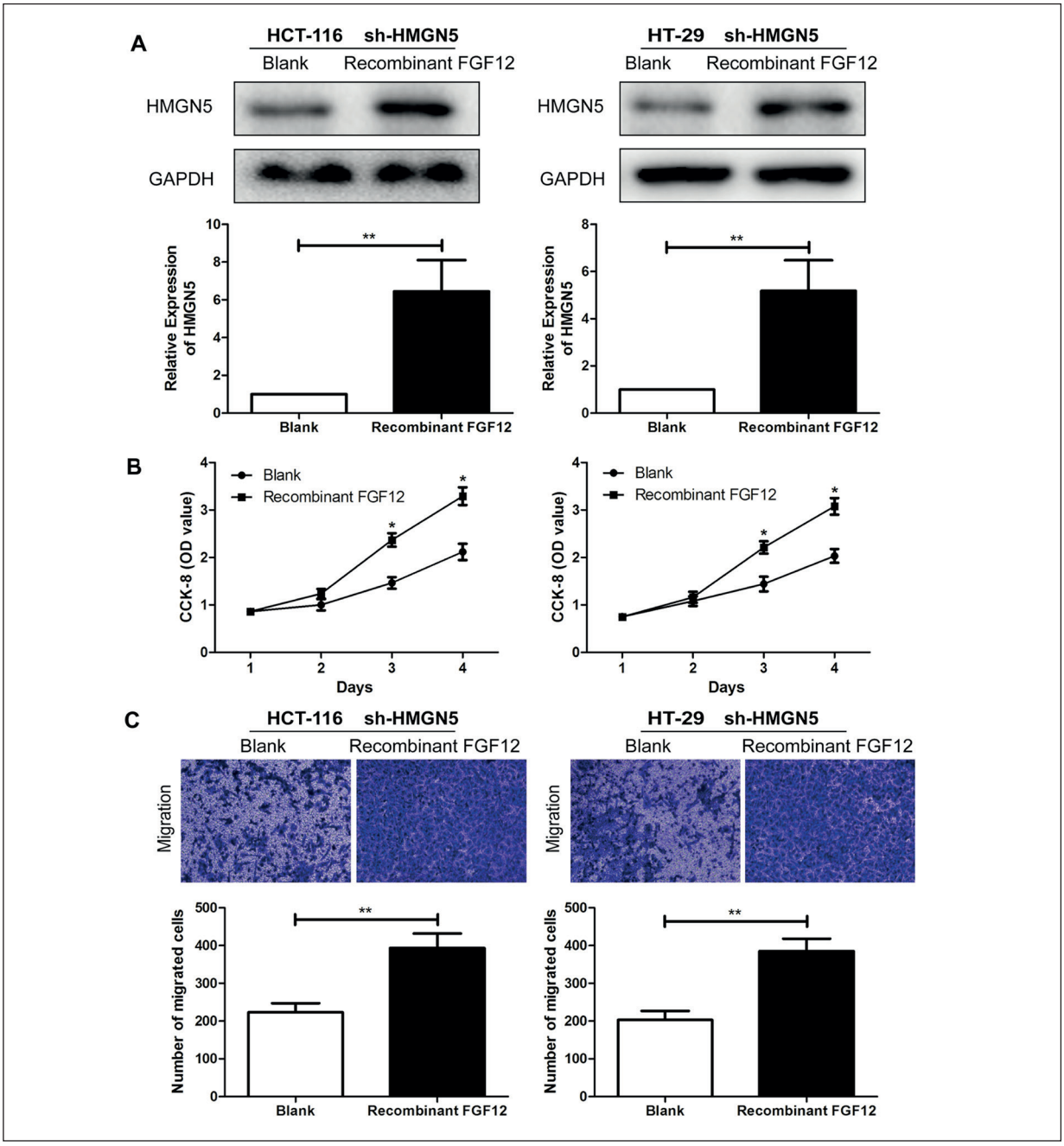

Figure 4. Recombinant FGF12 can reverse the effect of HMGN5 knockdown on the malignant progression of CRC. **A,** Expression efficiency of HMGN5 in HT29 and HT116 cell lines transfected with HMGN5 knockdown vectors after treatment with recombinant FGF12 determined using Western blotting. **B,** Proliferative activity of HT29 and HT116 cell lines transfected with HMGN5 knockdown vectors after treatment with recombinant FGF12 determined using CCK-8 assay. **C,** Migration ability of HT29 and HT116 cell lines transfected with HMGN5 knockdown vectors after treatment with recombinant FGF12 determined using transwell migration assay (magnification: 40×). *p<0.05, **p<0.01.

proliferative activity of CRC cells was evidently enhanced in sh-HMGN5 group after treatment with recombinant FGF12 compared to the sh-NC group (Figure 4B). Based on the transwell migration assay, the number of CRC cells passing through the membrane in the transwell chamber was notably larger in sh-HMGN5 group than that in sh-NC group after treatment with recombinant FGF12, suggesting that the cell migration ability was promoted (Figure 4C). It could be seen that

the inhibitory effect of HMGN5 knockdown on the malignant progression of CRC could be reversed by recombinant FGF12, indicating once again that there is a mutual regulatory effect between HMGN5 and FGF12.

Discussion

Due to the unhealthy diet and living habits of human, the incidence rate of malignant tumors is rising year by year, and the mortality rate is high around the world[1-3]. According to the Latest Global Cancer Data released by the World Health Organization in September 2018, the number of new cancer cases in Asia accounts for almost half of the total globally, and the number of cancer deaths in Asia is even more than half of the global total, dominated by Chinese population[2]. The occurrence of CRC is a cumulative process involving not only the monogenic mutation[4-7]. The occurrence and development of CRC is a gradual development process starting from benign adenoma, mostly in the order of "polyp-adenoma-cancer"[7,8]. Therefore, early detection and prompt prevention and diagnosis are important for CRC, thereby saving the lives of patients in time[10-12].

In this project, the expression of HMGN5 was detected in CRC, and the role of HMGN5 in the occurrence and development of CRC was further investigated. First, HMGN5 knockdown vectors were designed according to the sequences of HMGN5 and transfected into HT29 and HT116 cell lines. The level in sh-HMGN5 group significantly decreases compared to sh-NC group. The CCK-8 results found that the proliferative ability of HT29 and HT116 cells in sh-HMGN5 group was obviously inhibited than the sh-NC group. Invasiveness of tumor cells means that the tumor cells adhere to and pass through the extracellular matrix. The invasion of tumor cells into surrounding tissues and blood vessels of the tumor is the first step of its spread to other organs. When invading into the blood vessels, the tumor cells will flow with blood to other organs or tissues, adhere to and invade into the tissues again, forming metastases. Moreover, transwell assay indicated that the cells passing through the membrane in the transwell chamber were markedly decreased in sh-HMGN5 group than sh-NC group. The above findings indicated that HMGN5 can facilitate the proliferative and migrative ability of CRC cells, but its specific molecular mechanism remains unclear.

The interaction between HMGN5 and related pathways in CRC cell lines was further explored. It was found using qRT-PCR that knockdown of HMGN5 could markedly down-regulate the expressions of FGF12, FGFR, PI3K and AKT in CRC cells, suggesting that HMGN5 is closely related to the FGF/FGFR signaling pathway. As a key molecule in the FGF/FGFR signaling pathway, FGF12 can serve as the target gene of HMGN5 to participate in the occurrence and development of CRC according to bioinformatics analysis. Numerous studies have demonstrated that the role of FGF/FGFR signaling pathway in various types of cancers. Previous research pointed out that the expression of FGFR4 increased the activation of pro-survival STAT3 transcription factor and expression of cellular FLICE-like inhibitory protein, which leads to chemoresistance in CRC[20]. In addition, overexpression of FGFR4 has also been reported in radio-resistant CRC[21]. In this study, the above results were also confirmed by dual-luciferase reporter assay. Besides, the inhibitory effect of HMGN5 knockdown on the malignant progression of CRC could be reversed by recombinant FGF12, indicating once again that there is a mutual regulatory effect between HMGN5 and FGF12, and HMGN5 may promote the malignant progression of CRC by positively regulating FGF12. The previous research provides a new sight into explaining the mechanism of CRC progression which may be a new target for treatment in the future.

Conclusions

HMGN5 can promote the proliferative and migrative ability of CRC cells *via* targeted binding to FGF12. In addition, clinical data analyses demonstrate that HMGN5 is firmly related to the incidence rate of lymph node metastasis and distant metastasis in patients with CRC.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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