ORIGINAL PAPER

KRT15 promotes colorectal cancer cell migration and invasion through β-catenin/MMP-7 signaling pathway

Weida Chen[1] · Chengli Miao[1]

Abstract

KRT15 has been reported to act as an oncogene in colorectal cancer. However, whether KRT15 promotes colorectal cancer migration and invasion remain unclear. In this study, western blot and qRT-PCR assay were used to determine the expression of KRT15 in colorectal cancer cells. Wound-healing and transwell migration assay were performed to assess the migration of colorectal cancer cells. Matrigel transwell invasion assay was employed to examine the invasion of colorectal cancer cells. We found that KRT15 was highly expressed in colorectal cancer cells. Ectopic expression of KRT15 dramatically promoted colorectal cancer cell migration and invasion. Conversely, silencing KRT15 remarkably suppressed the migration and invasion of colorectal cancer cells. Importantly, we found that MMP-7 was crucial for KRT15-induced migration and invasion of colorectal cancer cells. Knockdown of MMP-7 significantly diminished the migration and invasion induced by KRT15; overexpression of MMP-7 almost completely rescued the inhibitory effects of KRT15 shRNAs on colorectal cancer cell migration and invasion. In addition, by gain- and loss-of function, we confirmed that β-catenin was responsible for the increased expression of MMP-7 induced by KRT15 colorectal cancer cell lines. In conclusion, KRT15 promotes migration and invasion of colorectal cancer cell at least partly through β-catenin/MMP7 signaling pathway, suggesting KRT15 is a potential therapeutic target for patients with metastatic colorectal cancer.

Keywords KRT15 · Colorectal cancer · Migration · Invasion · β-Catenin · MMP-7

Introduction

Colorectal cancer ranks third in terms of incidence, but second in terms of mortality in the world, with more than 1.9 million new colorectal cancer (including anus) cases and 935,000 deaths were estimated to occur in 2020, representing about one in 10 cancer cases and deaths [1]. Metastasis is the leading cause of cancer-related deaths in colorectal cancer patients [2]. Although there have been many therapeutic advances in the treatment of colorectal cancer, the 5-year overall survival rate is about 10% in metastatic cases [3]. Therefore, it is extremely urgent to elucidate the molecular mechanisms underlying colorectal cancer metastasis to improve the treatment.

Keratin-15 (KRT15), a type I keratin without a defined type II partner, is crucial for maintaining cytoplasmic stability [4]. KRT15 was first found to be primarily expressed in the basal keratinocytes of stratified tissues, including the fetal nail and fetal epidermis [4]. Subsequently, increasing studies reported that KRT15 was highly expressed in various cancers including esophageal carcinoma [5], urothelial cell carcinoma [6] and gastric cancer [7]. In addition, KRT15 high expression correlated with T stage, lymph node metastasis, tumor node metastasis stage and poor prognosis [5]. However, other reports showed that the expression of KRT15 was downregualted in prostate cancer [8], oral squamous cell carcinoma [9] and breast invasive carcinoma [10]. In colorectal cancer, Rao et al. recently reported that KRT15 was hard to detect in adjacent normal tissues, but was highly expressed in colorectal cancer tissues [11]. Moreover, the high expression of KRT15 was significantly associated with differentiation, T stage, lymph node metastasis and clinical stage and predicted poor prognosis in colorectal cancer

✉ Chengli Miao
miaochengli@pkuih.edu.cn

Weida Chen
chenweida@pkuih.edu.cn

1 Department of Retroperitoneal Tumor Surgery, Peking University International Hospital (PKUIH), Beijing 102206, People's Republic of China

[11]. However, it remains unclear whether KRT15 promotes colorectal cancer cell migration and invasion.

In this study, our results demonstrated that KRT15 activated β-catenin/MMP-7 signaling pathway, and thereby promoted the migration and invasion of colorectal cancer cells.

Materials and methods

Cell lines and cell culture

The human colorectal cancer cell lines SW480 and SW620 were obtained from the Shanghai Cell Bank, Chinese Academy of Sciences (Shanghai, China). The human normal colorectal epithelial cell (HCoEpiC) was purchased from the American Type Culture Collection (ATCC, Manassas, VA). All cells were maintained in Dulbecco's modified Eagle's medium (DMEM, Gibco) supplemented with 10% fetal bovine serum (FBS, Hyclone, USA), penicillin (100 U/ml) and streptomycin (100 mg/ml) and incubated at 37 °C in a humidified atmosphere. All cell lines were tested for mycoplasma using Mycoplasma Detection Kit (Thermo Fisher Scientific, San Jose, CA, USA) and confirmed by short tandem repeat (STR) profiling.

Quantitative real-time polymerase chain reaction assay

Quantitative real-time polymerase chain reaction assay was conducted as previously described [12]. Briefly, total RNA was extracted from human colorectal carcinoma cells using TRIzol reagent (Invitrogen, Carlsbad, CA). Reverse transcription was performed using PrimeScript™ RT Reagent Kit (Takara, Dalian, China) following the manufacturer's instructions. Then, quantitative real-time polymerase chain reaction (qRT-PCR) was subsequently performed using an ABI 7500 instrument (Applied Biosystems Inc) with SYBR Premix Ex Taq (Takara, Dalian, China). Data were normalized to GAPDH, and the relative expression of mRNA abundance was calculated using the $2^{-\Delta\Delta CT}$ method. The primers used are listed in Additional file 1: Supplementary Table S1.

Transwell assays

Transwell chambers (8 mm pore size, BD Falcon, CA, USA) and 24-well plates (Corning, NY, USA) were used to evaluate the migration and invasion of colorectal cancer cells. For transwell migration and invasion assays, 1×10^5 colorectal carcinoma cells in 200 μl serum-free DMEM were seeded into the upper chamber of a transwell without (transwell migration assay) or with (transwell invasion assay) matrigel (BD Biosciences, USA). After 24 h of incubation, non-migrated or invaded tumor cells were removed from the upper chamber using a cotton swab, and cells on the lower surface of the insert were fixed with methanol for 10 min, and stained using 0.5% crystal violet. Staining cells were visualized and photographed randomly using a CKX41 microscope (Olympus, Japan). Images of five random fields from three replicate wells were obtained and were counted.

Wound healing assay

Colorectal cancer cells were seeded in 6-well plates and grown to confluence. A 200 μl micropipette tip was used to scrape a wound across each cell monolayer. Nonadherent cells were washed away by rinsing with phosphate buffer. The plates were randomly imaged at 0 h and again after 24 h incubation using an phase-contrast microscope. The wound-healing rate was calculated as: $100\% \times$ [(wound width at 0 h − width at 24 h)/width at 0 h].

Plasmid constructs and transfection

Human KRT15, MMP-7 or β-catenin was cloned into the pCMV-Flag-His-PuroR vector by Transheep (Shanghai, China). Colorectal cancer cells were transfected with pCMV-Flag-His-PuroR/KRT15 or empty vector (Vector) using Lipofectamine 3000 (Invitrogen, Carlsbad, CA) according to the manufacturer's instructions. Human KRT15 or MMP-7 specific shRNAs were obtained from Sigma-Aldrich (Shanghai, China). The lentivirus were produced by transfection in 293T cells with control shRNA (shNC) or specific shRNA targeting KRT15 together psPAX2 (the packaging plasmid) and pMD2.G (the envelope plasmid) using Lipofectamine 3000 (Invitrogen, Carlsbad, CA). Viruses were collected after 48 h transfection and purified using 0.45-μm filters. SW480 and SW620 cells were infected with the indicated lentivirus in the presence of 8 μg/ml polybrene and selected with puromycin (1 μg/ml) for 2 weeks.

siRNA transfection

si-β-Catenin siRNA (6225, CST) and Control siRNA (6568, CST) were purchased from CST. The RNA was transfected with Lipo-RNAiMAX following the manufacturer's instruction (Invitrogen, Carlsbad, CA, USA) for 48 h.

Western blotting

Colorectal cancer cells were harvested and disrupted in RIPA lysis buffer (50 mM Tris at pH 7.4, 150 mM NaCl, 1% NP-40, 0.5% sodium deoxycholate, 0.1% SDS 1% Triton X-100 and protease inhibitors). Cell debris was removed via centrifugation at $14,000 \times g$ for 10 min at 4 °C. The nuclear protein was isolated using the nuclear protein and cytoplasmic protein extraction kit (Beyotime, Shanghai, China)

according to the manufacturer's instruction. Protein concentration was determined using Pierce BCA Protein Assay Kit (#23225, Thermo Scientific). For immunoblotting analysis, a total of 30 µg protein was separated using SDS-PAGE and transferred to polyvinylidene fluoride (PVDF) membrane (Bio-Rad, Hercules, CA, USA) (Bio-Rad, Hercules, CA). The membranes were blocked in 5% fat-free milk at room temperature for 2 h. The specific primary antibodies were incubated at 4 °C overnight and the corresponding horseradish peroxidase-conjugated secondary antibodies (1:5000 dilution, CST, USA) was incubated for 1 h at room temperature. Signals were visualized using enhanced chemiluminescence (Amersham; Buckinghamshire, UK). The primary antibodies used in this study were listed as follows: β-Catenin (D10A8) XP® Rabbit mAb (#8480, CST), MMP-7 (D4H5) XP® Rabbit mAb (#3801, CST), anti-KRT15 antibody (#ab239850, Abcam), β-Actin (8H10D10) Mouse mAb (#3700, CST) and HDAC1 (D5C6U) XP® Rabbit mAb (#34589, CST).

Statistical analysis

Data were analyzed with GraphPad Prism software version 7.00 for Windows (GraphPad Prism Software, San Diego, CA, USA) and expressed as the means ± standard deviation (SD). Statistical significance between two groups was estimated by Student's t test. Additionally, multiple group comparisons were analyzed with one-way ANOVA. A P value < 0.05 was accepted as statistically significant.

Results

Ectopic expression of KRT15 promoted migration and invasion in colorectal cancer cells

To investigate the function role of KRT15 in colorectal cancer cells, we first examine KRT15 expression levels in three colorectal cancer cell lines using western blotting analysis. As shown in Fig. 1A, KRT15 was significantly upregulated in all three tested colorectal cancer cell lines compared with the human normal colorectal epithelial HCoEpiC cells. Consistently, qRT-PCR analysis also showed that the mRNA level of KRT15 was much higher in colorectal cancer cells then that in HCoEpiC cells. Next, we stably overexpressed KRT15 using KRT15 expression vector (pCMV-Flag-His-PuroR/KRT15) in SW480 and SW620 cells. The overexpression efficiency was determined using qRT-PCR analysis and Western blot analysis, respectively. As illustrated in Fig. 1C and D, both mRNA and protein levels of KRT15 in SW480 and SW620 cells were significantly increased by more than 6 times compared with those cells transfected with empty vector. We then tested whether KRT15 promotes
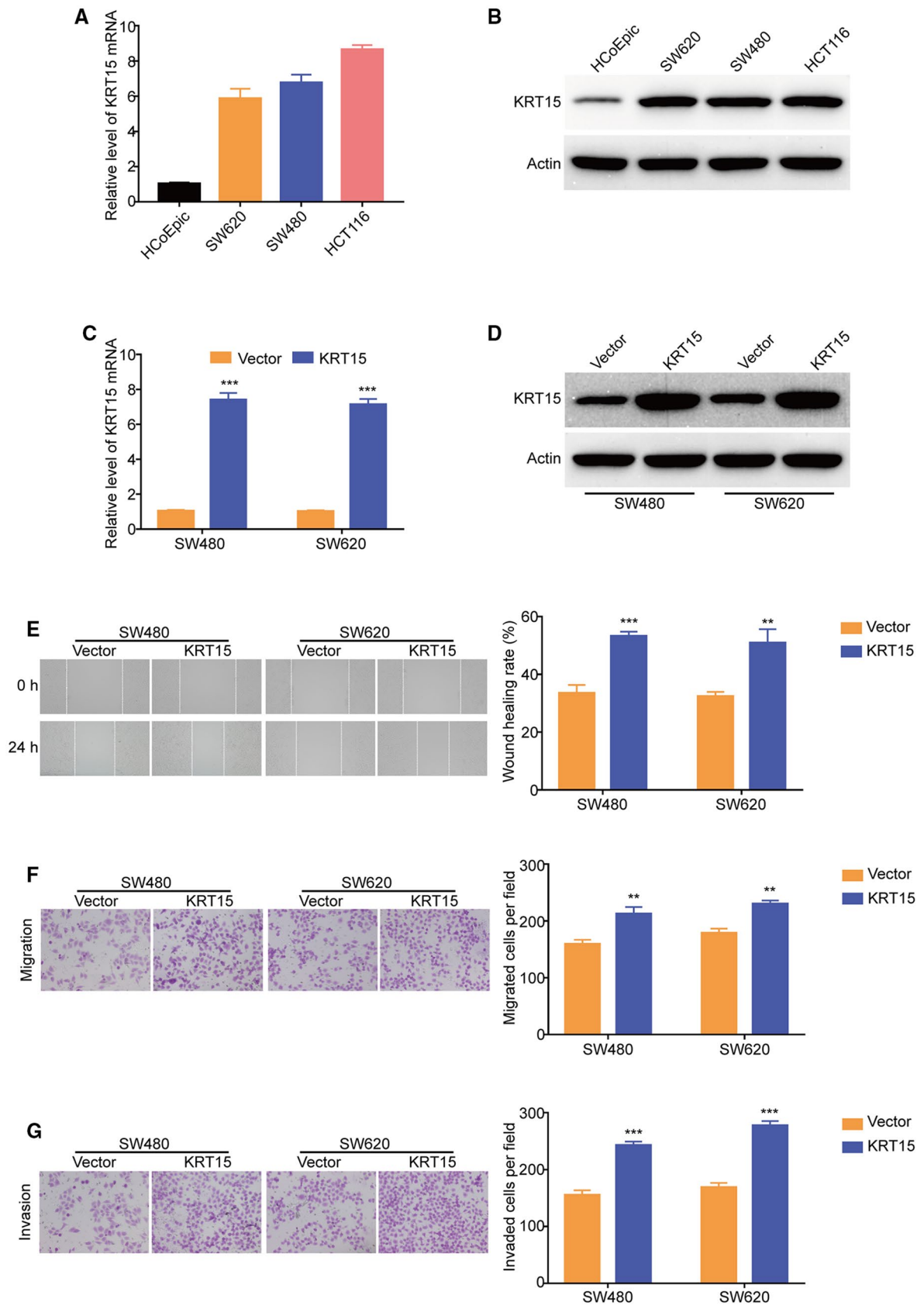
colorectal cancer cell migration using wound healing assay. As shown in Fig. 1E, the wound healing rate was obviously upregulated by KRT15 in both SW480 and SW620 cells. Transwell migration assay also revealed that forced expression of KRT15 apparently enhanced the migratory ability of SW480 and SW620 cells (Fig. 1F). Next, we examine whether KRT15 promotes colorectal cancer cell invasion using transwell invasion assay. The results showed that the invasive ability of SW480 and SW620 cells was significantly enhanced in response to KRT15 upregulation (Fig. 1G). Taken together, these findings indicated that KRT15 promoted the migration and invasion in colorectal cancer cells.

Silencing KRT15 suppressed migration and invasion in colorectal cancer cells

Subsequently, KRT15 was stably knocked down using two shRNA targeting KRT15 (shKRT15#1 and shKRT15#2) in SW480 and SW620 cells. qRT-PCR analysis and Western blot assays were used to determine the knockdown efficiency, respectively. As shown in Figs. 1A and 2B, both mRNA and protein levels of KRT15 in SW480 and SW620 cells were significantly reduced by KRT15 shRNAs compared with those cells transduced with shNC. We then tested whether silencing KRT15 inhibits colorectal cancer cell migration using wound healing assay. As shown in Fig. 2C, attenuation of KRT15 expression significantly hampered the migration speed of SW480 and SW620 cells. Transwell migration assay also revealed that knockdown of KRT15 remarkably suppressed the migratory ability of SW480 and SW620 cells (Fig. 2D). Next, we examine whether knocking down KRT15 decreases colorectal cancer cell invasion using transwell invasion assay. The results showed that the invasive ability of SW480 and SW620 cells was significantly suppressed in response to KRT15 upregulation (Fig. 2E). Taken together, these findings indicated that silencing KRT15 suppressed colorectal cancer cell migration and invasion.

KRT15 enhanced MMP-7 expression via in colorectal cancer cells

MMPs play important roles in progression and metastasis of colorectal cancer through extracellular matrix turnover, migration and invasion [13]. In our study, we analyzed whether KRT15 affects the expression of MMPs (including MMP-1, MMP-2, MMP-7, MMP-9 and MMP-13) using qRT-PCR analysis. As shown in Fig. 3A, forced overexpression of KRT15 barely the mRNA levels of MMP-1, MMP-2, MMP-9 and MMP-13. Intriguingly, the mRNA level of MMP-7 was significantly increased in response to KRT15 overexpression in SW480 and SW620 cells, compared with their control group (Fig. 4B). Conversely, silencing KRT15

◄**Fig. 1** Overexpression of KRT15 promoted migration and invasion in colorectal cancer cells. **A, B** The expression of KRT15 in CRC cell lines (SW480, SW620 and HCT116) compared with an immortal normal colorectal epithelial cell line (HCoEpic) detected using qRT-PCR (**A**) and western blotting (**B**). Actin served as the internal control. **C** qRT-PCR analysis of KRT15 mRNA in SW480 and SW620 cells transduced with KRT15 plasmid (KRT15) or control plasmid (vector). **D** Immunoblotting analysis validated that KRT15 was overexpressed in SW480 and SW620 cells transduced with KRT15 plasmid (KRT15) or control plasmid (vector). **E** Wound healing scratch assay showed overexpression of KRT15 promoted cell migration in colorectal cancer cells. Left: representative images of wound scratch. Right: histograms represent the analysis of the wound healing rate. **F** Transwell migration assay showed that enforced expression of KRT15 promoted migration of colorectal cancer cells. **G** Transwell invasion assay showed that overexpression of KRT15 enhanced invasion of colorectal cancer cells. **P < 0.01; ***P < 0.001

by lentiviral shRNAs drastically decreased the mRNA level of MMP-7 in both tested colorectal cancer cell lines. Additionally, Western blot analysis also verified that ectopic expression of KRT15 significantly elevated MMP-7 expression, while knocking down KRT15 significantly diminished MMP-7 expression. Together, these results indicated that KRT15 promoted MMP-7 expression at both mRNA and protein levels in colorectal cancer cells.

MMP-7 was essential for KRT15-induced migration and invasion in colorectal cancer cells

To further investigate the crucial role of MMP-7 in KRT15-mediated migration and invasion, MMP-7 was silenced by two lentiviral shRNAs against MMP-7 in SW480-KRT15 and SW480-Vector cells, the knockdown efficiency was assessed using immunoblotting analysis. As shown in Fig. 4A, the protein levels of KRT15 in SW480 cells were markedly reduced by MMP-7 shRNAs compared to those cells transduced with shNC. As expected, knocking down MMP-7 significantly inhibited the migration and invasion of SW480 cells, Moreover, the migration and invasion induced by KRT15 were also completely reversed by shRNA against MMP-7 (Fig. 4A and C). In contrast, ectopic expression of MMP-7 promoted the migration and invasion of SW480 cells (Fig. 4D–F); Furthermore, the KRT15 shRNAs-attenuated migration and invasion was considerably reversed by forced expression of MMP-7 (Fig. 4D–F). Taken together, these data indicate that MMP-7 is critical in KRT15-induced migration and invasion in colorectal cancer cells.

KRT15 promoted MMP-7 via upregulation of β-catenin signaling in colorectal cancer cells

Next, we asked how KRT15 regulated MMP-7 in colorectal cancer cells. Considering that MMP7 is an important downstream substrate of β-catenin signaling pathway, which is well known for its role in promoting tumor cell migration

and invasion in colorectal cancer, we therefore investigated whether KRT15 regulates the expression of β-catenin in colorectal cancer cells. Interestingly, overexpression of KRT15 significantly promoted, while silencing KRT15 remarkably decreased the level of β-catenin (Fig. 5A). In addition, we also observed that KRT15 mainly affected the expression of β-catenin in the cellular nuclear, but not cytoplasm (Fig. 5B). Next, we asked whether β-catenin is involved in KRT15-mediated upregulation of MMP-7. The results showed that overexpression of β-catenin obviously attenuated the decrease of MMP-7 induced by KRT15 shRNAs (Fig. 5C); conversely, silencing β-catenin by siRNA not only reduced the basal protein levels of MMP-7, but also drastically attenuated the promotive effect of KRT15 on MMP-7 in both tested colorectal cancer cell lines (Fig. 5D). Collectively, these findings demonstrated that KRT15 promoted MMP-7 via stimulating β-catenin signaling pathway in colorectal cancer cells.

Discussion

KRT15 has been found highly expressed in various cancers including colorectal cancer. Moreover, the high expression of KRT15 not only correlated with lymph node metastasis and clinical stage, but also predicted poor prognosis and could be used as an independent prognostic factor in colorectal cancer. Whereas, whether the role of KRT15 in colorectal cancer cell migration and invasion remain unexplored. In the present study, we demonstrated that KRT15 remarkably promoted the migration and invasion of colorectal cancer cells via activating β-catenin/MMP-7 signaling pathway, indicating KRT15 is a potential therapeutic target for the treatment of metastatic colorectal cancer.

Matrix metalloproteinases (MMPs), an important family of 24 proteolytic enzymes, which are capable of degrading and shedding multiple components of the extracellular matrix including growth factors, receptors and cell adhesion molecules [14]. Increasing experimental and clinical evidence has demonstrated the crucial role of MMPs in tumor invasion, neoangiogenesis, and metastasis [15]. MMP7, as an important member of the MMPs, exhibits highly proteolytic activity against multiple components of the extracellular matrix. MMP-7 was highly elevated in human colorectal cancer tissues, especially in the invasive fronts and the high expression of MMP-7 predicted poor overall survival, poor disease-free survival and decreased 5-year survival rate [16]. In addition, MMP-7 has been also demonstrated to play an important role in sterol-regulatory element binding protein 1 (SREBP1)-induced invasion and metastasis in colorectal cancer [17]. On the contrary, inhibition of MMP-7 by siRNA or specific antibody in colon carcinoma cells drastically reduced the abilities of migration and invasion [18].
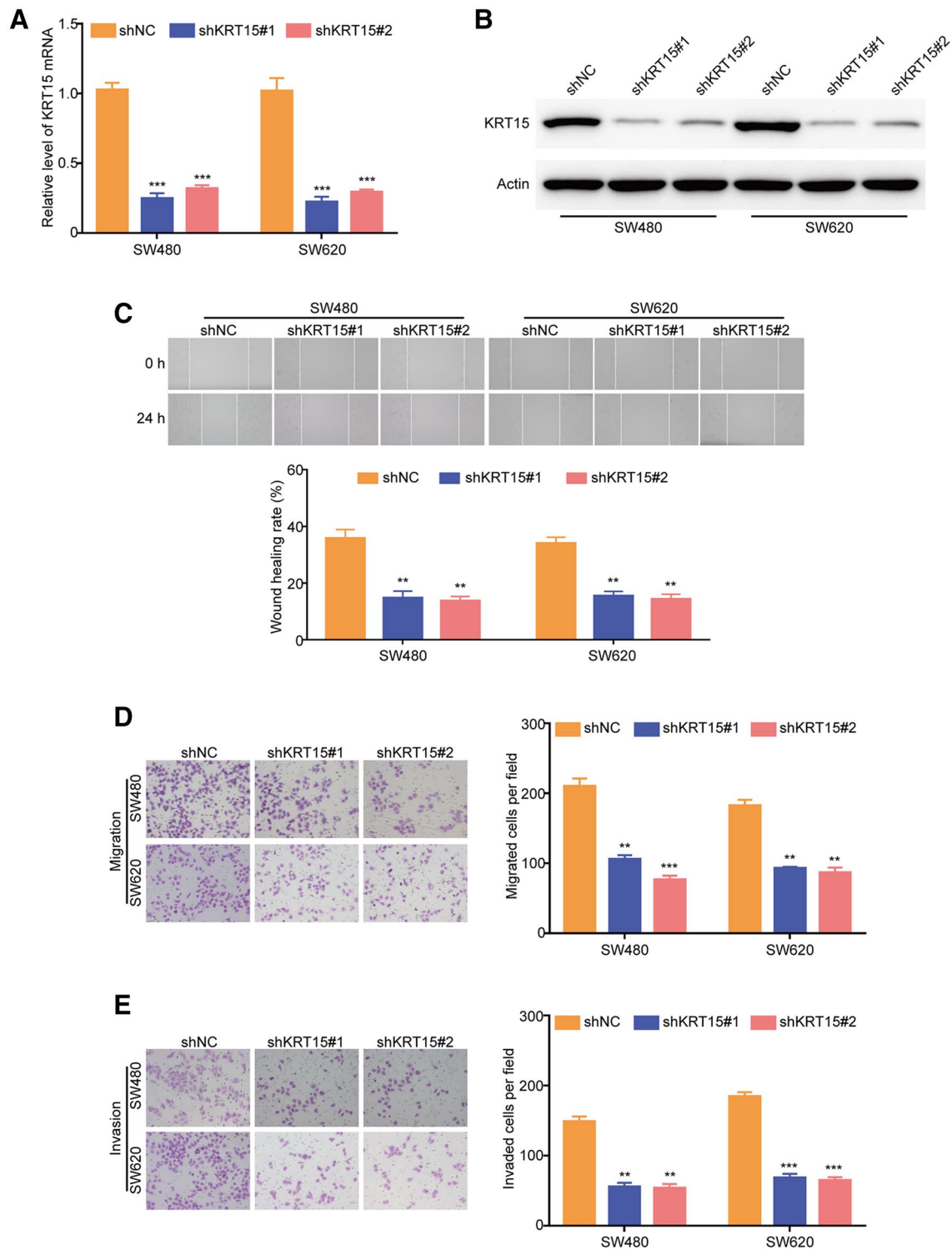
Fig. 2 A qRT-PCR analysis verified that mRNA level of KRT15 was silenced in SW480 and SW620 cells transduced with shRNAs against KRT15 (shKRT15#1 and shKRT15#2). **B** Immunoblotting analysis validated that protein level of KRT15 was silenced in SW480 and SW620 cells transduced with shRNAs against KRT15 (shKRT15#1 and shKRT15#2). Actin served as the internal control. **C** Wound healing scratch assay showed knockdown of KRT15 inhibited cell migration in colorectal cancer cells. Left: representative images of wound scratch. Right: histograms represent the analysis of the wound healing rate. **D** Transwell migration assay showed that knockdown of KRT15 inhibited migration of colorectal cancer cells. **E** Transwell invasion assay showed that knockdown of KRT15 suppressed invasion of colorectal cancer cells. **P < 0.01; ***P < 0.001
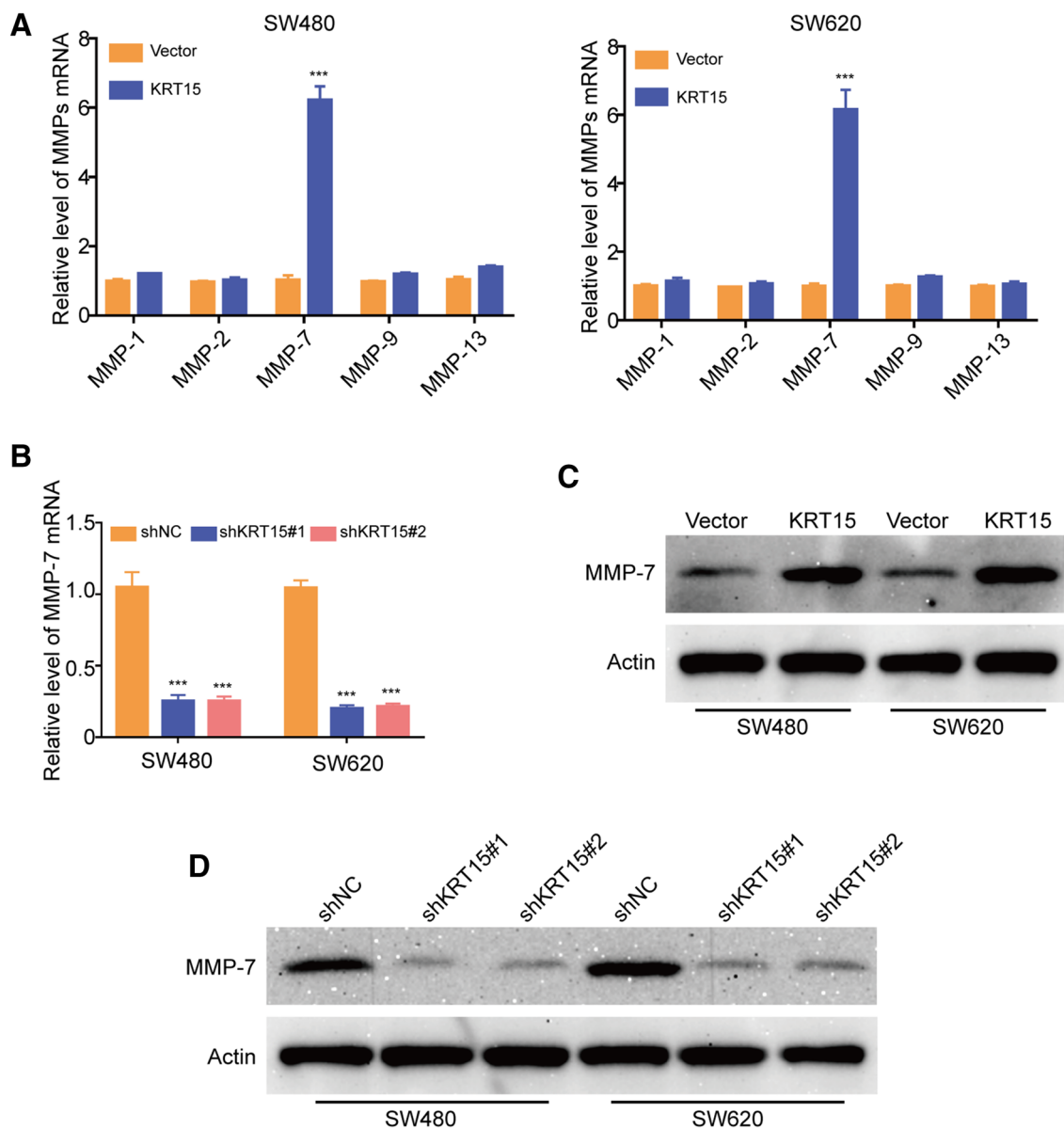
Fig. 3 KRT15 enhanced MMP-7 expression via β-catenin signaling pathway in colorectal cancer cells. **A** QRT-PCR analyzed the mRNA level of MMP-1, MMP-2, MMP-7, MMP-9 and MMP-13 in SW480 (left) and SW620 cells (right) transfected with KRT15 plasmid (KRT15) or control plasmid (vector). **B** Knocking down KRT15 decreased the mRNA level of MMP-7 in SW480 and SW620 cells transduced with shRNAs against KRT15 (shKRT15#1 and shKRT15#2) detected by QRT-PCR analysis. **C** Western blotting analysis showed that enforced overexpression of KRT15 promoted the protein level of MMP-7 in colorectal cancer cells. **D** Western blotting analysis showed that silencing KRT15 reduced the protein level of MMP-7 in colorectal cancer cells. ***$P < 0.001$. Actin served as the internal control

In this study, we demonstrated that MMP-7 was essential for KRT15-triggered migration and invasion in colorectal cancer cells, which was based on the following facts: (1) Enforced expression of KRT15 enhanced, while knockdown of KRT15 decreased the expression of MMP-7 at both the mRNA and protein levels. (2) Ectopic expression of KRT15 promoted, whereas knockdown of KRT15 reduced the capabilities of migration and invasion in colorectal cancer cells. (3) Knocking down MMP-7 significantly attenuated the migration and invasion induced by KRT15; vice versa, overexpression of MMP-7 almost completely restored the KRT15 shRNAs-attenuated migration and invasion.

Previous studies have demonstrated that MMP-7 is an important downstream substrate of β-catenin signaling and plays a crucial role in promoting tumor cell migration and invasion [19, 20]. Consistently with these findings, in
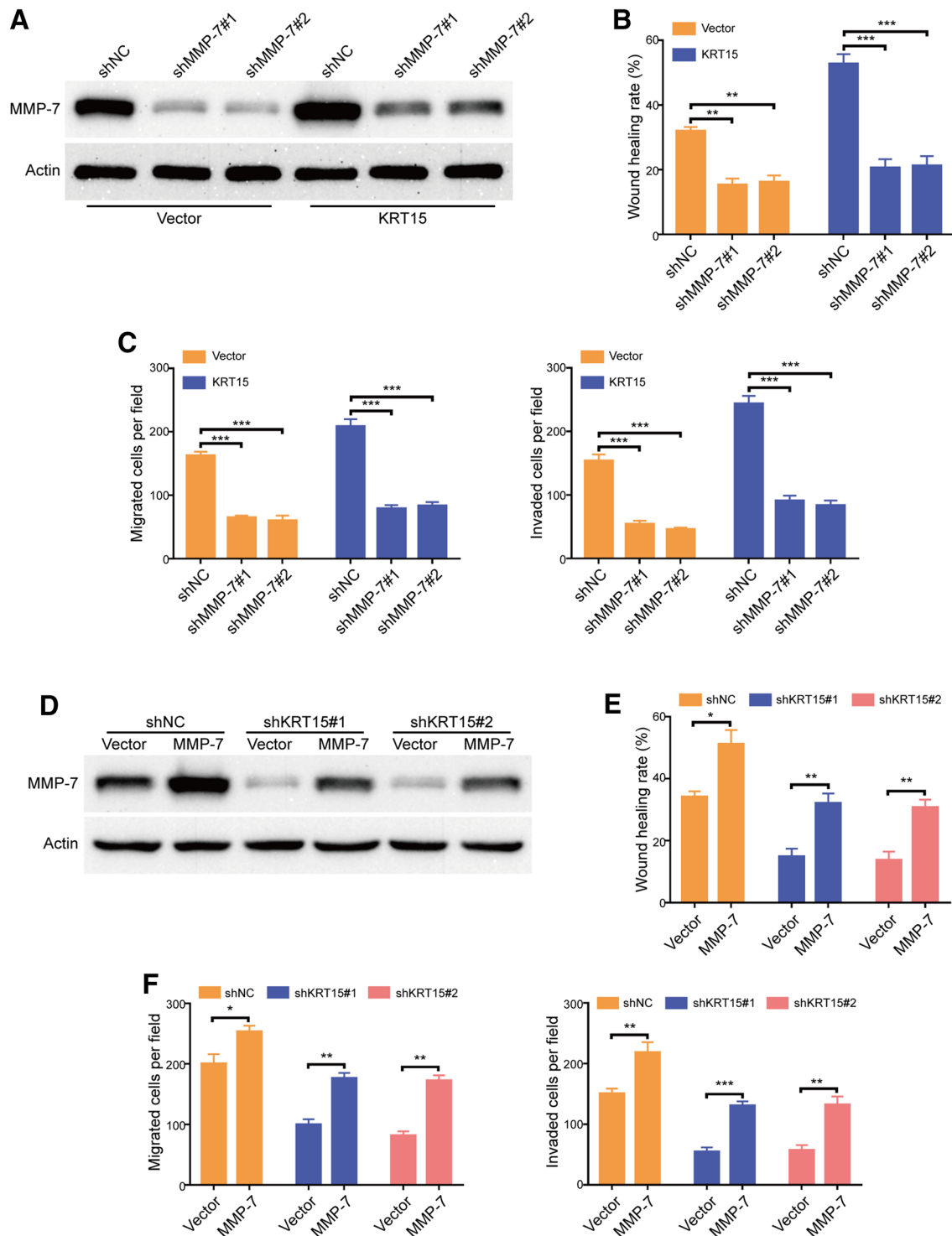
Fig. 4 MMP-7 was essential for KRT15-induced migration and invasion in colorectal cancer cells. **A** Immunoblotting analysis of MMP-7 expression in KRT15-silenced SW480 and SW620 cells transduced with MMP-7 plasmid (MMP-7) or control plasmid (vector). **B** Wound healing scratch assay showed MMP-7 attenuated the inhibition of KRT15 shRNA on cell migration in colorectal cancer cells. Left: representative images of wound scratch. Right: histograms represent the analysis of the wound healing rate. **C** Transwell assay showed MMP-7 attenuated the inhibition of KRT15 shRNA on cell migration (left) and invasion (right) in colorectal cancer cells. **D** Western blot analysis showed that MMP-7 was silenced in KRT15-overexpressing SW480 and SW620 cells transduced with shRNA against MMP-7 (shMMP-7#1 and shMMP-7#2) or control shRNA (shNC). **E** Wound healing scratch assay showed silencing MMP-7 attenuated the promotion of KRT15 on cell migration in colorectal cancer cells. Left: representative images of wound scratch. Right: histograms represent the analysis of the wound healing rate. **F** Transwell assay showed silencing MMP-7 attenuated the promotion of KRT15 on cell migration (left) and invasion (right) in colorectal cancer cells. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$. Actin served as the internal control
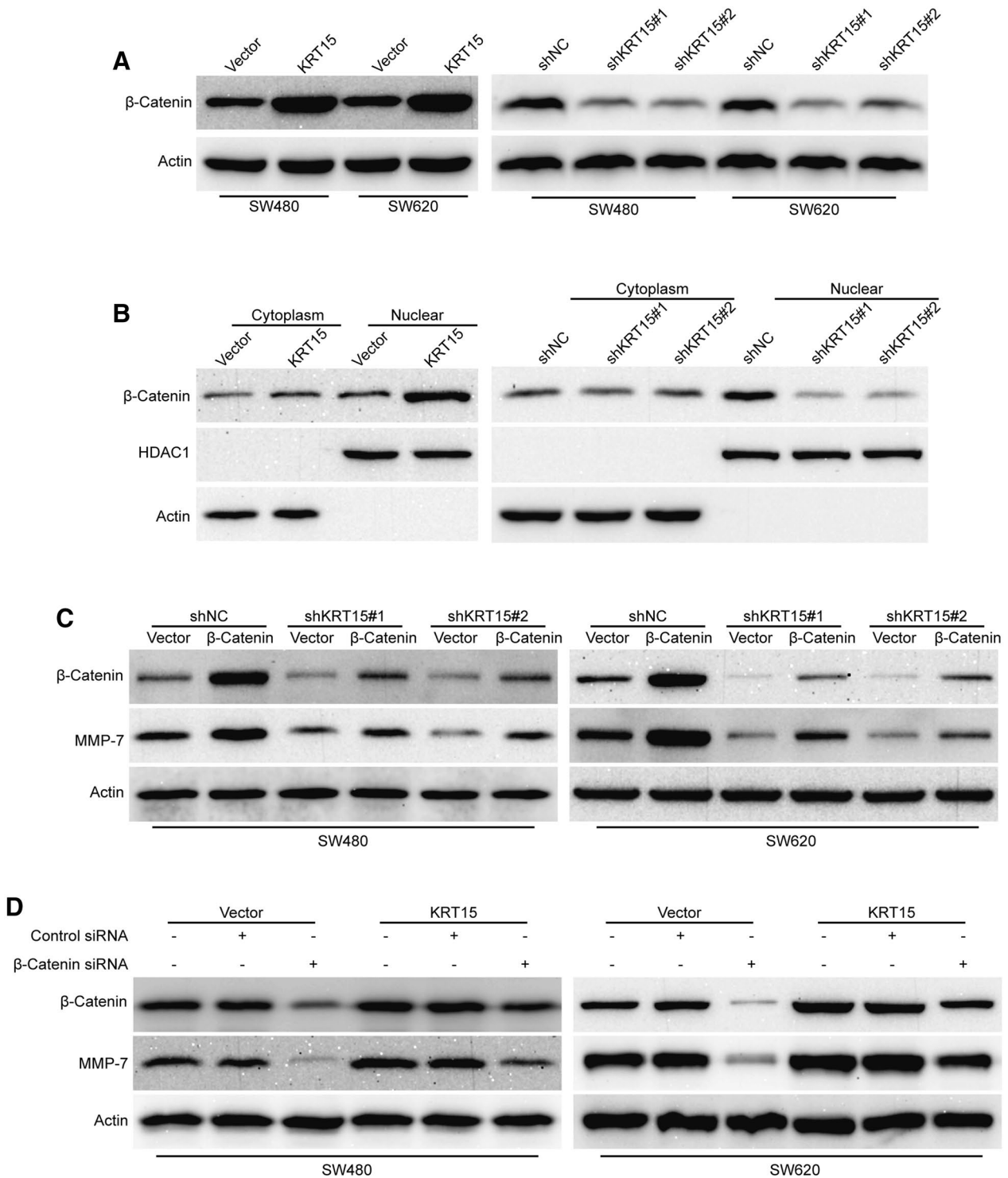
Fig. 5 KRT15 promoted MMP-7 via upregulation of β-catenin signaling in colorectal cancer cells. **A** Immunoblotting analysis of β-catenin expression in KRT15-overexpressing or -silenced SW480 and SW620 cells. **B** Western blotting analysis of subcellular localization for β-catenin using cell fractions from KRT15-overexpressing or -silenced SW480 cells. HDAC1 was used as the loading control (nuclear). **C** Overexpression of β-catenin attenuated the inhibitory effect of KRT15 shRNA on MMP-7 expression. **D** Silencing β-catenin by siRNA reduced the positive effect of KRT15 on MMP-7 in SW480 and SW620 cells. Actin served as the internal control

this study, we observed that silencing β-catenin by siRNA greatly not only reduced the basal protein levels of MMP-7 but also attenuated the promotive effect of KRT15 on MMP-7 expression in both tested colorectal cancer cell lines. These findings demonstrated KRT15 might active β-catenin/MMP-7 signaling pathway, and thereby promoted colorectal cancer cell migration and invasion.

In summary, our study reveals that KRT15 promotes colorectal cancer cell migration and invasion via activation of β-catenin/MMP-7 signaling pathway, suggesting KRT15 is a potential therapeutic target for metastatic colorectal cancer.

Declarations

Conflict of interest No potential conflicts of interest were disclosed.

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