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Increased Expression of the *YPEL3* Gene in Human Colonic Adenocarcinoma Tissue and the Effects on Proliferation, Migration, and Invasion of Colonic Adenocarcinoma Cells *In Vitro* via the Wnt/β-Catenin Signaling Pathway

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The aim of this study was to investigate the effects of the expression of the *YPEL3* gene in colonic adenocarcinoma cells grown *in vitro* and in colonic adenocarcinoma tissue from patients treated by surgical resection.

Material/Methods: The study included 108 patients diagnosed with primary colon cancer (Stages I to IV). The expression of the *YPEL3* gene in colonic adenocarcinoma tissue and adjacent normal colonic tissue was detected by real-time quantitative PCR (qRT-PCR). The normal human colonic cell line CCD-1Co and colorectal adenocarcinoma cell lines HT-29 and HCT-8 were induced to overexpress the *YPEL3* gene, and the effects on cell proliferation, migration, and invasion of colonic adenocarcinoma cells were investigated by the Cell Counting Kit-8 (CCK-8) assay, a transwell migration assay, and a transwell invasion assay, respectively. The effects of *YPEL3* gene overexpression on the Wnt/β-catenin signaling pathway were detected by Western blot.

Results: Increased expression levels of the *YPEL3* gene were present in colon adenocarcinoma tissue compared with adjacent normal colonic tissue in 98 of 108 patients. Overexpression of the *YPEL3* gene inhibited the proliferation, migration, and invasion of the HT-29 and HCT-8 colonic adenocarcinoma cells, and inactivated the Wnt/β-catenin signaling pathway; treatment with the Wnt agonist, CAS 853220-52-7, reduced the inhibitory effects of *YPEL3* overexpression on proliferation, migration, and invasion *in vitro*.

Conclusions: Expression of the *YPEL3* gene was upregulated in human colonic adenocarcinoma tissue, and also inhibited the proliferation, migration, and invasion of colonic adenocarcinoma cells *in vitro* by inactivating the Wnt/β-catenin signaling pathway.

MeSH Keywords: Cell Migration Assays • Cell Proliferation • Colonic Neoplasms • Wnt Signaling Pathway

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Background

Worldwide, colonic adenocarcinoma is the second most common cancer in women and the third most common cancer in men [1]. Colonic adenocarcinoma is considered to be the fourth most common cause of cancer-related death, and more than 70,000 men and 60,000 women are diagnosed with colonic adenocarcinoma each year, and more than 600,000 patients die from this disease per year [2]. The development of colonic adenocarcinoma is a complex process, involving varied internal and external factors. Activation of oncogenes and mutations of tumor suppressor genes are not only involved in the progression of colonic adenocarcinoma but also play key roles in the development of drug-resistance during the long-term treatments of this disease [3,4].

The *YPEL3* gene encodes the yippee-like 3 protein and is a p53-regulated gene that has inhibitory effects on both normal cells and tumor cells [5]. After activation by p53, the *YPEL3* gene may trigger cellular senescence or permanent growth arrest in certain types of human cancers [5,6]. *YPEL3* gene expression has been reported to be downregulated in certain cancers [7], while the role of the *YPEL3* gene in the development of colonic adenocarcinoma remains unclear. A recently published study has shown that *YPEL3* interacts with Wnt/β-catenin signaling pathway to suppress metastasis and epithelial-mesenchymal transition (EMT) in nasopharyngeal carcinoma [8]. Therefore, it is possible that the *YPEL3* gene exerts a role in colonic adenocarcinoma by interacting with the Wnt/β-catenin signaling pathway.

The aim of this study was to investigate the effects of the expression of the *YPEL3* gene in colonic adenocarcinoma cells grown *in vitro* and in colonic adenocarcinoma tissue from patients treated by surgical resection.

Material and Methods

Patients

A total of 108 patients with colonic adenocarcinoma who underwent surgery, were identified in the First Hospital of Zibo City, between January 2008 to January 2011. All patients were diagnosed by imaging studies and histopathology. Tumor staging was performed according to the criteria of the American Joint Committee on Cancer (AJCC): Stage 0, a primary tumor with submucosal invasion, and no lymph node metastases or distant metastases; Stage I, a primary tumor with invasion into the submucosal or muscle layer, and no lymph node metastases or distant metastases; Stage II, a primary tumor invading the bowel wall without involvement of the peritoneum, and no lymph node metastases or distant metastases; Stage III, a primary tumor with local invasion and lymph node metastases; Stage IV, a primary tumor invadinf other organs, with lymph node and distant metastases.

There were 21 patients with Stage 0 colonic adenocarcinoma; 21 patients with Stage I colonic adenocarcinoma; 23 patients with Stage II colonic adenocarcinoma; 23 patients with Stage III colonic adenocarcinoma; and 20 patients with Stages IV colonic adenocarcinoma. Table 1 summarises the clinical details of the 108 patients included in this study, with their tumor stage. Surgical resection was performed for all patients. Tumor tissues and adjacent normal colonic tissue were obtained from the surgical resection specimens. All participants signed informed consent to participate in the study. The study was approved by the local Ethics Committee of the First Hospital of Zibo City.

Cell lines, cell culture, and cell transfection

The human normal colonic cell line, CCD-1Co, and the colorectal adenocarcinoma cell lines HT-29 and HCT-8 were purchased from the American Type Cell Culture (ATCC) (Manassas, VA, USA). All cell lines were cultured under conditions described in the manufacturer's instructions. Cells were harvested when they reached logarithmic growth phase.

Table 1. Clinical characteristics of 108 patients with primary colonic adenocarcinoma in the study.

Stage	Gender		Age range (yrs)	Average age (yrs)
	Male	Female		
0	13	8	21–81	48±13.4
I	11	10	26–79	47±14.1
II	14	9	31–78	51±12.1
III	13	10	29–72	46±14.6
IV	7	13	32–77	48±11.7

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Establishment of expression of the *YPEL3* gene in colonic adenocarcinoma cell lines

YPEL3 cDNA (V0728) (GeneCopoeia) was inserted into pIRSE2-EGFP vector (Clontech, Palo Alto, CA, USA). Cells were cultured overnight before transfection to reach 80–90% confluence. Transfection was performed using the Lipofectamine 2000 reagent (11668-019, Invitrogen, Carlsbad, CA, USA).

Cell proliferation assay

Cells were collected and used to prepare cell suspensions. The cell suspension was transferred into 96-well plates with 4×10^3 cells per well. Cells were cultured in an incubator (37°C, 5% CO_2), and 10 µL of Cell Counting Kit-8 (CCK-8) assay solution was added at 24, 48, 72, and 96 hours. After incubation for another 5 hours, the optical density (OD) values (450 nm) were measured using a microplate reader.

Cell migration and cell invasion assay

The transwell cell migration assay was performed using a kit provided by BD Biosciences (USA). The upper chamber was filled with 4×10^4 cells; the lower chamber was filled with RPMI-1640 medium (Thermo Fisher Scientific, USA) containing 20% fetal calf serum (FCS) (Sigma-Aldrich, USA). After incubation for 24 hours, the membranes were collected and stained with 0.5% crystal violet (Sigma-Aldrich, USA) for 15 minutes. Cells were counted under an optical microscope (Olympus, Japan). The upper chamber was pre-coated with Matrigel (356234, Millipore, USA) before the invasion assay was performed.

Real-time quantitative polymerase chain reaction (qRT-PCR)

Total RNA was extracted from tumor tissues, adjacent normal colonic tissue, and the cells of the cell lines using Trizol reagent (Invitrogen, USA). RNA samples were tested using a NanoDrop™ 2000 Spectrophotometer (Thermo Fisher Scientific, USA), and only RNA samples with an A260/A280 ratio of between 1.8–2.0 were used in the reverse transcription assay to synthesize cDNA. PCR reaction system was prepared using SYBR® Green Real-Time PCR Master Mixes (Thermo Fisher Scientific, USA).

The following primers were used in PCR reactions:
5'-CCACGACGACCTCATCTC-3' (sense) and
5'-CATATTTCCAGCCCAAAGT-3' (antisense) for the *YPEL3* gene;
GACCTCTATGCCAACACAGT (forward) and
AGTACTTGCGCTCAGGAGGA (reverse) for β-actin.

PCR reaction conditions were as follows: 95°C for 40 s, followed by 40 cycles at 95°C for 15 s and 60°C for 45 s. Ct values were processed using the $2^{-\Delta\Delta CT}$ method.

Western blot

Cell lysis buffer (Clontech, USA) was used to extract total protein from cells. BCA assay was used to determine protein quality. The 10% SDS-PAGE gel electrophoresis was performed using 20 µg of protein from each sample, followed by transfer to PVDF membranes. Blocking was performed by incubation with 5% dried skimmed milk powder at room temperature for one hour. After washing with TBST, the membranes were then incubated with the following primary antibodies: rabbit anti-phospho-GSK antibody (1: 2000) (clone No. ab32391) (Abcam, Cambridge, MA, USA), anti-β-catenin antibody (1: 2000) (clone No. ab32572) (Abcam, Cambridge, MA, USA), anti-GSK-3β (Ser9) antibody (1: 2000) (clone No. ab75745) (Abcam, Cambridge, MA, USA), anti-MMP-7 antibody (1: 1000) (clone No. ab5706) (Abcam, Cambridge, MA, USA), anti-cyclin D1 antibody (1: 2000) (clone No. ab134175) (Abcam, Cambridge, MA, USA) and anti-GAPDH antibody (1: 1000) (clone No. ab9485) (Abcam, Cambridge, MA, USA) overnight at 4°C. After washing, membranes were incubated with anti-rabbit IgG-horseradish peroxidase (HRP) secondary antibody (1: 1000) (Clone No. MBS435036) (MyBioSource) at room temperature for 1 hour. After washing in substrate, the enhanced chemiluminescence (ECL) method (Sigma-Aldrich, USA) was used to detect the signal. Image J software was used to normalize the relative expression levels of each protein to the endogenous GAPDH control.

Statistical analysis

SPSS version 19.0 (SPSS Inc., Chicago, Ill, USA) was used in statistical analysis. Normal distribution data were expressed as ($x\pm s$), and comparisons between two groups were performed using Student's t-test. Non-normal distribution data were analyzed by the non-parametric Mann-Whitney U test, and $p<0.05$ was considered to be statistically significant.

Results

Expression of the *YPEL3* gene in tumor tissue and adjacent normal colonic tissue

Expression levels of the *YPEL3* gene in tumor tissue and adjacent normal colonic tissue in 108 patients with colonic adenocarcinoma were measured by real-time quantitative PCR (qRT-PCR). The results showed that expression levels of the *YPEL3* gene were significantly increased in colonic adenocarcinoma tissue compared with normal adjacent colonic tissue ($p<0.05$) in 98 out of 108 patients (Figure 1).

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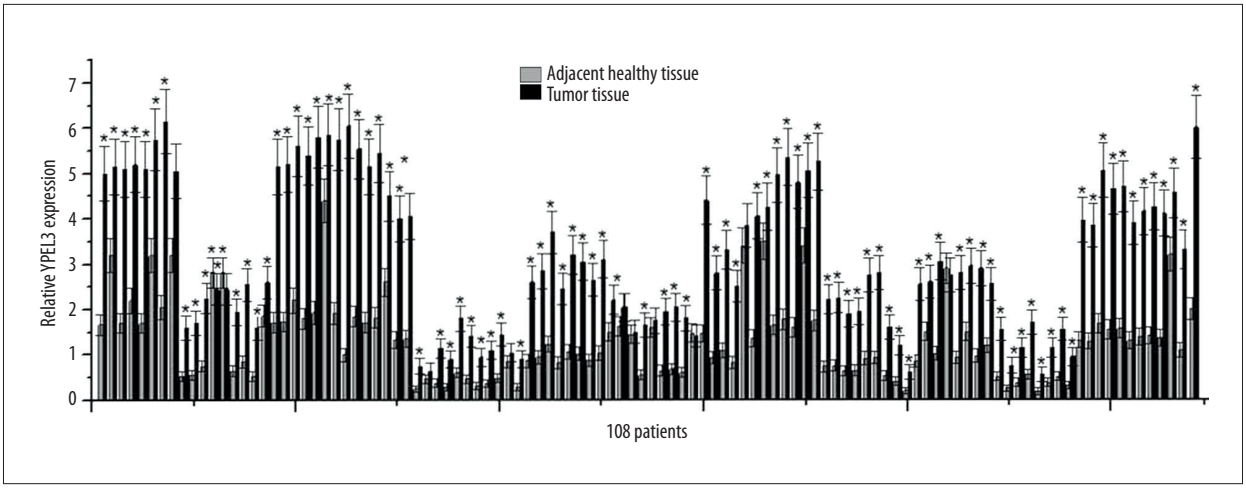

Figure 1. Expression levels of the *YPEL3* gene in tumor tissue and adjacent normal colon in 108 patients with colonic adenocarcinoma. * Compared with adjacent normal colonic tissue.

Expression of the *YPEL3* gene in tumor tissue of patients with different tumor stages

Real-time quantitative PCR (qRT-PCR) was also performed to detect the expression of the *YPEL3* gene in tumor tissues of patients with different stages of colonic adenocarcinoma. As shown in Figure 2, the expression levels of the *YPEL3* gene were significantly decreased with the progression of colonic adenocarcinoma ($p<0.05$). These findings suggested that the *YPEL3* gene was involved in the development of colonic adenocarcinoma, and the decreased expression level of *YPEL3* may promote the progression of this disease.

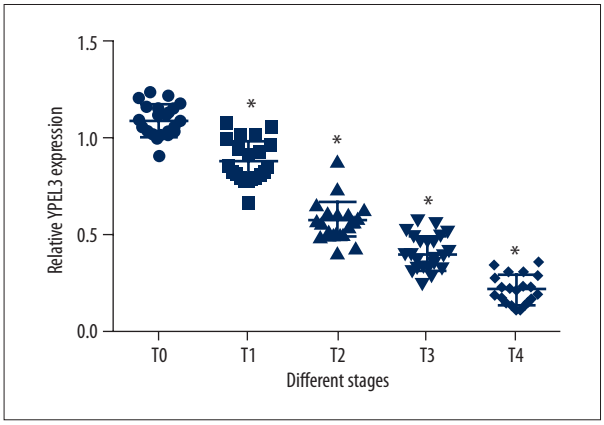

Figure 2. Expression of the *YPEL3* gene in tumor tissue of patients with different tumor stages. * Compared with one stage before, $p<0.05$.

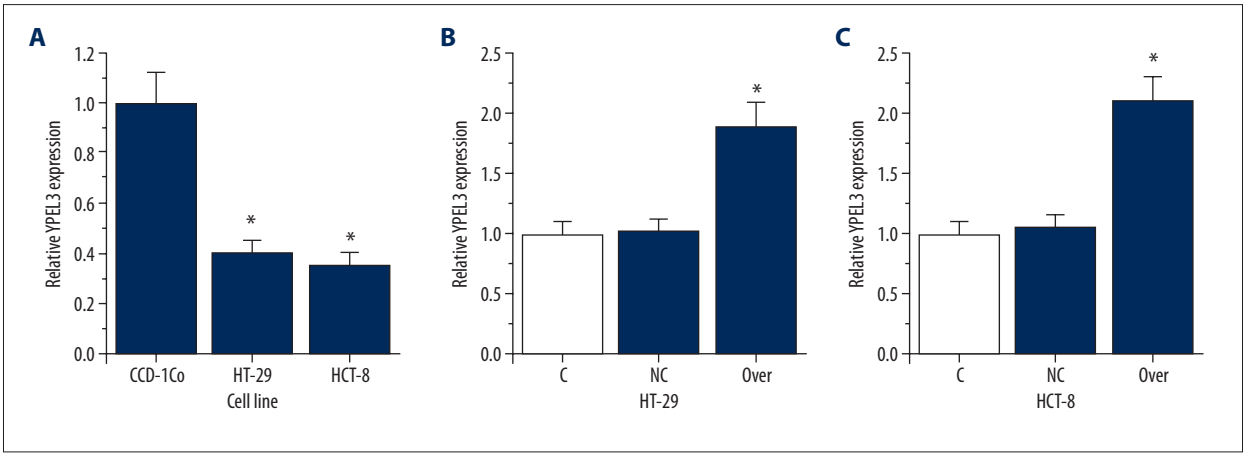

Figure 3. Expression of the *YPEL3* gene in different cell lines with different treatments. (**A**) Expression of *YPEL3* in different cell lines. (**B**) Expression of *YPEL3* in HT-29 cells with different treatment. (**C**) Expression of *YPEL3* in HCT-8 cells with different treatment. * Compared with normal colon cell line CCD-1Co or control cells, $p<0.01$; C – control; NC – negative control, transfected with empty vector; Over – overexpression.

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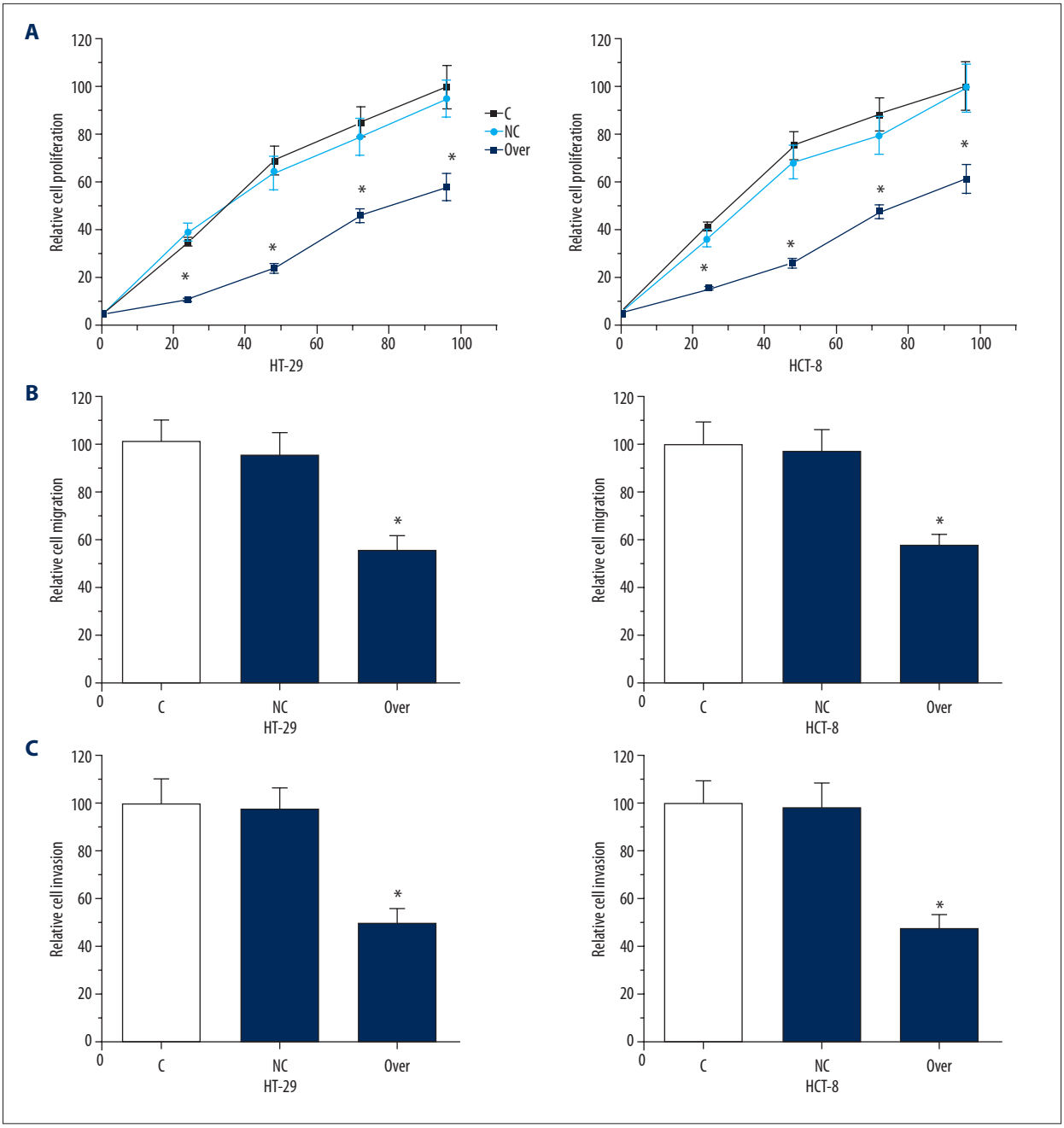

Figure 4. Effects of overexpression of the *YPEL3* gene on proliferation, migration and invasion of colonic adenocarcinoma cell lines HT-29 and HCT-8. (**A**) Effects of *YPEL3* overexpression on the proliferation of colonic adenocarcinoma cell lines HT-29 and HCT-8. (**B**) Effects of *YPEL3* overexpression on the migration of colonic adenocarcinoma cell lines HT-29 and HCT-8. (**C**) Effects of *YPEL3* overexpression on the invasion of colonic adenocarcinoma cell lines HT-29 and HCT-8. * Compared with control cells, $p<0.05$.

Expression of the *YPEL3* gene in different cell lines with different treatments

As shown in Figure 3A, the expression levels of the *YPEL3* gene were lower in the colonic adenocarcinoma cell lines, HT-29 and HCT-8, compared with the normal colon cell line, CCD-1Co, (Figure 3A). Compared with control cells and negative control cells, the expression levels of *YPEL3* were increased in HT-29 and HCT-8 cells transfected with the *YPEL3* gene expression vector, indicating successfully established *YPEL3* gene over-expression cell lines.

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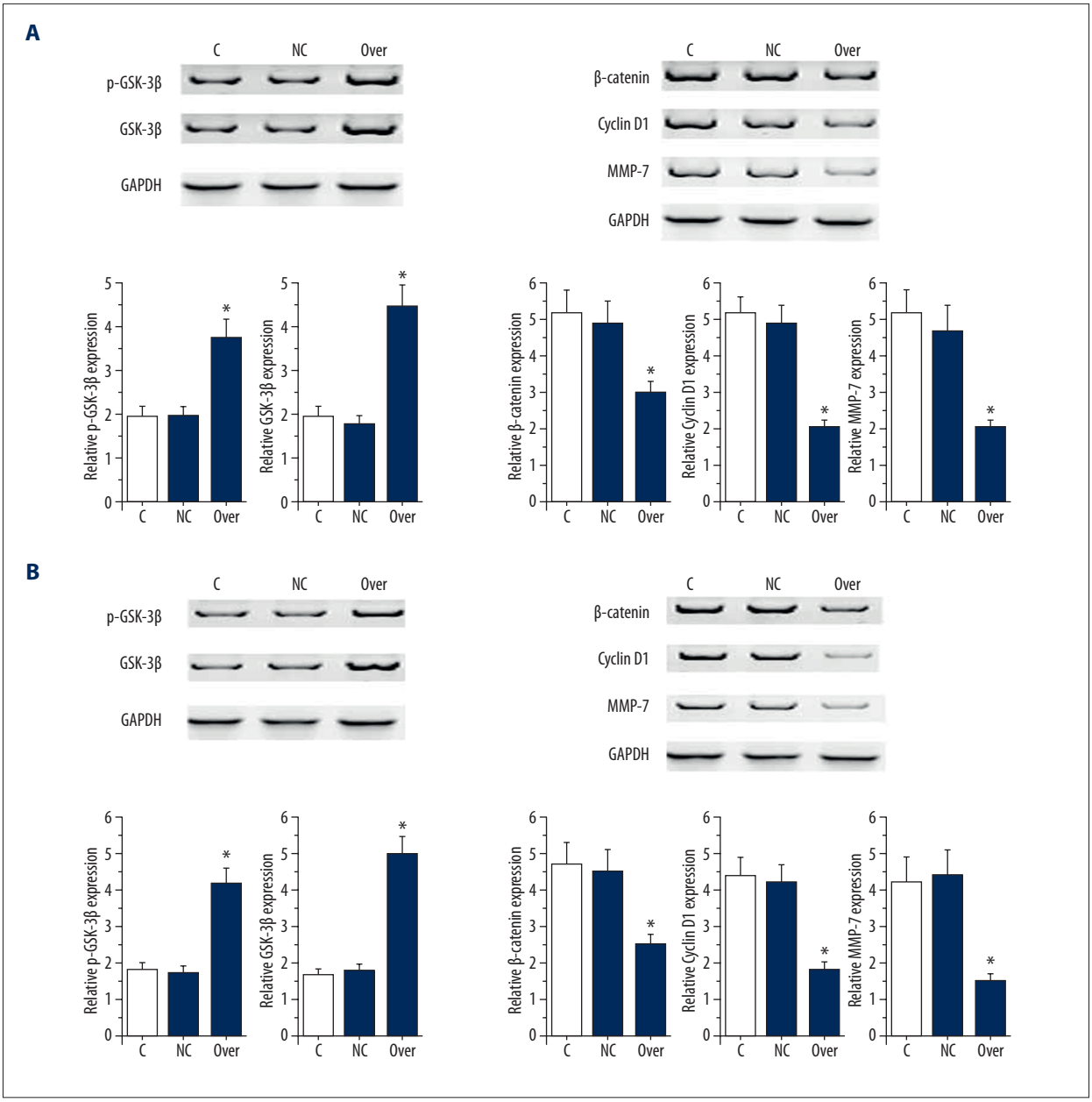

Figure 5. Effects of overexpression of the *YPEL3* gene on Wnt/β-catenin signaling pathway in colonic adenocarcinoma cell lines HT-29 and HCT-8. (**A**) Effects of *YPEL3* overexpression on Wnt/β-catenin signaling pathway in HT-29 cell line. (**B**) Effects of *YPEL3* overexpression on Wnt/β-catenin signaling pathway in HCT-8 cell line. * Compared with control cells, p<0.05

Effects of overexpression of the *YPEL3* gene on proliferation, migration, and invasion of colonic adenocarcinoma cell lines, HT-29 and HCT-8

The CCK-8 assay, the transwell cell migration assay, and the transwell cell invasion assay were performed to explore the effects of overexpression of the *YPEL3* gene on proliferation, migration, and invasion of colonic adenocarcinoma cell lines, HT-29 and HCT-8. As shown in Figure 4A, compared with control cells and negative control cells, cell proliferation was inhibited after *YPEL3* overexpression in both HT-29 and HCT-8 cells (p<0.05). Similarly, cell migration (Figure 4B) and cell invasion (Figure 4C) of both HT-29 and HCT-8 cell lines were also significantly inhibited after overexpression of the *YPEL3* gene (p<0.05). These data indicated that *YPEL3* expression could negatively regulate proliferation, migration, and invasion of colonic adenocarcinoma cells *in vitro*.

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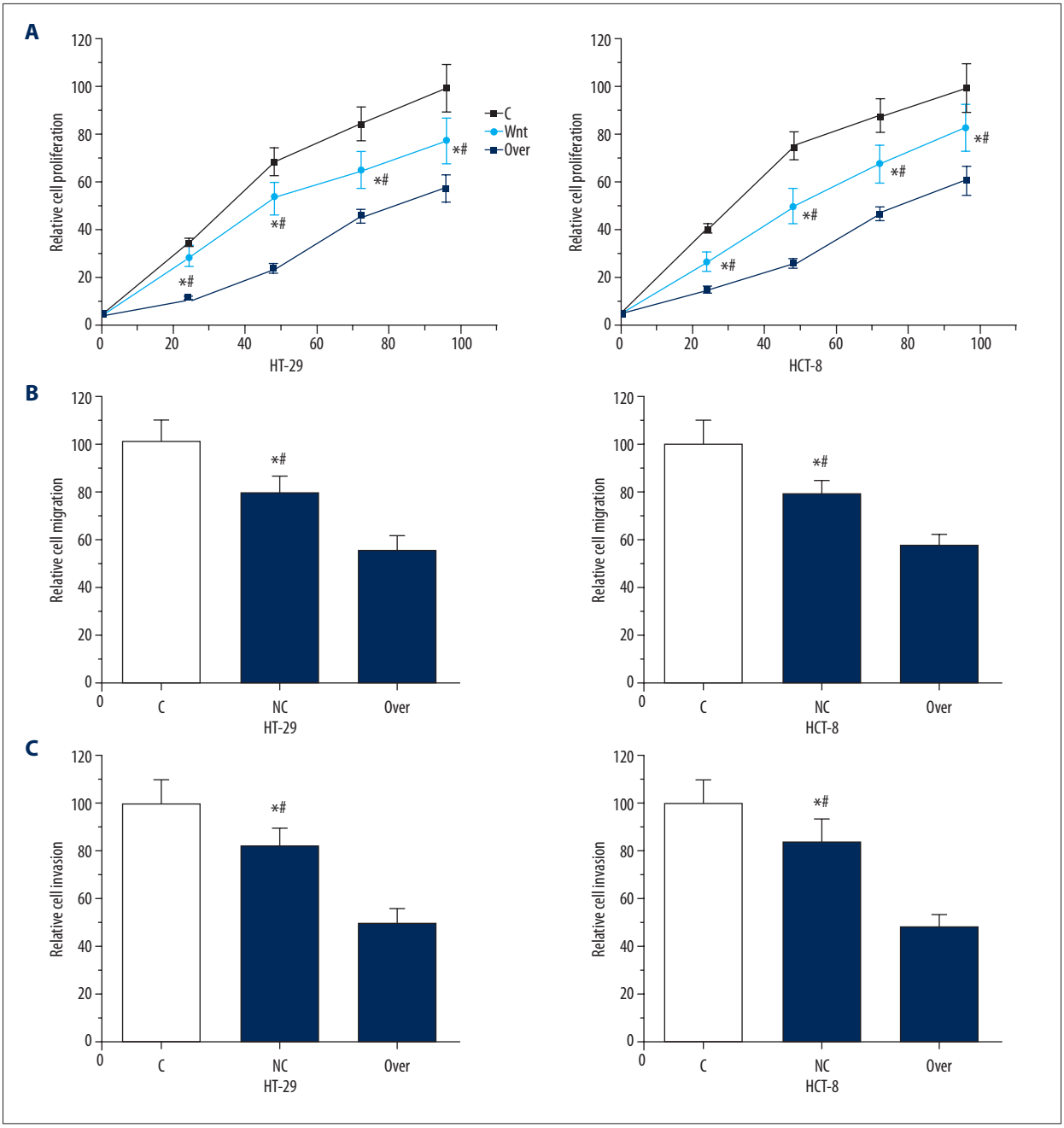

Figure 6. Treatment with the Wnt agonist reduced the inhibitory effects of overexpression of the *YPEL3* gene on proliferation, migration, and invasion of the colonic adenocarcinoma cell lines HT-29 and HCT-8. (**A**) Relative proliferation ability of HT-29 and HCT-8 cells with different treatment. (**B**) Relative migration ability of HT-29 and HCT-8 cells with different treatment. (**C**) Relative invasion ability of HT-29 and HCT-8 cells with different treatment. * Compared with control cells, $p<0.05$; # compared with cells with overexpression of the *YPEL3* gene, $p<0.05$.

Overexpression of the *YPEL3* gene inactivated Wnt/β-catenin signaling pathway in the HT-29 and HCT-8 cell lines

The effects of *YPEL3* overexpression on the Wnt/β-catenin signaling pathway were explored. P-GSK-3β and GSK-3β were shown to be negative regulators of the Wnt/β-catenin signaling pathway (Figure 5). In this study, compared with control cells, the expression levels of p-GSK-3β and GSK-3β were increased in HT-29 and HCT-8 cells with *YPEL3* overexpression (Figure 5). In contrast, expression levels of β-catenin, as well as the downstream genes *cyclin D1* and *MMP-7* were decreased

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in HT-29 and HCT-8 cells with overexpression of the *YPEL3* gene, compared with control cells. These findings support the hypothesis that *YPEL3* overexpression might inactivate the Wnt/β-catenin signaling pathway.

Treatment with the Wnt agonist reduced the inhibitory effects of overexpression of the *YPEL3* gene on proliferation, migration, and invasion of colonic adenocarcinoma cell lines, HT-29 and HCT-8

The Wnt agonist, CAS 853220-52-7, (100 ng/ml) (sc-222416) (Santa Cruz Biotechnology) was used to treat HT-29 and HCT-8. As shown in Figure 6A, the proliferation ability of HT-29 and HCT-8 cells was significantly reduced when compared with control cells, but was significantly increased when compared with cells with overexpression of the *YPEL3* gene ($p<0.05$). Also, the cell migration (Figure 6B) and the cell invasion (Figure 6C) abilities of HT-29 and HCT-8 cells were significantly reduced when compared with control cells but were significantly increased when compared with cells with overexpression of the *YPEL3* gene ($p<0.05$). These findings support that treatment with the Wnt agonist had inhibitory effects on *YPEL3* overexpression, and on cell proliferation, cell migration, and cell invasion of colonic adenocarcinoma cell lines, HT-29 and HCT-8.

Discussion

As a group of heterogeneous diseases, more than 30% cases of primary colonic adenocarcinoma are caused by genetic factors [9]. Previously published studies have shown that the activation of oncogenes and loss of function of tumor suppressor genes in colonic epithelial cells are associated with the development of colorectal adenocarcinoma [10]. It has previously been reported that CDK8 can activate β-catenin and play a role as an oncogene in colonic adenocarcinoma [11]. During the initiation of colonic adenocarcinoma, *KRAS* plays an oncogenic role by activating embryonic stem cell-like cell programs to promote cell proliferation [12]. In contrast, *HUWE1*, as a critical colonic tumor suppressor gene, which can prevent the accumulation of DNA damage, inhibit *MYC* signal transduction, and reduce the development of tumors [13].

In addition to the direct involvement of genetic factors in the initiation, development, and progression of colonic adenocarcinoma, mutations in certain genes may participate in the drug response of the tumor or tumor drug resistance to affect the treatment outcomes of colonic adenocarcinoma. For example, *KRAS* mutation has been shown to be a predictive biomarker for poor treatment outcomes of targeted therapy to epidermal growth factor receptor (EGFR) in the treatment of metastatic colonic adenocarcinoma; mutations in exon 2 of the *KRAS* gene may abolish the response of colonic adenocarcinoma cells to anti-EGFR therapy [3].

The *YPEL3* gene has been previously shown to act as a tumor suppressor gene in different types of human cancer [14]. Expression of the *YPEL3* gene has been reported to be downregulated in colon cancer [7], indicating that *YPEL3* may also function as tumor suppressor gene in this disease. The findings of the present study support those of previous studies, as *YPEL3* expression was found to be significantly downregulated in tumor tissue when compared with adjacent normal colonic tissue in 98 out of 108 patients with colonic adenocarcinoma, a finding that further confirms the role of *YPEL3* as a tumor suppressor gene in colonic adenocarcinoma.

The p53 pathway is a key player in inhibiting cellular proliferation, and the activation of the *YPEL3* gene, as a part of this signaling pathway, can trigger cellular senescence or permanent growth arrest in certain types of human cancer and inhibit tumor cell proliferation [5,6]. In a recent study, Oki et al. reported that *YPEL4*, which is another family member of the *YPEL* gene family, could regulate adrenal cell proliferation to affect adrenal tumor diameter [15]. However, based on published literature, and to the best of our knowledge, the effects of the *YPEL3* gene on tumor cell proliferation in colonic adenocarcinoma have been previously unreported. In the present study, overexpression of the *YPEL3* gene inhibited the proliferation of two colonic adenocarcinoma cell lines, indicating the anti-proliferation role of the *YPEL3* gene.

Epithelial-mesenchymal transition (EMT) is a key step in tumor metastasis [16]. A recent study has shown that the *YPEL3* expression can suppress metastasis and EMT in nasopharyngeal carcinoma [8]. In this study, *YPEL3* overexpression inhibited the migration and invasion of two colonic adenocarcinoma cell lines, indicating the anti-migration and anti-invasion role of *YPEL3* in colonic adenocarcinoma cells *in vitro*. These data suggest that the *YPEL3* gene may function as tumor suppressor gene in colon cancer by inhibiting tumor cell proliferation, migration, and invasion.

Activation of Wnt/β-catenin signaling pathway plays pivotal roles in several human diseases, as Wnt/β-catenin signal transduction can upregulate the expression of the EMT-associated proteins to promote tumor cell invasion and metastasis [16,17]. In a recent study, Zhang et al. have shown that the *YPEL3* gene can interact with the Wnt/β-catenin signaling pathway to suppress EMT and metastasis of nasopharyngeal carcinoma [8]. In the present study, overexpression of the *YPEL3* gene increased the expression levels of inhibitors of the Wnt/β-catenin signaling pathway and decreased the expression of proteins involved in Wnt/β-catenin signal transduction in two colonic adenocarcinoma cell lines. Also, treatment with

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Wnt agonist reduced the inhibitory roles of *YPEL3* on proliferation, invasion, and migration of colonic adenocarcinoma cells *in vitro*. The results suggest that the *YPEL3* gene can inactivate Wnt/β-catenin signaling pathway to inhibit tumor metastasis of colonic adenocarcinoma.

Conclusions

The findings of this study showed that the expression of the *YPEL3* gene was upregulated in human colonic adenocarcinoma tissue. The expression of the *YPEL3* gene also inhibited the proliferation, migration, and invasion of colonic adenocarcinoma cells *in vitro* by inactivating the Wnt/β-catenin signaling pathway. Treatment of colonic adenocarcinoma cells *in vitro* with the Wnt agonist, CAS 853220-52-7, reduced the inhibitory effects of overexpression of the *YPEL3* gene on proliferation, migration, and invasion of colonic adenocarcinoma cells. The findings of this study support the hypothesis that the *YPEL3* gene may act as a tumor suppressor gene in colonic adenocarcinoma by inactivating the Wnt/β-catenin signaling pathway.

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