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DEC1 mediates IL-6-induced EMT in CRC *via* PI3K/AKT/NF- κ B activation

Enfang Shan^{1,2,✉}, Weifeng Du¹, Ziheng Zhang², Jingwan Hu², Ying Huo², Wei Liu², Jian Yang^{2,✉}

¹School of Nursing, Nanjing Medical University, Nanjing, Jiangsu 211166, China;

²Department of Pharmacology, Nanjing Medical University, Nanjing, Jiangsu 211166, China.

Abstract

Colorectal cancer (CRC) represents a leading global malignancy. This study investigated the role of differentiated embryonic chondrocyte expressed gene 1 (DEC1) in interleukin-6 (IL-6)-induced invasion and migration of CRC. *In vitro*, IL-6 upregulated DEC1 expression and modulated the levels of epithelial-to-mesenchymal transition (EMT)-associated proteins in CRC cells. *DEC1* overexpression amplified the IL-6-induced invasion and migration phenotypes, increasing the expression of N-cadherin and vimentin but reducing E-cadherin expression. Conversely, *DEC1* knockdown attenuated these phenotypes, decreasing the expression of N-cadherin and vimentin but increasing E-cadherin expression. These findings suggest that IL-6 induced EMT through increasing DEC1. Moreover, *DEC1* overexpression increased the levels of basal and IL-6-stimulated phosphatidylinositol 3 kinase (PI3K) p110 α , p-Akt, and p-p65, indicating activation of the PI3K/Akt/NF- κ B signaling pathway. Conversely, *DEC1* knockdown diminished these effects. Notably, treatment with the inhibitor LY294002 or the NF- κ B inhibitor EVP4593 significantly reversed the IL-6-induced upregulation of DEC1, the increase in N-cadherin and vimentin, and the reduction in E-cadherin. These *in vitro* findings were further corroborated *in vivo*. *Dec1*^{+/+} CRC mice exhibited elevated *Il6* mRNA levels and enhanced tumor invasion compared with *Dec1*^{-/-} CRC mice. *Dec1* deficiency increased E-cadherin and decreased N-cadherin and vimentin, accompanied by inhibition of the PI3K/Akt/NF- κ B signaling pathway in mice. Taken together, our results demonstrate that DEC1 mediates IL-6-induced invasion and migration of CRC *via* activation of the PI3K/Akt/NF- κ B signaling pathway.

Keywords: differentiated embryonic chondrocyte expressed gene 1, colorectal cancer, epithelial-mesenchymal transition, interleukin-6

Introduction

Colorectal cancer (CRC) is the third most common malignancy and the second leading cause of cancer-related mortality worldwide^[1]. Despite significant

advances in early screening and therapeutic strategies, metastatic colorectal cancer remains a major treatment challenge, with a 5-year survival rate of only approximately 14% for patients presenting with distant metastase^[2]. During epithelial tumor

✉Corresponding authors: Enfang Shan, E-mail: shanenfang@njmu.edu.cn, ORCID: 0000-0003-1920-732X; Jian Yang, E-mail: jianyang@njmu.edu.cn, ORCID: 0000-0003-2590-2388.

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metastasis, tumor cells undergo invasion and migration phenotypic changes to adapt to diverse microenvironments^[3]. The epithelial-to-mesenchymal transition (EMT) serves as a primary biological process that regulates such phenotypic changes, in which epithelial cells lose their polarity and intercellular adhesion, thereby acquiring a motile mesenchymal phenotype^[4]. The enhanced migratory and invasive capacities conferred by EMT are critical for the initiation of tumor metastasis, and the acquisition of a mesenchymal phenotype is frequently associated with poor clinical prognosis^[5].

Numerous studies have linked chronic inflammation with cancer progression and metastatic growth^[6]. The cytokine storm formed by the excessive release of various inflammatory mediators creates a microenvironment that facilitates tumor cell proliferation, immunosuppression, and metastasis^[7]. Interleukin-6 (IL-6), a key pro-inflammatory cytokine, has been implicated in inducing EMT in CRC^[8]. Moreover, IL-6 promotes CRC progression by stimulating several pleiotropic cascades, including the phosphatidylinositol 3 kinase (PI3K)/protein kinase B (Akt) pathway and nuclear factor-kappa B (NF-κB) pathway^[9]. However, the specific molecular mechanism of IL-6-induced CRC invasion and migration remains to be further explored.

Human differentiated embryonic chondrocyte expressed gene 1 (DEC1), also known as basic helix-loop-helix 40 (BHLHE40), belongs to the basic helix-loop-helix (bHLH) transcription factor family^[10]. It is widely expressed in tissues and associated with cell proliferation, differentiation, apoptosis, biological rhythm, and lipid metabolism^[11]. In recent years, DEC1 has been found to be associated with tumor development and to exhibit tissue-specific expression in a variety of tumors^[12]. DEC1 is implicated in promoting EMT and invasion in diverse malignancies, including hepatocellular carcinoma^[13], pancreatic cancer^[14], and breast cancer^[15]. Consistently, our previous study found that DEC1 is involved in the proliferation and apoptosis of CRC^[16]. However, its specific role in CRC invasion, migration, and particularly IL-6-induced EMT, remains unclear.

This study aims to investigate the role of DEC1 in IL-6-induced invasion and migration in colorectal cancer (CRC). Specifically, we seek to explore whether DEC1 mediates these biological processes through the activation of the PI3K/Akt/NF-κB signaling pathway. The findings of this work are intended to provide a theoretical basis for the development of novel therapeutic strategies targeting CRC metastasis.

Materials and methods

Cell culture and reagents

SW480 and DLD-1 human CRC cell lines (ATCC, Manassas, VA, USA) were authenticated by STR profiling. Genomic DNA was extracted using an Axygen kit, amplified with a 20-STR multiplex panel, and analyzed on an ABI 3730XL Genetic Analyzer (Applied Biosystems, Waltham, MA, USA). STR genotypes were compared with the DSMZ cell bank database. Results are listed in [Supplementary Tables 1 and 2](#). Both cell lines showed a complete match with no multi-allelic signals. The cells were cultured in RPMI 1 640 medium (Gibco, Grand Island, NY, USA) containing 10% FBS (Gibco, Grand Island, NY, USA), 50 U/mL penicillin, and 50 µg/mL streptomycin at 37 °C in a 5% CO₂ incubator. For IL-6 (Bioworld, Nanjing, Jiangsu, China) treatment experiments, cells were incubated with either increasing doses of IL-6 (0, 2.5, 5, 10, and 25 ng/mL) for 24 h, or 25 ng/mL IL-6 for various durations (0, 4, 8, 12, and 24 h).

DEC1 overexpression

SW480 and DLD-1 cells were seeded in 6-well plates at a density of 1×10^6 cells per well. Transfection was performed using the GeneJet (Ver. II) reagent (SigmaGen, Gaithersburg, MD, USA) according to the manufacturer's instructions. Briefly, 800 ng of either the Flag-DEC1 (a gift from Dr. Yan) expression plasmid or the corresponding empty vector control was transfected per well. The transfection mixture was replaced with fresh complete medium after 6 h, and cells were harvested for subsequent experiments 24 h post-transfection.

DEC1 knockdown

SW480 and DLD-1 cells were transfected with DEC1-siRNA (Sigma-Aldrich, St. Louis, MO, USA, target sequence: GACCGATTAAACGAGTGCATCGCCCAGCTGAAGGATCTCCTACCCGAACATCTCAAACCTTACAACCTTTGGGTCACTTGGAAGAAAGCACTAACAACCTAATTGATCAGCAGCAGCAGAAAATCATTGCCCTGCAGAGTGGTTTACAAGCTGGTGAGCTGTCAGGGAGAAATGTCGAAACAGGTCAAGAGATGTTCTGCTCAGGTTTCCAGACATGTGCCCGGGAGGTGCTTCAGTATCTGGCCAAGCACGAGAACACTCGGGACCTGAA GTCTTCGCAGCTTGTCACCCACCTCCACCGGG TGGTCTCGGAGCTGCTGCAGGGTGGTACCTCC AGGAAGCCATCAGACCCAGCTCCCAAAGTGA

TGGACTTCAAGGAAAAACCCAGCTCTCC) or control siRNA using GeneJet (Ver. II). After 24 h, the medium was refreshed, and cells were incubated for another 24 h. The transfected cells were then treated with IL-6 (25 ng/mL) for 24 h prior to the following experiments.

Wound healing assay

SW480 and DLD-1 cells in 6-well plates were scratched with a pipette tip. Cells were then transfected with Flag-*DEC1* or *DEC1*-siRNA. Following a 24 h transfection period, the medium was replaced with fresh medium containing IL-6 (25 ng/mL), and the incubation continued for 24 h. Images were acquired with a microscope (Olympus, Shinjuku, Tokyo, Japan), and the wound area was measured using ImageJ software (NIH, USA).

Transwell invasion assay

SW480 and DLD-1 cells were transfected with either Flag-*DEC1* or *DEC1*-siRNA for 24 h. Transwell chambers were pre-coated with Matrigel (BD Biosciences, NJ, USA) and allowed to solidify. Following transfection, cells (1×10^5 cells/well) were harvested and resuspended in low-serum medium (1% FBS) with or without IL-6 (25 ng/mL). Then, 200 μ L of cell suspension was seeded into the upper chamber. The lower chamber was filled with 600 μ L of complete medium containing 10% FBS. After 24 h of incubation, non-invading cells on the upper surface of the membrane were gently removed with a cotton swab. Cells that had invaded to the lower surface were fixed with 100% methanol, stained with 0.1% crystal violet, and imaged under an inverted microscope (Olympus) at 400 $\times$ magnification.

Western blotting

Proteins from cell lysates were separated by 10% SDS-PAGE and electrophoretically transferred to PVDF membranes (Millipore, Bedford, MA, USA). Following transfer, membranes were blocked with 5% non-fat milk in Tris Buffered Saline with Tween 20 (TBST) for 1 h at room temperature and probed with primary antibodies at 4 $^{\circ}$ C overnight. Primary antibodies used were as follows: rabbit anti-GAPDH (1 : 5 000; Cat. #AP0063, Bioworld, Nanjing, Jiangsu, China), rabbit anti-DEC1 (1 : 2000; a gift from Dr. Yan), rabbit anti-PI3K p110 α (1 : 1 000; Cat. #BS6052, Bioworld), rabbit anti-p-Akt (Ser473) (1 : 1 000; Cat. #AP0724, Bioworld), rabbit anti-Akt (1 : 1 000; Cat. #BZ17037, Bioworld), rabbit anti-p-p65 (1 : 1 000; Cat. #BZ16389, Bioworld), rabbit anti-p65 (1 : 1 000; Cat. #AP0076, Bioworld), mouse

anti-N-cadherin (1:1 000; Cat. #MB4328, Bioworld), mouse anti-E-cadherin (1 : 1 000; Cat. #MB66613, Bioworld), and rabbit anti-vimentin (1 : 1 000; Cat. #BS1491, Bioworld). After thorough washing, membranes were incubated with secondary antibodies (anti-Rabbit [1 : 5 000; Cat. #BS13278, Bioworld] or anti-Mouse [1 : 5 000; Cat. #BS12478, Bioworld]). Immunoreactive bands were visualized using an ECL detection reagent (Vazyme, Nanjing, Jiangsu, China).

AOM/DSS-induced CRC model

Dec1^{+/+} (WT) and *Dec1*^{-/-} (KO) male mice aged 6–8 weeks were injected intraperitoneally with 10 mg/kg (body weight) azoxymethane (AOM) (Sigma-Aldrich, St. Louis, MO, USA). After recovering for 7 days, the mice were subjected to three separate cycles involving 7 days of 2.5% dextran sulfate sodium salt (DSS) (MP Biomedicals, Santa Ana, CA, USA) in drinking water, each followed by 14 days of regular water. The last cycle was followed by regular drinking water until sacrifice at day 86. Colon tissues were collected and processed in two ways: one portion was fixed in 4% paraformaldehyde, dehydrated through a graded series of ethanol, cleared with xylene, and paraffin-embedded; the other portion was snap-frozen at –80 $^{\circ}$ C for further analysis.

The animal experiments were conducted in accordance with a protocol approved by the Institutional Animal Care and Use Committee of Nanjing Medical University (Approval No. IACUC-1704004).

Total Protein Extraction from Mouse Intestinal Tissue

Total protein was extracted from mouse colorectal tissue. 50 mg tissue was minced in a tube, mixed with 500 μ L RIPA lysis buffer (Bioworld), and homogenized in an ice-water bath (5–10 s pulses, 10-min lysis on ice, repeated 3 $\times$). After centrifugation at 12 000 rpm, 4 $^{\circ}$ C for 15 min, 400 μ L supernatant was collected; 1 μ L was taken for quantification by BCA kit (Thermo, Waltham, MA, USA). 5 $\times$ loading buffer (Beyotime, Shanghai, China) was added, boiled for 5 min for denaturation, and stored at –80 $^{\circ}$ C.

Real-time PCR

Total RNA was isolated with TRIzol (Invitrogen, Carlsbad, CA, USA). Reverse transcription was performed with the HiScript II Q RT SuperMix kit (Vazyme, Nanjing, Jiangsu, China). Quantitative real-time PCR was performed with SYBR Green Master in a 7300 Real-time PCR System (Applied Biosystems, Waltham, MA, USA). The PCR amplification was

performed with commercial kits (Vazyme, Nanjing, Jiangsu, China) according to the manufacturer's instructions. The qPCR primer sequences are: β -actin forward, 5'-ATGCTCCCCGGGCTGTAT-3', β -actin reverse, 5'-CATAGGAGTCCTTCTGACCCATTC-3', IL-6 forward, 5'-CTGCAAGAGACTTCCATC CAGTT-3', IL-6 reverse, 5'-GAAGTAGGGAAGGCC GTGG-3'.

Hematoxylin and eosin (H&E) staining

Colon tissues embedded in paraffin were sectioned at 5 μ m thickness. Tissue sections were stained using an H&E staining kit (Jiancheng, Nanjing, Jiangsu, China). The histological slides were examined under a microscope (Olympus). A pathologist blinded to the experimental groups examined H&E-stained tissue sections and assigned hyperplasia severity scores according to a published method^[16]. Briefly, Grade 0 shows normal mucosa. Grade 1 presents mildly thickened crypts with intact epithelium. Grade 2 features moderately thickened crypts, dark epithelial nuclei, fewer goblet cells and occasional branching crypts. Grade 3 indicates severe lesions: crypts over four times thicker than normal, heavily stained epithelium, scarce goblet cells, active cell division and widespread crypt branching.

Mendelian randomization (MR) analysis

Expression quantitative trait loci (eQTL) data for *DEC1* (*BHLHE40*) were selected from the eQTLGen Consortium (<https://www.eqtlgen.org/>) to serve as the exposure. Genome-wide association study (GWAS) summary statistics for CRC (dataset finn-b-C3_COLORECTAL_EXALLC) were obtained from the IEU Open GWAS database (<https://gwas.mrcieu.ac.uk/>) as the outcome. Single-nucleotide polymorphisms (SNPs) significantly associated with *DEC1* expression ($P < 5 \times 10^{-8}$) were identified as instrumental variables (IVs). After removing those in linkage disequilibrium ($r^2 < 0.001$, distance $> 10,000$ kb), a total of 32 independent SNPs were retained for analysis. The primary analytical approach was the inverse variance weighted (IVW) method, supplemented by MR-Egger regression, the weighted median, simple mode, and weighted mode methods for validation. Cochran's Q test was employed to assess heterogeneity among IVs, and the MR-Egger intercept test was used to evaluate horizontal pleiotropy. Additionally, a leave-one-out analysis was conducted to assess the robustness of the results. All analyses were performed in R using the TwoSampleMR package.

Bioinformatics analysis

Using the TCGA-COAD dataset from The Cancer Genome Atlas (TCGA), we compared *DEC1* (*BHLHE40*) expression between 481 primary CRC tissues and 41 normal colorectal tissues. Furthermore, *DEC1* expression levels were assessed across different pathological stages (I–IV) of CRC. To validate these findings, data from the GEO dataset GSE39582 were integrated to examine *DEC1* expression in normal ($n = 19$) and CRC tissues ($n = 566$). Functional enrichment analysis of differentially expressed genes (DEGs) was subsequently performed using the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases to identify relevant biological pathways.

Statistical analysis

Data are presented as the mean $\pm$ standard deviation (SD). For Western blotting quantification, band intensities were first normalized to the corresponding loading control (GAPDH or β -actin) and then normalized to the control group. All experiments were performed with at least three independent biological replicates. For each biological replicate, technical duplicates or triplicates were included where applicable.

Statistical comparisons between two groups were performed using a two-tailed Student's *t*-test. For comparisons among three or more groups, one-way or two-way analysis of variance (ANOVA) was used. Prior to ANOVA, normality of the data distribution was assessed using the Shapiro–Wilk test, and homogeneity of variances was verified using Levene's test. When ANOVA assumptions were met, post-hoc comparisons were conducted using Tukey's honestly significant difference (HSD) test. If the assumptions were violated, the Kruskal–Wallis test (followed by Dunn's post-hoc test) was applied instead. A *P* value < 0.05 was considered statistically significant. All statistical analyses were performed using GraphPad Prism 9.0 or R (version 4.4.1).

Results

The positive causal association between *DEC1* and CRC

To investigate the potential causal relationship between *DEC1* (*BHLHE40*) gene expression and CRC risk, we conducted an MR analysis. The MR analysis revealed a positive causal effect of *BHLHE40* gene expression on CRC risk. The primary IVW analysis indicated that each unit increase in genetically

predicted *BHLHE40* expression was associated with an odds ratio (OR) of 1.55 for CRC (95% confidence interval [CI]: 1.15–2.08, $P = 0.0036$). Results from other complementary methods were consistent and supported this positive association, with the weighted median method yielding an OR of 1.78 ($P = 0.0044$) and the MR-Egger method showing an OR of 6.30 ($P = 0.0248$). Sensitivity analyses showed no evidence of significant heterogeneity ($P = 0.985$) or horizontal pleiotropy ($P = 0.076$). The leave-one-out analysis demonstrated that sequential exclusion of individual SNPs did not materially alter the results, indicating the robustness of our findings. The scatter plot, forest plot, and funnel plot (Fig. 1A–C) visually illustrate these statistical conclusions.

Analysis of the TCGA-COAD dataset showed that *BHLHE40* expression was significantly higher in primary CRC tumor tissues ($n = 481$, 5.23 ± 1.89) than in normal tissues ($n = 41$, 2.17 ± 1.05) ($P < 0.001$), indicating its upregulation in CRC (Fig. 1D). Analysis of the GSE39582 dataset revealed that *BHLHE40* expression was significantly upregulated in CRC tissues ($n = 566$, 9.93 ± 0.655) compared with

normal tissues ($n = 19$, 8.73 ± 0.8234) ($P < 0.001$) (Fig. 1E).

IL-6 promoted EMT along with *DEC1* upregulation

In vitro, we used IL-6 to simulate the tumor inflammatory microenvironment. SW480 and DLD-1 cells showed typical epithelial features in complete medium: cobblestone-like appearance and clustered structure. By contrast, after incubation with IL-6 (25 ng/mL) for 24 h, the cells showed typical mesenchymal features: a fibroblast-like morphology and loss of cell adhesion (Supplementary Fig. 1A). A wound healing assay was used to assess whether IL-6 affects the migration ability of these cells. Stimulation with 25 ng/mL IL-6 significantly reduced the width of the wound area in SW480 (Supplementary Fig. 1B and 1C) and DLD-1 cells (Supplementary Fig. 1D and 1E). Changes in cell morphology and wound width indicated that the cells underwent EMT under IL-6 stimulation.

To verify the regulation of *DEC1* in CRC invasion and migration induced by IL-6, we cultured SW480

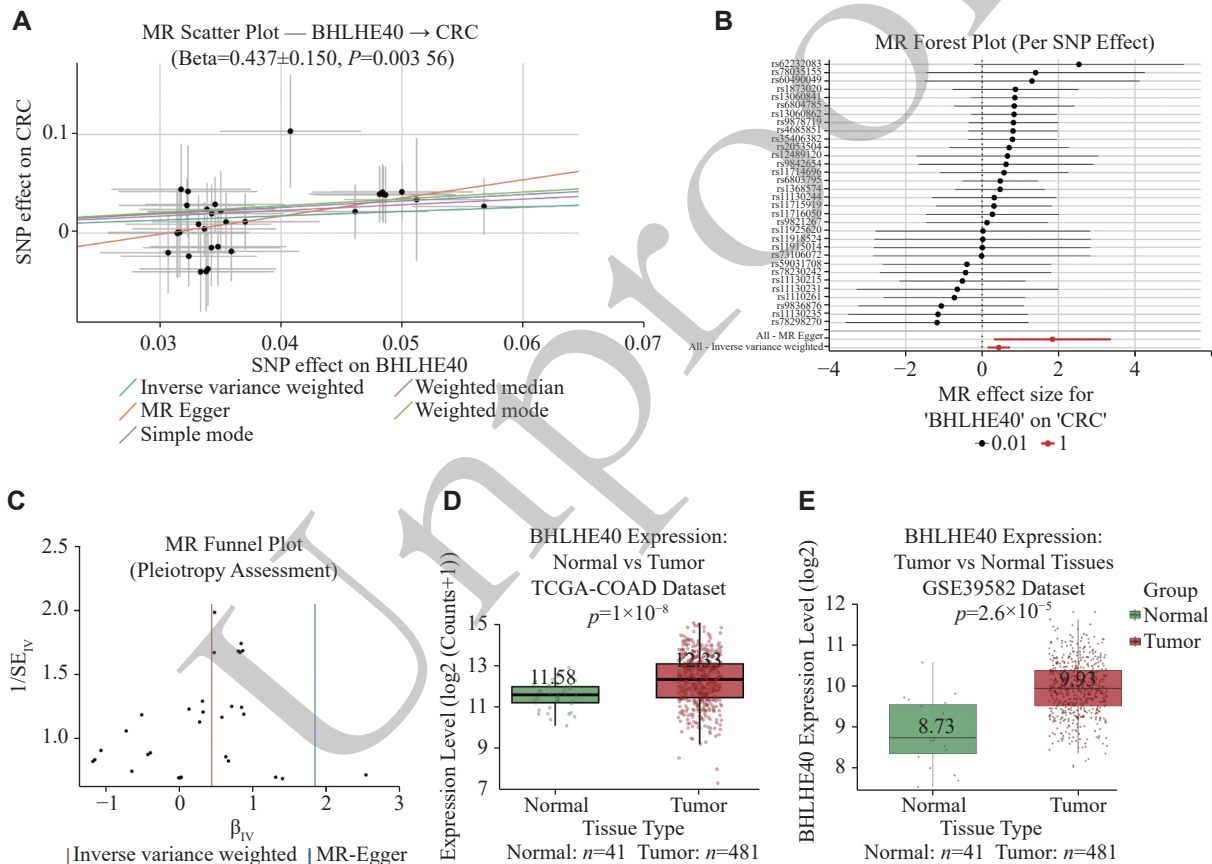


Fig. 1 The causal association between *DEC1* (*BHLHE40*) and colorectal cancer (CRC). A–C: The scatter plot (A), forest plot (B), and funnel plot (C) of *DEC1*. D: *BHLHE40* expression in tumor samples ($n = 481$; 5.23 ± 1.89) and normal colorectal tissues ($n = 41$; 2.17 ± 1.05). E: Expression analysis of *DEC1* in the GSE39582 dataset. Box plot comparing *DEC1* expression levels between normal colorectal tissues ($n = 19$) and CRC tissues ($n = 566$).

cells in a 6-well plate and treated the cells with increasing doses of IL-6 (0, 2.5, 5, 10, and 25 ng/mL) for 24 h or with a fixed dose of IL-6 (25 ng/mL) for various durations (0, 4, 8, 12, and 24 h). IL-6 increased the expression of DEC1 in both dose-dependent (Fig. 2A and 2B) and time-dependent manners (Fig. 2D and 2E). Similar results were found in DLD-1 cells (Supplementary Fig. 2A and 2B). Moreover, IL-6 treatment resulted in a dose-dependent (Fig. 2A and 2C) and time-dependent (Fig. 2D and 2F) increase in mesenchymal marker (N-cadherin and vimentin) expression but a decrease in epithelial marker (E-cadherin) expression, which was accompanied by a concurrent increase in DEC1 expression. These results demonstrate that IL-6 enhances DEC1 expression along with the upregulation of EMT markers in CRC cells.

DEC1 promoted IL-6-induced EMT

To determine whether DEC1 is involved in IL-6-induced invasion and migration of CRC cells, we transfected SW480 and DLD-1 cells with a *DEC1* overexpression plasmid. When cells were treated with IL-6 or transfected with the *DEC1* overexpression plasmid alone, the protein levels of N-cadherin and vimentin were significantly upregulated in SW480

cells (Fig. 3A). Conversely, the level of the epithelial marker E-cadherin was significantly reduced under these conditions. Notably, simultaneous IL-6 treatment and *DEC1* overexpression further increased the protein levels of N-cadherin and vimentin but decreased E-cadherin expression (Fig. 3A). Similar results were found in DLD-1 cells, where IL-6 treatment and *DEC1* overexpression upregulated the expression of EMT protein markers (Supplementary Fig. 3A–3D). Furthermore, transwell invasion assays revealed that IL-6 treatment or *DEC1* overexpression treatment alone promoted cell passage through the chamber, while simultaneous IL-6 treatment and *DEC1* overexpression further increased the number of invaded cells (Fig. 3E and 3F). Similarly, wound healing assays showed that IL-6 reduced the wound area, and *DEC1* overexpression further decreased the IL-6-reduced wound area in both SW480 (Fig. 3G and 3H) and DLD-1 (Supplementary Fig. 3E) cells.

Next, the *DEC1* knockdown plasmid was transfected into SW480 cells to further validate the results. Upon *DEC1* knockdown alone, the expression of E-cadherin was increased (Fig. 4A and 4B), while the expression of N-cadherin and vimentin was reduced (Fig. 4A, 4C, and 4D). Moreover, *DEC1* knockdown restored IL-6-reduced E-cadherin

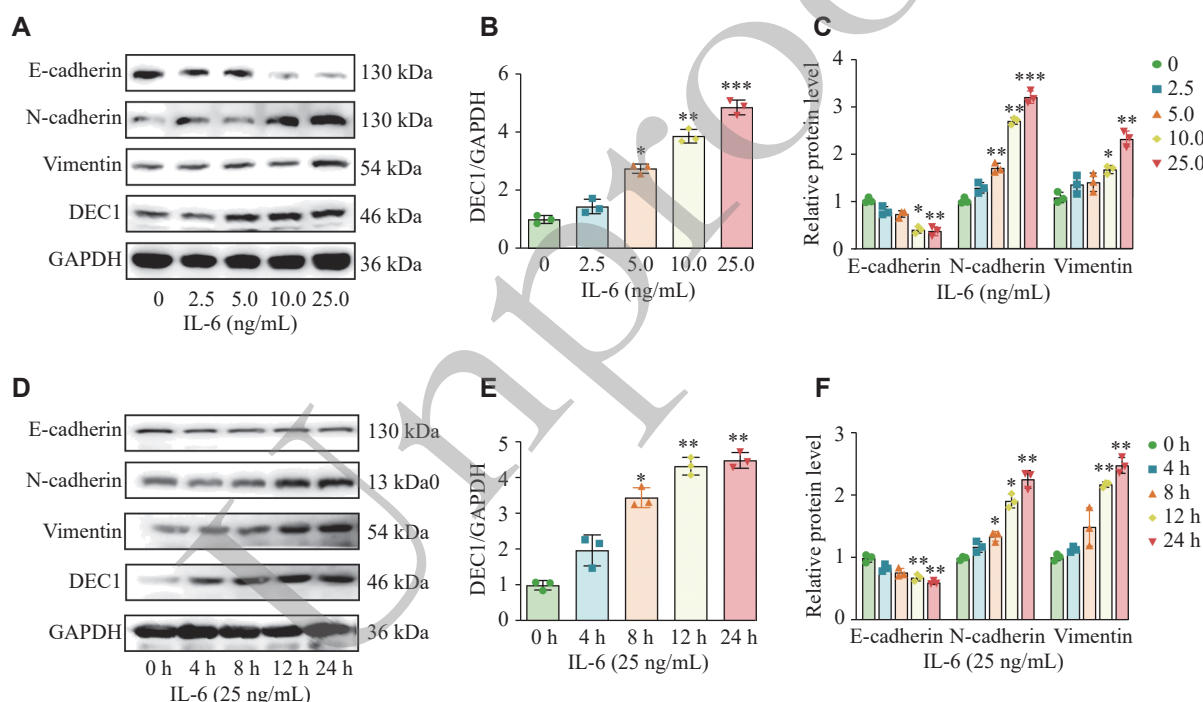


Fig. 2 The effects of IL-6 on the expression of DEC1 and EMT markers in colorectal cancer (CRC) cells. A–C: SW480 cells were treated with a gradient concentration of IL-6 (0, 2.5, 5, 10, and 25 ng/mL) for 24 h. The expression of DEC1, E-cadherin, N-cadherin and vimentin (one-way ANOVA) in SW480 cells were analyzed by Western blotting. D–F: SW480 cells were administered with 25 ng/mL IL-6 for different time durations. The expression of DEC1, E-cadherin, N-cadherin and vimentin (one-way ANOVA) were detected. Data are presented as mean $\pm$ standard deviation from at least three independent experiments. Significance levels relative to the control (0 ng/mL or 0 h): * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$.

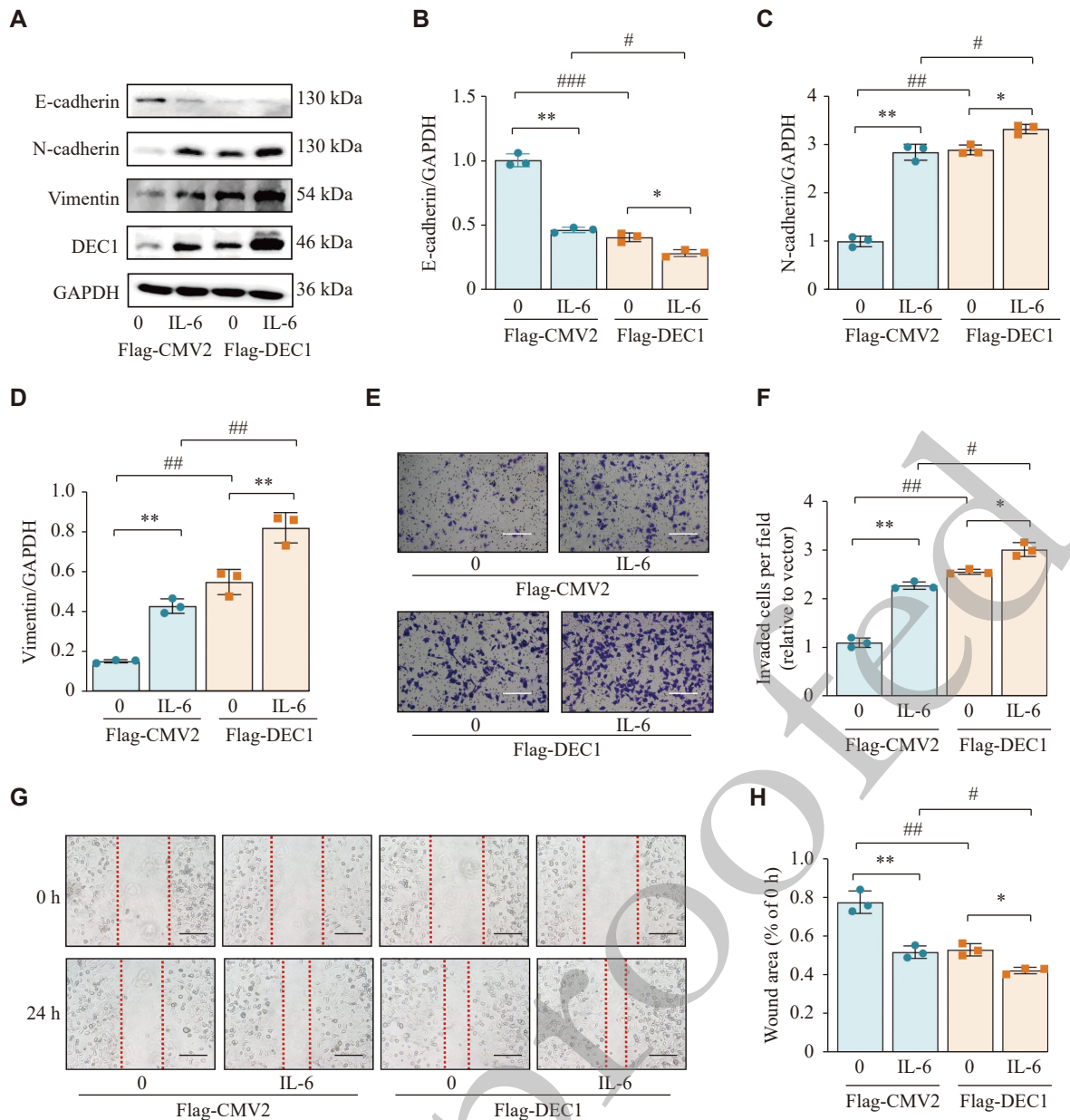


Fig. 3 DEC1 overexpression enhanced IL-6-induced CRC cell invasion. SW480 cells were treated with DEC1-overexpression plasmid and/or IL-6 (25 ng/mL). A–D: Protein levels of migration and invasion-associated genes were determined by Western blotting, including E-cadherin, N-cadherin and vimentin (two-way ANOVA). E and F: The results of the transwell invasion assay (two-way ANOVA). Scale bar = 20 μm. G and H: The sizes of wound healing were photographed and measured (two-way ANOVA). Scale bar = 80 μm. Data are presented as mean ± standard deviation from at least three independent experiments. * $P < 0.05$ and ** $P < 0.01$ vs. the corresponding 0. # $P < 0.05$, ## $P < 0.01$, ### $P < 0.001$ vs. the corresponding Flag-CMV2.

expression (Fig. 4A and 4B) and inhibited IL-6-induced N-cadherin and vimentin expression (Fig. 4A, 4C, and 4D). As evidenced by both Transwell invasion and wound healing assays, DEC1 knockdown inhibited basal and IL-6-induced invasion and migration of SW480 cells (Fig. 4E–4H).

In the TCGA-COAD cohort, DEC1 expression was positively correlated with IL-6 ($r = 0.363$), VIM ($r = 0.578$), and CDH2 ($r = 0.428$) (all $P < 0.001$). DEC1 expression was also correlated with the EMT score ($r = 0.56$), which was derived from vimentin and N-

cadherin. IL-6 showed positive correlations with both DEC1 ($r = 0.35$) and the EMT score ($r = 0.35$) (Supplementary Fig. 3F and 3G).

Collectively, these findings indicate that DEC1 promotes the invasion and migration of CRC cells, at least partially, by enhancing IL-6-induced EMT.

DEC1 mediated IL-6-induced invasion and migration in CRC cells through the PI3K/Akt/NF-κB pathway

Integrated GO and KEGG analyses were performed

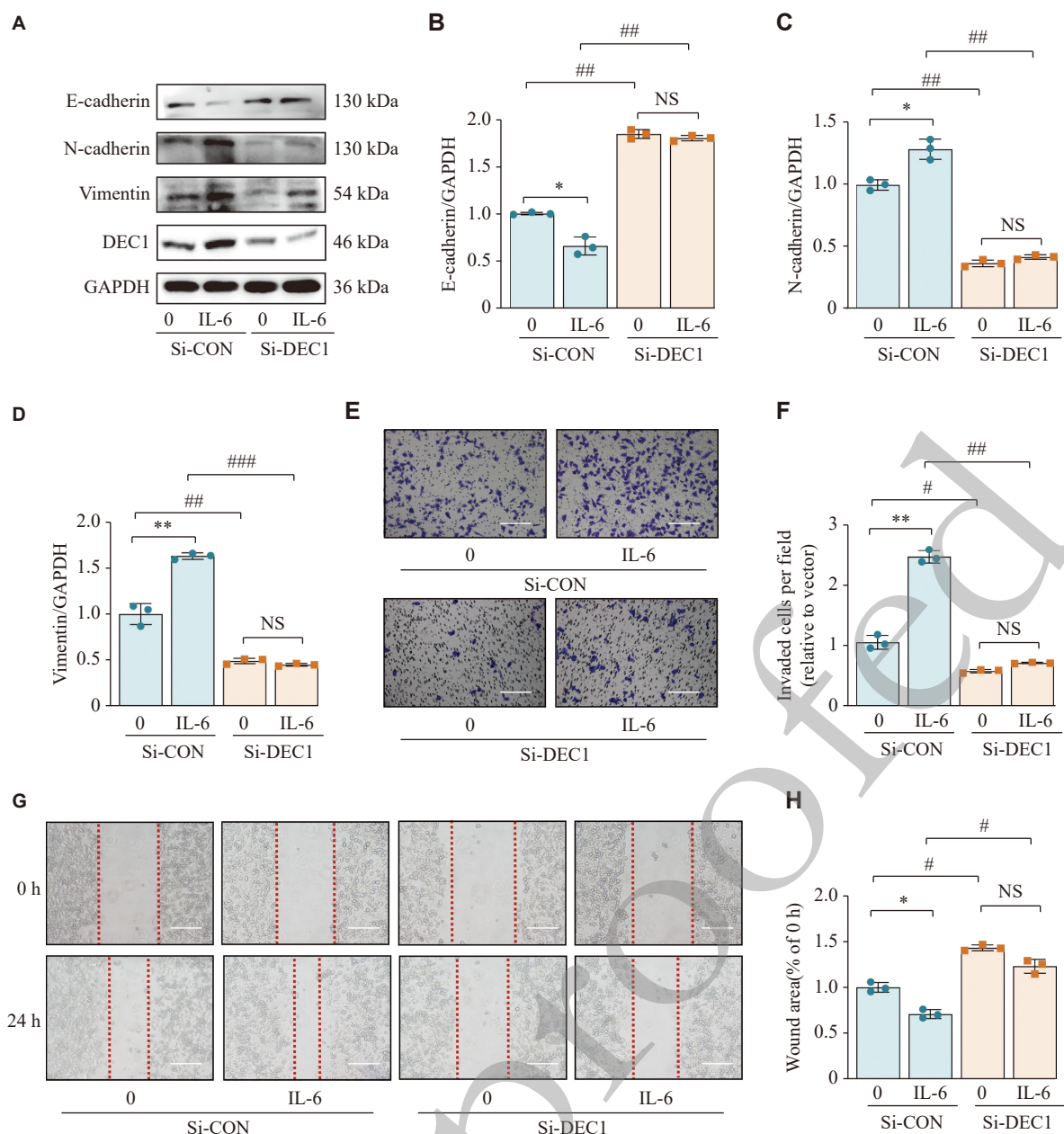


Fig. 4 *DEC1* knockdown inhibited IL-6-induced CRC cell invasion. SW480 cells were treated with si-*DEC1* and/or IL-6 (25 ng/mL). A–D: The protein expression of E-cadherin, N-cadherin and vimentin (two-way ANOVA) were determined by Western blotting. E and F: Transwell invasion results were photographed under a microscope (two-way ANOVA). Scale bar = 20 μ m. (G, H) The sizes of wound healing regulated by IL-6 or si-*DEC1* were photographed (two-way ANOVA). Scale bar = 80 μ m. Data are presented as mean $\pm$ standard deviation from at least three independent experiments. NS $P > 0.05$, * $P < 0.05$, ** $P < 0.01$ vs. the corresponding 0. # $P < 0.05$, ### $P < 0.001$ vs. the corresponding si-Control.

on DEGs between normal and CRC tissues. Specifically, GO analysis revealed significant enrichment of EMT-related biological processes, such as gastrulation and endoderm development, along with extracellular matrix organization ([Supplementary Fig. 4A](#)). At the molecular and cellular levels, genes were enriched for integrin binding, collagen binding, and localization to focal adhesions and the collagen-containing extracellular matrix ([Supplementary Fig. 4B](#) and [4C](#)). The most significantly enriched KEGG

pathway was the PI3K-Akt signaling pathway, along with concurrent enrichment in focal adhesion and ECM-receptor interaction, suggesting a coordinated signaling network ([Supplementary Fig. 4D](#)). These results establish PI3K-Akt-mediated signaling as a core regulator linking EMT to CRC invasion.

Our previous results have also demonstrated that DEC1 activates the PI3K/Akt pathway^[17], which is a key signaling axis involved in the promotion of tumor invasion and migration^[18]. *DEC1* overexpression or

IL-6 treatment alone increased total PI3K and its downstream target p-Akt/Akt. Conversely, *DEC1* knockdown inhibited the PI3K/Akt pathway. Moreover, *DEC1* overexpression significantly increased IL-6-stimulated PI3K and p-Akt/Akt (Fig. 5A and 5B); conversely, *DEC1* knockdown decreased IL-6-stimulated PI3K and p-Akt/Akt (Fig. 5C and 5D). It is known that IL-6 activates the NF-κB pathway in cancer cells^[19]. Next, we tested the effect of DEC1 on NF-κB activation and found that *DEC1* overexpression significantly increased p-NF-κB (p-p65)/NF-κB (p65) (Fig. 5A and 5B) with or without IL-6 stimulation. Conversely, *DEC1* knockdown significantly decreased IL-6-stimulated p-NF-κB (p-p65)/NF-κB (p65) (Fig. 5C and 5D), a trend consistent with that of the PI3K/Akt pathway. The results suggest that the activation of the PI3K/Akt/NF-κB pathway contributes to DEC1-regulated invasion and migration.

To further explore whether DEC1 exerts its effects through regulation of the PI3K/Akt/NF-κB pathway, we used LY294002, a PI3K/Akt pathway inhibitor, and EVP4593, an NF-κB inhibitor. First, we found

that IL-6 activated PI3K, p-Akt, and p-NF-κB (p-p65) (Fig. 6A and 6B). LY294002 abolished the IL-6-induced increase in PI3K, p-Akt/Akt, and p-NF-κB (p-p65)/NF-κB (p65) (Fig. 6A and 6B). Furthermore, LY294002 reversed the IL-6-induced increase in DEC1 (Fig. 6A and 6), the increase in N-cadherin and vimentin, and the reduction in E-cadherin (Fig. 6C and 6D). LY294002 attenuated EMT phenotypes activated by *DEC1* overexpression (Supplementary Fig. 5A). Additionally, EVP4593 reversed the increase in PI3K, p-Akt/Akt, and p-NF-κB (p-p65)/NF-κB (p65) induced by IL-6 (Fig. 6E and 6F). EVP4593 also reversed the IL-6-induced increase in DEC1 (Fig. 6E and 6F), the increase in N-cadherin and vimentin, and the reduction in E-cadherin (Fig. 6G and 6H). EVP4593 attenuated EMT phenotypes activated by *DEC1* overexpression (Supplementary Fig. 5A). *PIK3CA* (the catalytic subunit of PI3K) knockdown in *DEC1*-overexpressing cells reversed the IL-6-induced EMT phenotype: E-cadherin was restored, vimentin and N-cadherin were reduced (Supplementary Fig. 5B–5E). Using JASPAR 2026 (Matrix ID: MA0464.3/MA0464.2), we scanned the

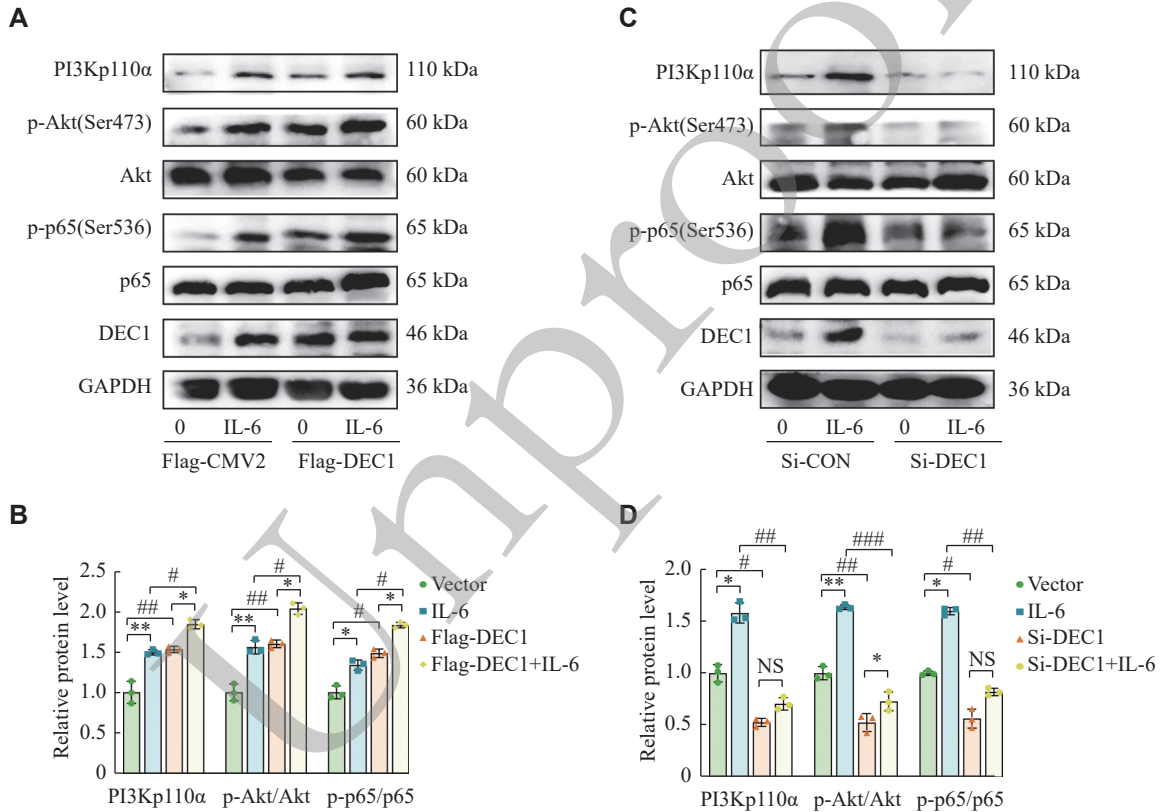


Fig. 5 *DEC1* overexpression enhanced, whereas *DEC1* knockdown decreased the PI3K p110α/Akt/NF-κB pathway activated by IL-6. After 24 h of transfection with si-Control or si-*DEC1*, SW480 cells were treated with or without IL-6 (25 ng/mL) for 24 h: A and B: The expression of PI3K p110α, p-Akt/Akt, p-NF-κB (p65)/NF-κB (p65) (two-way ANOVA) were determined by Western blotting. C and D: The cytoplasmic and nuclear protein levels of NF-κB (p65) were examined. All experiments described in this figure were repeated at least three times independently. NS $P > 0.05$, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs. the corresponding 0. # $P < 0.05$, ## $P < 0.01$, ### $P < 0.001$ vs. the corresponding Flag-CMV2 or si-Control.

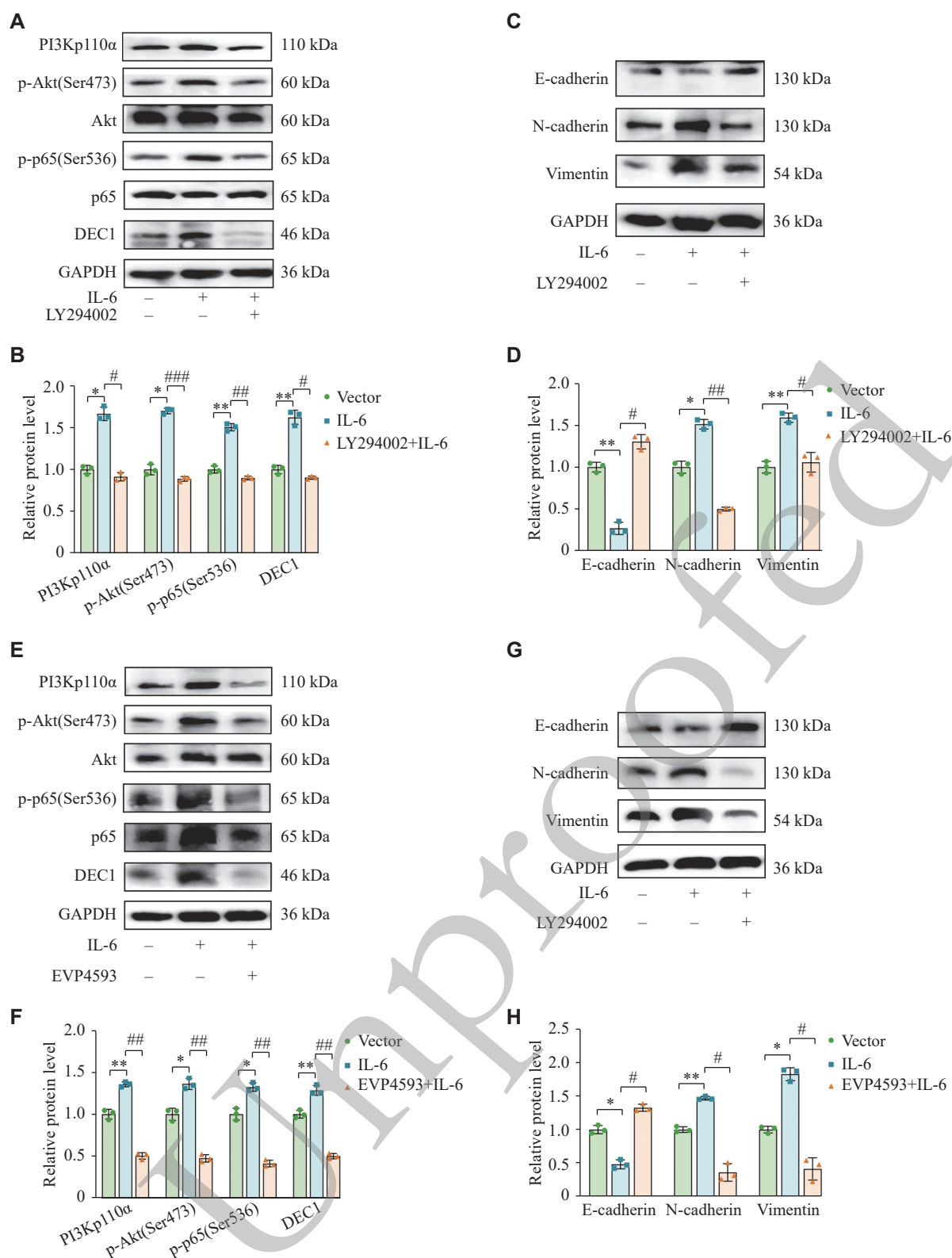


Fig. 6 LY294002 and EVP4593 reversed IL-6 induced the increase in DEC1, PI3K p110α, p-Akt, p-NF-κB (p65) expression and EMT level. A–D: SW480 cells were treated with LY294002 (10 μM) or IL-6 (25 ng/mL), which were analyzed for DEC1, PI3K p110α, p-Akt/Akt, p-NF-κB (p65)/NF-κB (p65) (two-way ANOVA) (A, B), E-cadherin, N-cadherin and vimentin (two-way ANOVA) (C, D). E–H: SW480 cells were treated with EVP4593 (50 nM) 30 minutes prior to the addition of IL-6 (25 ng/mL) for 24 hours. Cell lysates were analyzed for the levels of DEC1, PI3K p110α, p-Akt/Akt, p-NF-κB (p65)/NF-κB (p65) (two-way ANOVA) (E, F), E-cadherin, N-cadherin and vimentin (two-way ANOVA) (G and H). Data are presented as mean ± standard deviation from at least three independent experiments. * $P < 0.05$ and ** $P < 0.01$, vs. the control group. # $P < 0.05$, ## $P < 0.01$, and ### $P < 0.001$, vs. the IL-6 group.

human *PIK3CA* promoter (2000 bp upstream of the transcription start site [TSS]) for BHLHE40 binding sites (relative score threshold > 0.8). The top-ranked site (relative score = 0.866) was located at positions -1854 to -1847 (upstream of the TSS), with the predicted sequence 5'-TCACCTGA-3', which highly matches the canonical E-box motif (**Supplementary Fig. 5F** and **5G**). This suggests that BHLHE40 may directly regulate *PIK3CA* transcription via this core promoter element. These results indicate that DEC1 mediates IL-6-induced invasion and migration of CRC through the PI3K/Akt/NF- κ B pathway.

Dec1 deficiency inhibited the invasion and migration in AOM/DSS-induced CRC mice

In vivo, we used *Dec1*^{+/+} and *Dec1*^{-/-} mice to establish colitis-associated CRC induced by AOM/DSS. Tail genotyping was performed to confirm the genotype (**Supplementary Fig. 6**). Compared with *Dec1*^{+/+} littermates, *Dec1*^{-/-} mice exhibited a marked reduction in both the number of tumors and the tumor volume (**Fig. 7A**). Histologically, *Dec1* deficiency reduced tumor progression. Compared with *Dec1*^{+/+} CRC mice, *Dec1*^{-/-} CRC mice showed minor tumor invasion into the submucosa (**Fig. 7B**). Compared with *Dec1*^{+/+} CRC mice, *IL-6* mRNA levels in *Dec1*^{-/-} CRC mice significantly decreased (**Fig. 7C**). In terms of EMT-related proteins, E-cadherin expression in *Dec1*^{-/-} CRC mice was significantly higher, but N-cadherin and vimentin levels were significantly lower than those in *Dec1*^{+/+} CRC mice (**Fig. 7D–7G**). These results indicate that *Dec1* deficiency can reduce the EMT of colitis-associated CRC, thereby inhibiting invasion and migration. Protein levels of PI3K, Akt, and NF- κ B (p65) in the colon tissue of CRC mice were detected by Western blotting. *Dec1*^{-/-} CRC mice exhibited significantly reduced protein levels of PI3K and lower phosphorylation ratios of Akt (p-Akt/Akt) and NF- κ B (p-p65/p65) compared with their *Dec1*^{+/+} counterparts, consistent with the trend of EMT phenotypes (**Fig. 7H–7K**). These results suggest that DEC1 regulates the PI3K/Akt/NF- κ B pathway in the invasion and migration of colitis-associated CRC.

Discussion

Multiple factors, notably chronic inflammation, have been reported as pivotal contributors to CRC development^[20]. Inflammation causes invasive carcinoma, which leads to tumor cells spreading through blood vessels and lymph nodes, invading other organs, and aggravating the disease^[21].

Inflammatory cytokines enhance the expression of EMT markers^[22]. The acquisition of EMT-like changes in tumor cells results in increased invasion, which is highly correlated with the poor prognosis of tumor patients^[23].

IL-6 has been demonstrated to induce EMT across various tumor types, such as colorectal, gastric, bladder, and lung cancers^[24]. As a key inflammatory cytokine, IL-6 serves as a critical inducer of EMT in tumor cells^[24]. In the present study, we demonstrated that IL-6 upregulated the expression of the mesenchymal markers (*e.g.*, N-cadherin and vimentin) but downregulated the expression of the epithelial marker (E-cadherin) in a dose- and time-dependent manner. Given that the EMT/inflammation axis is involved in the first step of tumor formation, targeting inflammatory factors and blocking their induction of tumors through gene regulation may represent a new therapeutic perspective.

Past studies in our laboratory have found that IL-6 activates DEC1 expression in normal mouse liver tissues^[25]. DEC1 is highly expressed in many cancer tissues, including CRC, liver cancer, and breast cancer^[26,27]. Our findings further indicate that DEC1 plays a critical role in mediating IL-6-induced EMT: (1) IL-6 significantly upregulated the expression of DEC1 and EMT markers in a time- and dose-dependent manner. The expression of DEC1 was highly correlated with the expression of EMT markers. (2) *DEC1* overexpression downregulated the epithelial marker E-cadherin and upregulated the mesenchymal markers N-cadherin and vimentin. Conversely, *DEC1* knockdown significantly upregulated E-cadherin expression but downregulated N-cadherin and vimentin expression. (3) Functional experiments assessing invasion and migration, including transwell invasion and wound healing assays, revealed that *DEC1* overexpression promoted, but *DEC1* knockdown inhibited, IL-6-induced invasion and migration of CRC cells. (4) In the AOM/DSS-induced colitis-associated CRC model, *Dec1* deficiency significantly decreased the expression of *Il6* mRNA, reduced the invasion of the tumor into the submucosa, and slowed the progression of EMT. Our data establish an essential role for DEC1 in the inflammation-associated progression of CRC, particularly in enhancing cell invasion and migration.

The PI3K/Akt signaling pathway is a central driver of tumorigenesis and development^[28]. IL-6 can activate the PI3K/Akt pathway, which triggers a series of downstream effects^[29]. Our previous studies have found that DEC1 participates in MPP⁺-induced neurotoxicity, which involves the PI3K/Akt/GSK3 β

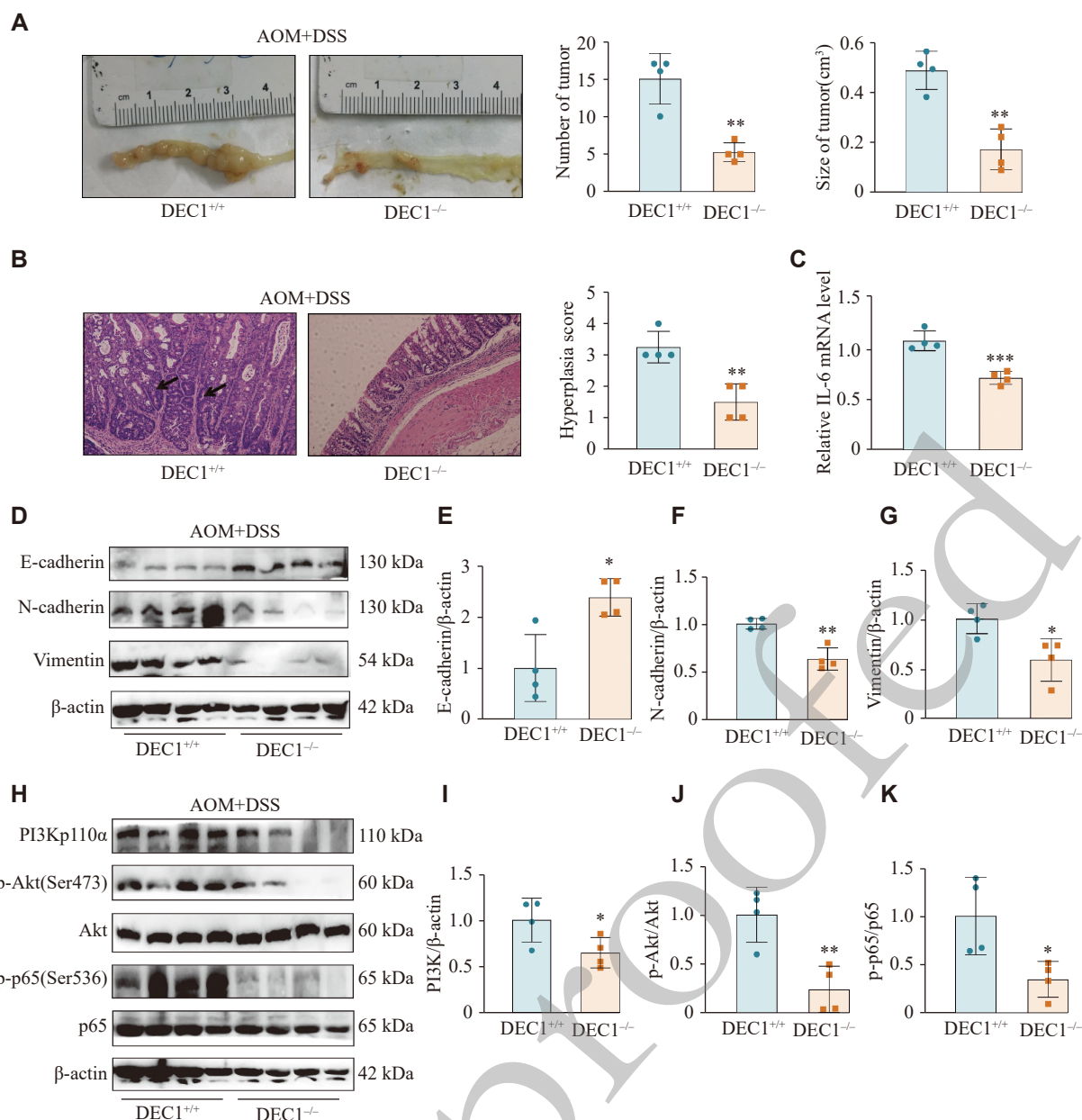


Fig. 7 DEC1 enhanced epithelial-to-mesenchymal transition in colitis-associated colorectal cancer (CRC) mice. A: Number and size (t-test) of tumor in *Dec1*^{+/+} and *Dec1*^{-/-} in colon tissues from CRC mice. B: Hematoxylin and eosin staining of the tumors in *Dec1*^{+/+} and *Dec1*^{-/-} CRC mice (200×) (t-test). Scale bar=40 μm. C: Expression of *Il6* (t-test) mRNA in CRC was analyzed by real-time PCR. D–G: The protein (from *Dec1*^{+/+} and *Dec1*^{-/-} CRC mice) expression of migration and invasion-associated genes, including E-cadherin, N-cadherin, and vimentin (t-test), was analyzed by Western blotting. H–K: Western blot results of PI3K/Akt/NF-κB (t-test) signaling pathway in *Dec1*^{+/+} and *Dec1*^{-/-} CRC mice. Data are presented as mean ± SD (*n* = 4 per group). Statistical significance versus *Dec1*^{+/+} CAC mice is indicated as follows: **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

signaling pathway^[30]. Consistent with these findings, the present study reveals that DEC1 regulates IL-6-induced EMT in CRC through activation of the PI3K/Akt pathway: (1) *In vitro*, under IL-6 stimulation, *DEC1* overexpression significantly increased, but *DEC1* knockdown decreased the expression of PI3K and its downstream p-Akt/Akt. (2) The PI3K/Akt pathway inhibitor LY294002 significantly reversed the IL-6-induced upregulation of PI3K and p-Akt/Akt. LY294002 downregulated IL-

6-induced DEC1 expression, inhibited N-cadherin and vimentin expression, and upregulated E-cadherin expression, thereby inhibiting EMT. (3) *In vivo*, *Dec1* deficiency reduced the levels of PI3K and p-Akt/Akt.

While our data demonstrated that the PI3K pathway is necessary for DEC1-enhanced IL-6-induced EMT, we did not directly assess STAT3 activation or function in the present study. Given our previous report that DEC1 activates STAT3 in CRC^[16], and the known crosstalk between PI3K and STAT3, we

cannot completely rule out a modulatory role for STAT3. Future studies using STAT3-specific inhibitors or CRISPR-mediated *STAT3* silencing will be required to clarify the potential involvement of STAT3 and to determine whether STAT3 contributes to other DEC1-associated phenotypes in the context of IL-6 stimulation. Although JASPAR prediction and *PI3K* silencing support a transcriptional regulatory relationship between DEC1 and *PIK3CA*, direct evidence is still lacking. Future studies using ChIP assays will be required to establish direct molecular interactions.

NF- κ B activated by IL-6 promotes inflammation and tumorigenesis^[31,32]. The PI3K/Akt/NF- κ B signaling pathway mediates tumor cell invasion and migration in CRC^[33,34]. Moreover, our study identifies DEC1 as a key upstream regulator that drives IL-6-induced EMT in CRC, specifically through activation of this pathway: (1) Under IL-6 stimulation, *DEC1* overexpression significantly upregulated the expression of p-NF- κ B (p-p65), whereas *DEC1* knockdown downregulated the expression of p-NF- κ B (p-p65). (2) The NF- κ B inhibitor EVP4593 reversed the IL-6-induced increase in PI3K and its downstream p-Akt/Akt. Similarly, EVP4593 also reversed the IL-6-induced increase in DEC1 expression, which in turn downregulated N-cadherin and vimentin expression but upregulated E-cadherin expression, thereby inhibiting EMT. (3) *Dec1* deficiency inhibited the expression of p-NF- κ B (p65) in AOM/DSS-induced CRC. Our results demonstrate that IL-6 promotes EMT in CRC by inducing DEC1 expression. This DEC1-mediated process involves the PI3K/Akt/NF- κ B pathway, which facilitates cancer cell invasion and migration. However, the interaction between inflammatory factors and tumor cells involves complex molecular mechanisms, and the specific mechanism remains to be further elucidated.

Collectively, the present study demonstrates that DEC1 participates in the EMT induced by IL-6 through the PI3K/Akt/NF- κ B signaling pathway, thereby regulating invasion and migration in CRC. The main findings of our study provide a basis for an in-depth understanding of the role of DEC1 in inflammation-induced invasion and migration in CRC (*Supplementary Fig. 7*).

Author Contributions

Conceptualization, Jian Yang, Enfang Shan and Ziheng Zhang; methodology, Enfang Shan, Weifeng Du, Ziheng Zhang and Ying Huo; software, Weifeng Du, Ziheng Zhang and Jingwan Hu; validation, Wei

Liu, Ziheng Zhang and Jingwan Hu; formal analysis, Enfang Shan and Ziheng Zhang; investigation, Enfang Shan, Ziheng Zhang, Jingwan Hu and Weifeng Du; resources, Jian Yang and Enfang Shan; data curation, Ziheng Zhang, Jingwan Hu, Ying Huo and Wei Liu; writing—original draft preparation, Jian Yang, Enfang Shan and Ziheng Zhang; writing—review and editing, Jian Yang and Enfang Shan; visualization, Enfang Shan and Weifeng Du, supervision, Enfang Shan; project administration, Jian Yang and Enfang Shan; funding acquisition, Jian Yang and Enfang Shan. All authors have read and agreed to the published version of the manuscript.

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