

# RETRACTED ARTICLE: Kinesin Superfamily Member 18B (KIF18B) Promotes Cell Proliferation in Colon Adenocarcinoma

This article was published in the following Dove Press journal:  
*Cancer Management and Research*

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**Background:** The role of kinesin superfamily proteins (KIFs) has been reported in a variety of tumors and KIFs contributed to the proliferation of cancer cells. But few studies were focus on colon adenocarcinoma.

**Methods:** Through bioinformatics analysis and immunohistochemistry (IHC) assays, the expression of KIF18B in colon adenocarcinoma tissues was determined. Stable KIF18B-depleted cell lines were constructed using lentivirus-mediated shRNA of KIF18B. Cell colony formation assay and EdU-K8 assay were performed to assess cell proliferation degree, and the expression level of Ki67 and PCNA was used to indicate cell proliferation in vitro and verified using xenograft tumors in vivo.

**Results:** KIF18B is highly expressed in colon adenocarcinoma tissues and has a negative correlation with the prognosis and tumor grade of colon adenocarcinoma. Interfering with KIF18B inhibits cell proliferation in vitro and in vivo.

**Conclusion:** KIF18B can be used as a prognostic marker for colon adenocarcinoma and maybe a therapeutic target for colon adenocarcinoma treatment.

**Keywords:** kinesin superfamily proteins, KIF, KIF18B, colon adenocarcinoma, proliferation, biomarker, therapeutic

## Introduction

Colon cancer is a common malignant tumor in the digestive tumor, and its incidence has significantly increased year by year. The incidence and mortality of colon adenocarcinoma is all ranked 3rd among all malignant tumors.<sup>1-4</sup> The number of new colon adenocarcinoma cases in the United States is expected to be 101,420 and the death toll is 51,020.<sup>4</sup> At present, the pathogenesis of colon adenocarcinoma remains unclear, and the molecular mechanism of its occurrence and progression is of great significance for the treatment of colon adenocarcinoma. Excessive proliferation of cells is closely related to the occurrence of tumors, and the defects of cell cycle and proliferation are more likely to promote cancer progression.<sup>5-7</sup>

Intracellular transport is essential for promoting cell survival and maintaining cell function. The kinesin superfamily proteins (KIFs) are transported intracellularly in a manner that relies on microtubules and ATP.<sup>8-11</sup> KIFs have highly conserved amino acid sequence among all eukaryotic phyla cells and were widely expressed in mouse and human cells. By searching database, there are about 45 KIFs that were identified.<sup>10</sup> KIFs not only participate in intracellular transport but

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also involve in the movement of chromosomes and spindles in mitosis.<sup>12-14</sup> As was reported, KIF18B promotes tumor progression in a variety of cancers.<sup>15,16</sup> Previous study indicated that KIF18B contributor and facilitator metastasis of cutaneous melanoma by enhancing the expression of N-cadherin, vimentin and Snail. In lung adenocarcinoma, KIF18B promoted cell proliferation, migration, and invasion via activating Rac1 and mediating the AKT/mTOR pathway. Through the wide involvement of KIF18B in cancer progression, whereas, in colon adenocarcinoma, the role of KIF18 has not been revealed.

## Methods

### Bioinformatics Analysis

The web tool of GEPIA (<http://gepia.cancer-pku.cn/>) was used to analyze the correlation between KIF18B expression and the prognosis. For expression on box plots and Disease-Free Survival (DFS) plots, The specific parameters: |Log2FC| Cutoff $\leq$ 1, p-value Cutoff $\leq$ 1, Jitter Size=0.4, Matched Normal data: Match TCGA normal and GTEx data. The TCGA colon adenocarcinoma database includes 275 cancer specimens and 349 adjacent normal specimens.

### Human Tissues Specimens

Seventy-one colon adenocarcinoma specimens were obtained from HanDan Central Hospital (HeBei, China) from 2011 to 2018 who were diagnosed with colon adenocarcinoma and not received chemotherapy or radiotherapy. The patient signed a consent form for the use of the specimens prior to surgery and the permission for the study was granted by the Ethics Committee of HanDan Central Hospital.

### Immunohistochemistry

The tissues were fixed in 10% formalin and embedded in paraffin. After cutting into 4  $\mu$ m, they were dewaxed and hydrated. IHC staining was performed according to the instructions (ENS004302, NeoBioscience, Shenzhen, China). Simply, antigen retrieval was performed in citrate buffer with high temperature for 20 min and the primary antibody (ab121798, 1:100, Abcam, Cambridgeshire, UK) was incubated overnight at 4°C. After washing three times with PBST buffer, sections were incubated with HRP-conjugated secondary antibody for 1 hour at 37°C. Finally, sections were incubated with 3,3'-Diaminobenzidine (DAB) and counter-stained with hematoxylin. The H-score was assigned to each IHC image and samples were classed as high KIF18B expression

(H-score $\geq$ 200) or low KIF18B expression (H-score < 200).<sup>17,18</sup>

### Cell Lines and Transfection

The cell lines of colon adenocarcinoma, HCT 116 and HT29, were obtained from ATCC (Manassas, USA), and they are incubated with McCoy's 5a Medium Modified (30-2007, ATCC) containing 10% FBS (FBS, BioLegend, Beit HaEmek, Israel), 1% Penicillin-Streptomycin (15,140,122, Thermo, Waltham, US) 37°C with 5% CO<sub>2</sub>. Lentiviral-mediated shRNA is used to interfere with KIF18B expression. ShRNA-KIF18B: 5'-GCCGCCGAAATTGCAGAAAT-3', negative control sequence: 5'-ATGTCGATTCGTATCATGGCAT-3'. Briefly, the shRNA sequence and the control sequence were ligated into the pLV3.7 plasmid. PLL3.7-shKIF18B or PLL3.7-control the lentiviral packaging plasmid were co-transfected into 293FT cells. After 48 h, the cell supernatant was collected, and the virus was purified by ultracentrifugation and added to the cells. After 72 hours, positive cells were screened by the addition of puromycin (P8230, Solarbio, Beijing, China).

### qRT-PCR

According to the instructions, RNA from cells and animal tissues was extracted using Trizol reagent (15,596,018, Thermo). Use the kit to reverse the RNA to cDNA (K1691, Thermo). Each well containing: 10  $\mu$ L Faststar Universal SYBR Green Master (04913850001, Roche, Basel, Switzerland), 0.6  $\mu$ L forward primer, 0.6  $\mu$ L reverse primer, 0.5  $\mu$ L cDNA, 8.2  $\mu$ L ddH<sub>2</sub>O. The programs: 95°C 10min, 95°C 30s then 60°C 1min 40 cycle, 60°C 5min. Using 2<sup>- $\Delta\Delta$ Ct</sup> to calculate differential genes. Primer: GAPDH forward, 5'-ACAACCTTGGTATCGTGGAAAGG-3' and GAPDH reverse, 5'-GCCATCACGCACAGTTTC-3'<sup>19</sup> KIF18B forward, 5'-GCTGCAAGTAGTGGTACGGG-3' and KIF18B reverse, 5'-CCTCAGGGTAAACACCAGCA-3'<sup>20</sup>

### Western Blot

Total proteins for Western blot were extracted using RIPA reagent (R0010, Solarbio), subsequently the concentrations of total proteins were quantified using Quick Start Bradford Protein Assay (5,000,205, BIO-RAD, Hercules, USA). The proteins were separated by SDS-PAGE gel, and then transferred onto PVDF membrane (LC2002, Thermo), blocked with 5% milk in TBST buffer for 1 hour at room temperature. After washing, the PVDF membrane was incubated with primary antibodies in TBST buffer at 4°C for overnight, and then

membranes were incubated with secondary antibodies at room temperature for 1 hour. Signals were then detected with ECL substrate (32,106, Thermo).

Antibodies: KIF18B, HPA027831, Sigma, 1:1000;  $\beta$ -actin, D191047-0100, Sangon Biotech, China, 1:1000; PCNA, ab29, Abcam, 1:1000; Ki67, 9449, Cell Signaling Technology, 1:1000.

## Detection Cell Proliferation with CCK-8

$2 \times 10^3$  cells hKIF18B or control cells were seeded into 96-well with 200  $\mu$ L complete medium. After 48 h, according to the instruction, the 10  $\mu$ L CCK-8 reagent (96,992, Sigma) was added into each well and incubator for 4 h. Then, OD<sub>450</sub> value was examined using the enzyme mark instrument.

## Cell Colony Formation

For cell colony formation,  $10^3$  cells were added into 6-well containing 2mL complete medium, and incubator for 14 days. Then, cells were fixed with formaldehyde for 30min, washed three times using PBS, stained with crystal violet for 10min, and calculated the number of formations.

## In vivo Tumorigenicity Assay

The xenograft tumor research was approved by HanDa Central Hospital.  $3 \times 10^6$  HCT116 cells (shKIF18B or control cells) suspended in 150  $\mu$ L PBS were subcutaneously injected into the abdomen of nude-BALB/c mice (6–8 weeks, 3/group, Beijing JPK Bioscience CO. LTD). Observed tumor growth every 7 days and estimated tumor volume using formula (volume = length  $\times$  width<sup>2</sup>/2).<sup>21</sup> After 28 days, all mice were sacrificed, and the protein expression levels were analyzed using Western blot.

## Statistical Analysis

Statistical analysis was performed using SPSS software in windows. The Student's *t*-test (two-sided) was used to analyze statistical differences between the two groups, with 3 replicates in each group of experiments. The association between KIF18B expression and clinicopathological information was accessed using the chi-square test.

## Results

### KIF18B is Upregulated in Human Colon Adenocarcinoma Tissues According to the TCGA Database

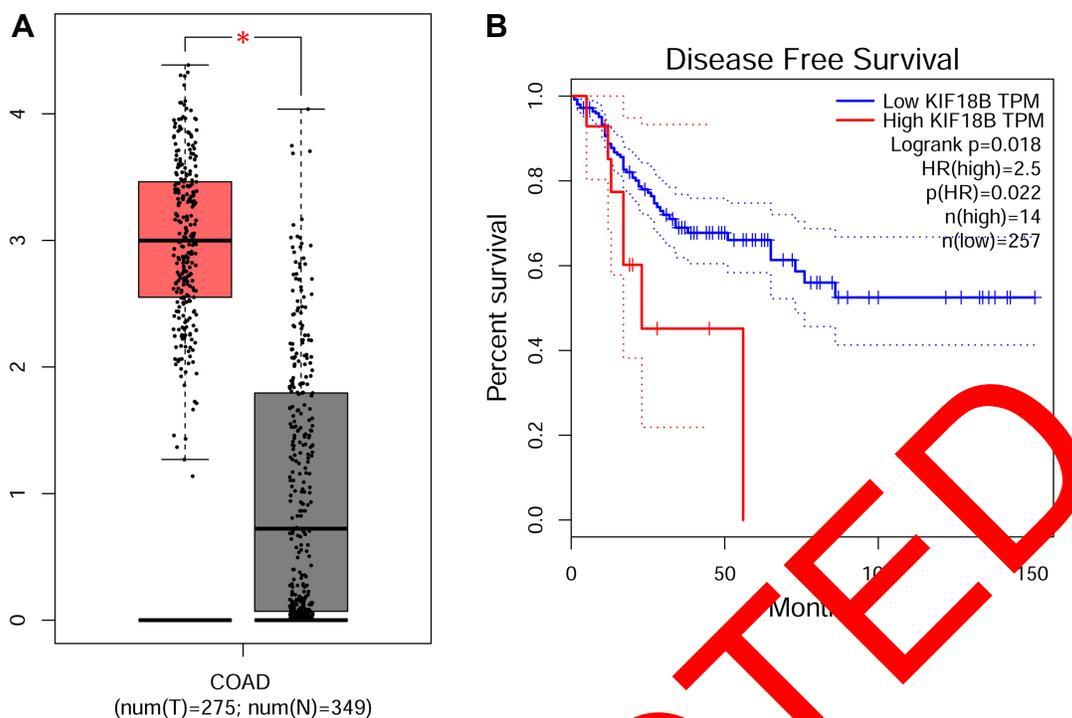
In order to investigate the role of KIF18B in colon adenocarcinoma (COAD) progression, we first assessed the mRNA level of KIF18B from TCGA database. This cohort, containing 275 samples of COAD and 349 normal control samples, showed that KIF18B was upregulated in COAD tissues compared with normal tissues (Figure 1A). Then, according to the prognostic information, we found that patients with high expression of KIF18B had poor Disease-Free Survival (Figure 1B). We therefore thought that KIF18B was highly expressed in COAD tissues and associated with the prognosis.

### KIF18B was Overexpressed Detecting by IHC

Subsequently, the protein expression level of KIF18B in samples of COAD tissues was detected through immunohistochemical (IHC) assays. We collected 71 paraffin tissues of colon adenocarcinomas and the adjacent normal tissues (Table 1). According to the results of IHC staining, all samples were separated into high expression (n=14) or low expression group (n=57, Figure 2A and B). Combining the data of clinicopathological characteristics, we thought that patients with high expression of KIF18B have obviously higher tumor stage ( $p=0.034$ ).

### Interfering with KIF18B Expression Using shRNA

Through the results of TCGA and IHC staining, we found that the role of KIF18B was worthy of study in colon adenocarcinoma. To further investigate the involvement of KIF18B in colon adenocarcinoma progression, we selected two colon adenocarcinoma cell lines, HCT116 and HT29. We used shRNA plasmids of KIF18B to interfere with its expression and used the puromycin screen to establish two cell lines that were KIF18B stably knocked down. Subsequently, the mRNA and protein expression levels of KIF18B in stably depleted cells were detected through qPCR and Western blot assays (Figure 3A and 3B).



**Figure 1** KIF18B mRNA levels were upregulated in human colon adenocarcinoma (COAD) tissues compared with normal tissues in TCGA database. **(A)** The expression level of KIF18B of COAD in TCGA database, including 275 colon adenocarcinoma samples and 349 normal samples. \* $P < 0.05$ . **(B)** The COAD patients with high KIF18B expression have poor Disease-Free Survival (DFS). These data was analyzed using GEPIA website.

## KIF18B Promotes COAD Cell Proliferation in vitro

Then, the colony formation assay was performed to assess the effects on cell proliferation with negative control and KIF18B knockdown (shKIF18B) cells. The result showed that cell proliferation was inhibited after KIF18B knockdown in COAD cells (Figure 4A). Similarly, the CCK8 assays also confirmed this phenomenon (Figure 4B). In previous studies, Ki67 and PCNA were often used as molecular markers for cell proliferation, and their expression levels were positively correlated with cell proliferation. We therefore examined the protein expression levels of Ki67 and PCNA and verified the previous conclusion (Figure 4C and D). Therefore, we showed that KIF18B promoted cell proliferation of COAD cells in vitro.

## KIF18B Depletion Inhibits Xenograft Growth in vivo

Then, the mice xenograft models were used to evaluate the effects of KIF18B in vivo.  $3 \times 10^6$  shKIF18B and shControl HCT116 cells were subcutaneously injected into the abdomen, then measured tumor size every 3 days. After 29 days, all mice were sacrificed and tumors were taken out

(Figure 5A). The expression levels of KIF18B and Ki67 were detected by Western blot in tumor tissues, showing fewer Ki67 expression levels in KIF18B-depleted tumors (Figure 5B and C). From the results, we thought KIF18B promoted tumor progression in vivo.

## Discussion

KIFs are a class of proteins that were associated with the progression of intracellular transport and mitosis.<sup>11,14,22–26</sup> The disorder of KIFs expression suppresses normal mitosis and causes chromosome inhomogeneity. These factors all promote tumorigenesis. As was reported, KIF18B promoted tumor development in a variety of cancers, such as cervical cancer,<sup>20</sup> liver cancer,<sup>27</sup> lung cancer,<sup>28</sup> and clear cell renal cell carcinoma (ccRCC),<sup>29</sup> whereas it was not been reported in colon adenocarcinoma.

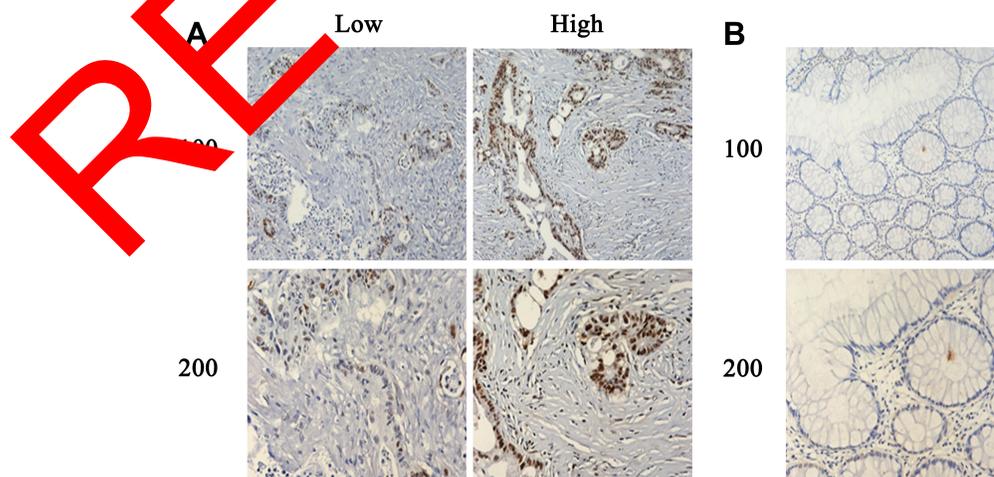
Firstly, we found differential expression of KIF18B in colon and control tissues through the TCGA database, and found COAD patients with high expression had shorter DFS. Next, we used the patient's colon adenocarcinoma paraffin-embedded specimen to detect the expression level of KIF18B through IHC assays and found KIF18B was highly expressed in colon adenocarcinoma tissues and correlated with the pathological

**Table I** Relationships of KIF18B and Clinicopathological Characteristics in 71 Patients with Colon Cancer

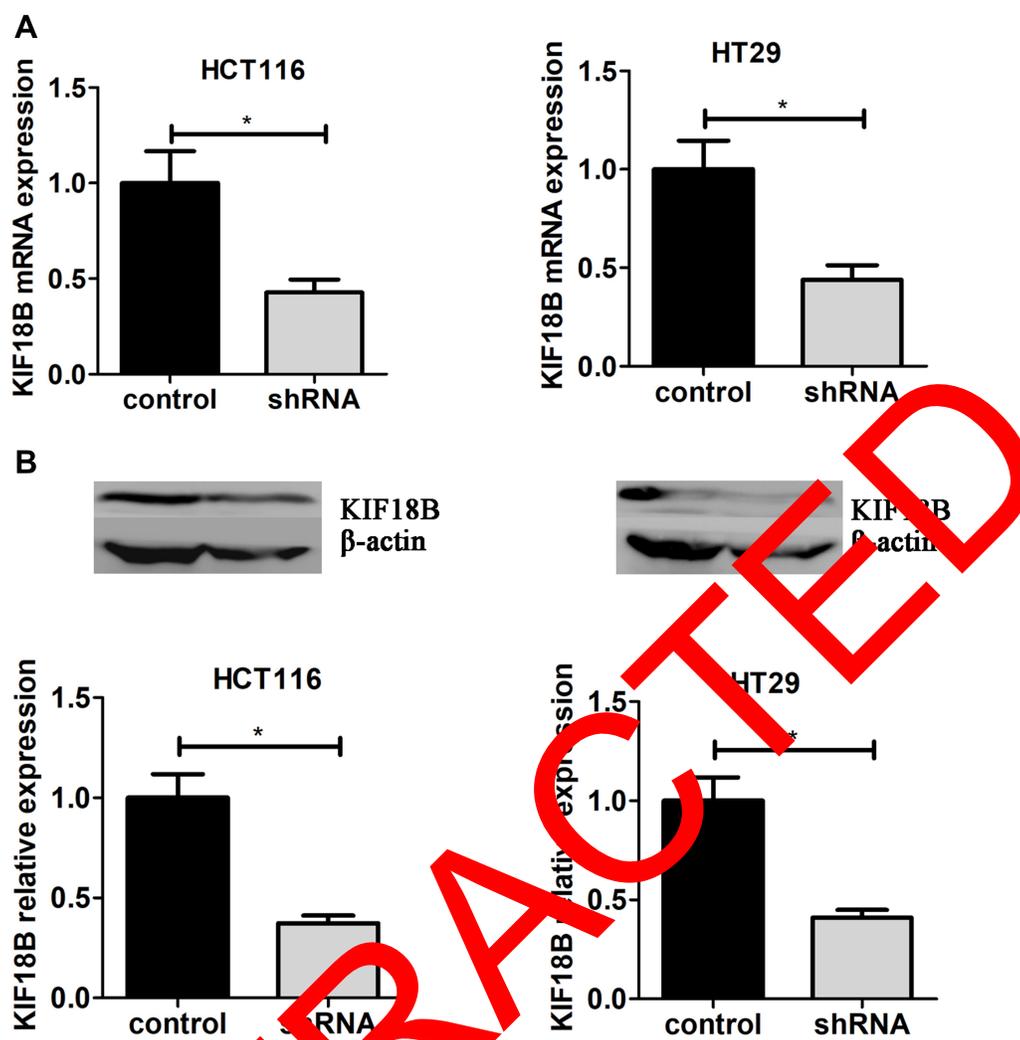
Feature	All n=71	KIF18B Expression		$\chi^2$	P
		Low	High		
		n=14	n=57		
Age (year)					
<55	36	5	31	1.568	0.211
≥55	35	9	26		
Gender				0.448	0.503
Male	40	9	31		
Female	31	5	26		
Tumor stage				4.508	0.034*
T2	28	9	19		
T3/T4	43	5	38		
Tumor grade				0.029	0.864
Low	29	6	23		
High	42	8	34		
Metastasis				0.171	0.679
Yes	32	7	25		
No	39	7	32		

Note: \*P < 0.05.

stage. Notably, Wu et al draw the similar conclusion in cervical cancer. <sup>15</sup> To further investigate the role of KIF18B in colon adenocarcinoma, we established a colon adenocarcinoma cell line that stably knocked down KIF18B using shRNA plasmid. The cell proliferation was detected by cell colony formation and CCK-8 assays. Then, the protein levels of Ki67 and PCNA were performed using Western blot. Cell proliferation assays showed that the knockdown of KIF18B inhibited cell proliferation in colon adenocarcinoma cell lines. In estrogen receptor-positive breast cancer, Huang et al reported that KIF18B enhanced cell proliferation and apoptosis resistance. Additionally, Wu et al showed the similar results in cervical cancer, and founding that KIF18B promoted cell proliferation by activating Wnt/ $\beta$ -catenin signaling. <sup>15</sup> In xenograft models, shKIF18B



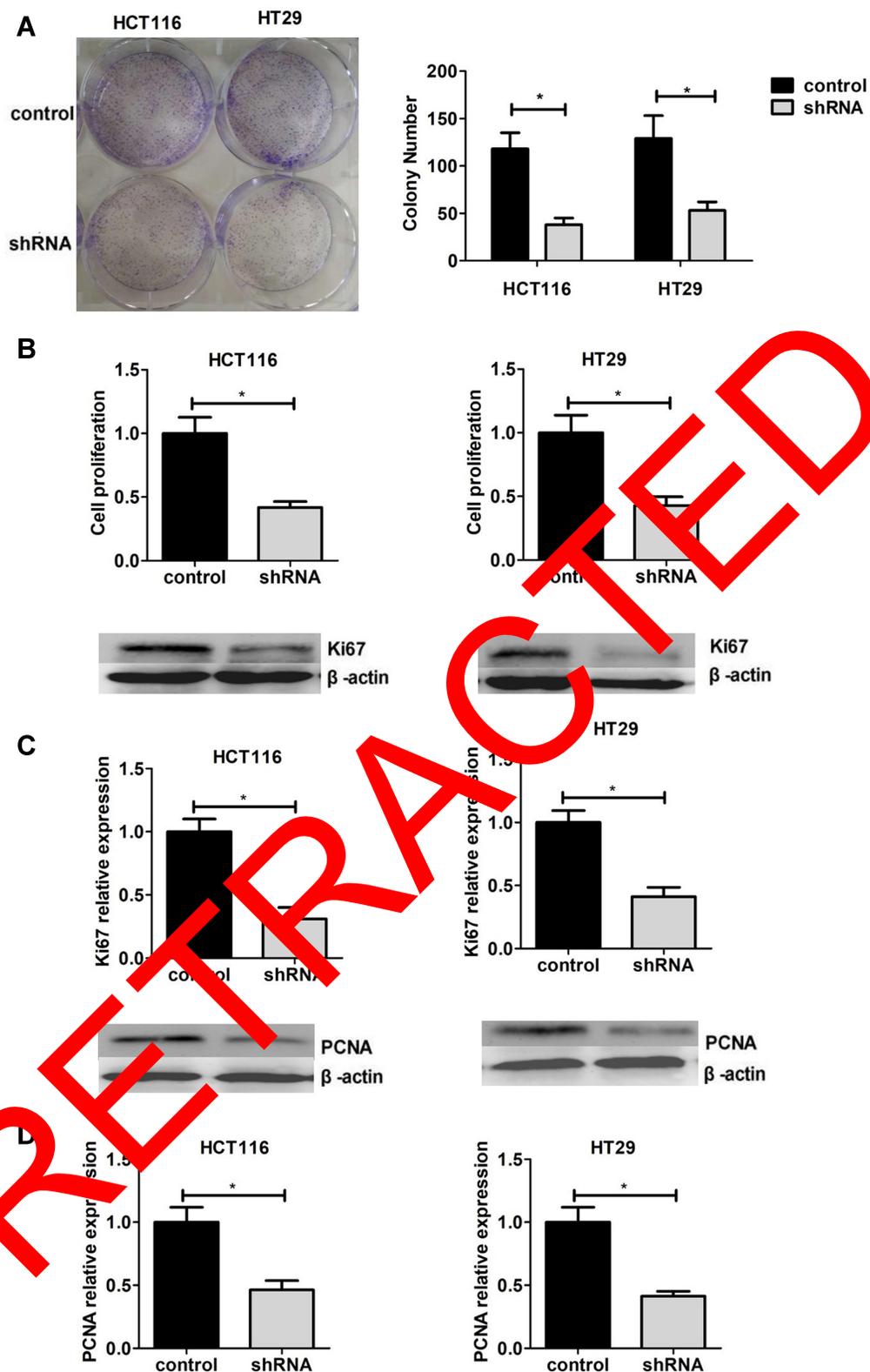
**Figure 2** Typical IHC images of COAD and adjacent normal tissues (A and B) KIF18B was more highly expressed in colon adenocarcinoma tissues than that in normal tissues. Consistent with other studies, KIF18B was mainly expressed in the nucleus.



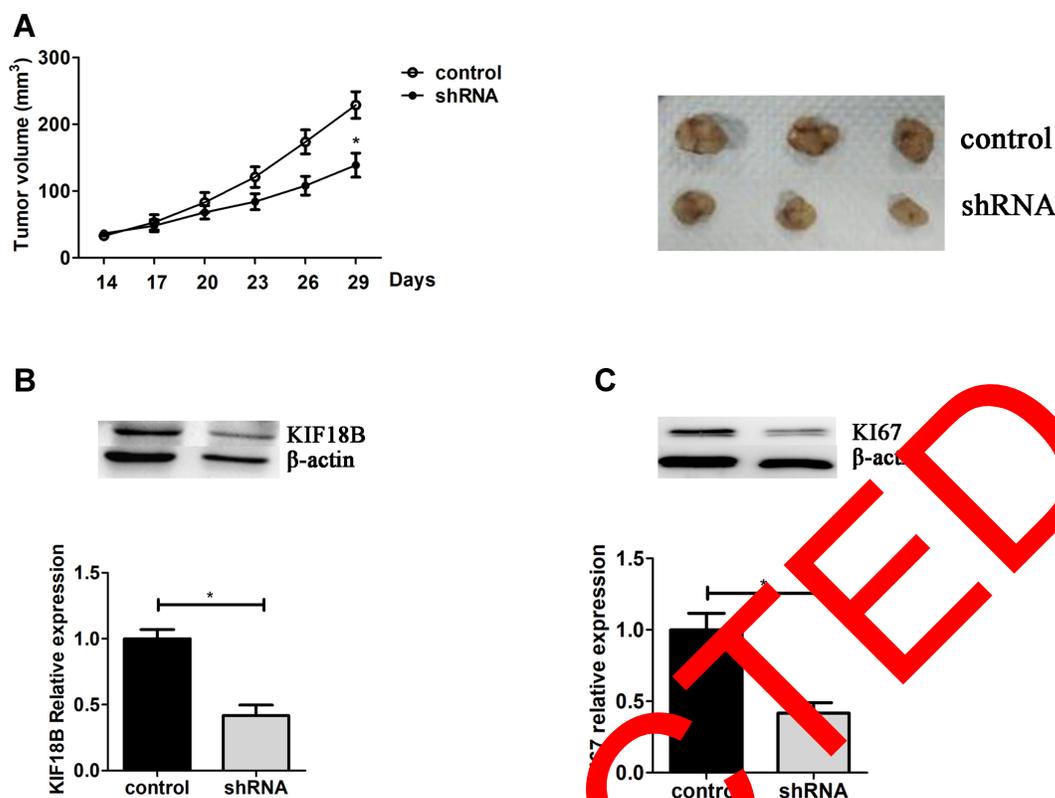
**Figure 3** Interfering with KIF18B expression using shRNA (A) Interfering KIF18B expression using lentivirus-mediated shRNA. After adding virus and puromycin selection, Both mRNA and protein levels of KIF18B were assessed through qPCR (A) and Immunoblot assays (B). \* $P < 0.05$ .

cells and control cells were inoculated into nude mice, and founding that sh-KIF18B disturbed the ability of tumorigenesis, and tumor with lower KIF18B and Ki67 expression compared with that in control group. In hepatoma cancer cells and cervical cancer cells, knockdown of KIF18B inhibited cell proliferation by inhibiting cell cycle.<sup>25,30</sup> Microtubule motor protein, Eg5, promotes mitosis of tumor cells by formation of monopolar spindles, making Eg5 as a potential therapy target for anti-tumor. Roy et al revealed that KIF18B was essential for bipolar spindle assembly in tumor cells which was Eg5-independent by performed a genome-wide siRNA screen.<sup>31</sup> Ji et al detected the correlation between KIF18B and clinical characteristics in lung adenocarcinoma (LUAD) according to the TCGA database and Oncomine dataset and found that KIF18B was

significantly up-regulated in LUAD tissues. High level of KIF18B was associated with the poor prognosis of LUAD patients. Knockdown of KIF18B inhibited the expression of Rac1-GTP which was an essential protein affecting migration and invasion of cancer cells. Moreover, Western blot assay demonstrated that the phosphorylation of AKT and mTOR was decreased after KIF18B depletion.<sup>32</sup> In breast cancer, differentially expressed KIF18B has been identified in breast cancer and normal tissues. Of these, 16 were significantly up-regulated in cancer tumors, and 11 were related to the poor OS, relapse-free survival (RFS) and distant metastasis-free survival (DMFS), including KIF18B.<sup>33</sup> This was a simple study of KIF18B in colon adenocarcinoma, for the clinical application of KIF18B, the further molecular mechanisms were still needed to study.



**Figure 4** Interfering with KIF18B expression inhibited cell proliferation in HCT116 and HT29 cells. (**A** and **B**). Cell proliferation was detected using cell colony formation assay (**A**) and CCK-8 (**B**) assays in sh-KIF18B and control cells. The expression of Ki67 (**C**) and PCNA (**D**) was detected in sh-KIF18B and control cells through Western blot assays. \* $P < 0.05$ .



**Figure 5** KIF18B depletion inhibits xenograft growth in vivo. **(A)** After inoculation, measure tumor sizes every 3 days to draw tumor growth curve. After 29 days, all mice were sacrificed and the tumors were taken out for photos. Total protein was obtained from tumor tissues and the expression level of KIF18B and KI67 was detected using Western blot **(B and C)**. \* $P < 0.05$ .

## Conclusion

KIF18B was highly expressed in colon adenocarcinoma tissues and negatively correlated with patients' prognosis.

Knockdown of KIF18B inhibited cell proliferation and tumor growth in vitro and in vivo. KIF18B may be a novel biomarker and therapeutic target for colon adenocarcinoma.

## Abbreviation

KIF18B, kinesin family member 18B; IHC, immunohistochemistry; DAB, 3,3-diaminobenzidine; HRP, horseradish peroxidase; PCNA, proliferating cell nuclear antigen; PBS, phosphate-buffered saline; PAGE, polyacrylamide gel electrophoresis; QRT-PCR, quantitative real-time polymerase chain reaction; shRNA, short hairpin RNA.

## Data Sharing Statement

The dataset supporting the conclusions of this article is included within the article.

## Ethics Approval and Consent to Participate

All applicable international, national, and/or institutional guidelines for the care and use of human specimens and animals were followed. In our hospital, we have achieved the informed consents of patients before the surgeries in the surgical informed consents and agreement. We can not provide these materials because of the Chinese language and privacy protection. The animal study was carried out in accordance with the guidelines approved by the Animal Experimentation Ethics Committee of Department of pathology in HanDan Central Hospital. The protocol was approved by the Committee, all surgery was performed under sodium pentobarbital anesthesia, and all efforts were made to minimize suffering. The guidelines outlined in the Declaration of Helsinki were met.

## Consent for Publication

All of the authors have agreed to publish this article in your journal if it is accepted.

## Disclosure

The authors declare that they have no competing interests for this work.

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