ORIGINAL RESEARCH

RAB10 Facilitates Colorectal Cancer Progression through Activation of the NF-κB Signaling Pathway

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ABSTRACT

Background • Colorectal cancer (CRC) is the third most prevalent malignancy globally, ranking as the second leading cause of cancer-related mortality. Emerging evidence highlights *RAB10*'s involvement in the progression of various malignant tumors; however, its specific role in CRC remains unclear.

Objective • To explore the oncogenic role of *RAB10* in colorectal cancer progression by investigating its impact on NF-κB activation, aiming to identify a novel genetic biomarker for enhanced diagnosis and treatment of CRC.

Methods • This study collected CRC tissue samples and utilized The Cancer Genome Atlas (TCGA) database for *RAB10* expression verification through Western blot (WB). Cellular phenotype experiments were conducted on CRC cell lines, including quantitative real-time-polymerase chain reaction (qRT-PCR), CCK-8, transwell assay, and wound healing assay (HCT116 and SW480). Additionally, the impact of *RAB10* on NF-κB signaling was assessed through qRT-PCR and WB.

Results • *RAB10* exhibited upregulation in CRC tissue samples compared to normal counterparts. Furthermore, *RAB10* promoted the proliferation, migration, and invasion of HCT116 and SW480 cells. Notably, *RAB10* induced NF-κB activation in CRC *in vitro*.

Conclusion • This study revealed the oncogenic function of *RAB10*, explaining its role in activating NF-κB in CRC. The findings present *RAB10* as a potential genetic biomarker for CRC diagnosis and treatment. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

The colon and rectum, integral parts of the large intestine, are the origin sites for colorectal cancer (CRC).[1] Although CRC can manifest at any age, it predominantly affects the elderly.[2, 3] Presently, the annual incidence rate and mortality of CRC, reaching 930,000 in 2020, pose a growing health threat.[3, 4] Globally, CRC has emerged as the leading cause of cancer-related deaths, with China experiencing a significant rise to the second-highest overall incidence rate.[5, 6]

The increasing urgency to address CRC is due to its growing prevalence, emphasizing the need to alleviate its substantial impact on public health. Precision medicine has attained high advocacy as our understanding of tumors has shifted from the broad, organ-level perspective to a focus on cellular and molecular intricacies.[7] Therefore, genes or molecules associated with CRC are critically important and require in-depth exploration.

RAB10, also known as GTP-binding protein *RAB10*, is a member of the small GTPase of the RAS superfamily, which is a GTP-binding protein.[8] It plays a crucial role in regulating the transport of intracellular vesicles through a cycle involving continuous binding and ATP hydrolysis, facilitating protein transport between different organelles.[9, 10] Notably, RAB10 exhibits varying degrees of high expression in various malignant tumors, including hepatocellular carcinoma,[11] glioma,[12] cervical cancer,[13] and osteosarcoma.[14]

RAB GTPases, including *RAB10*, have been reported to play a role in predicting the response to immunotherapy and are linked to the prognosis of CRC.[15] Additionally, *RAB10* has the capability to promote apoptosis in tumors.[16] Considering its distinctive role in tumor development and autophagy, *RAB10* emerges as a crucial target for tumor treatment, deserving increasing attention. However, the specific role of *RAB10* in CRC remains unclear.

The NF-κB signaling pathway plays a crucial role in advancing the progression of various cancers, such as pancreatic cancer[17] and lung cancer,[18] among others. Additionally, this pathway is a pivotal regulator influencing multiple aspects of CRC cell behavior, including proliferation, apoptosis, angiogenesis, inflammation, metastasis, and drug resistance.[19] However, the potential regulatory relationship between *RAB10* and NF-κB in colorectal cancer remains unknown.

This study aimed to investigate the oncogenic role and regulatory mechanism of *RAB10* in CRC. This study can potentially establish a molecular foundation for CRC diagnosis and treatment.

MATERIALS AND METHODS

Study Design

The study design involved confirming the expression level of RAB10 through Western blot (WB) analysis in both the TCGA database and CRC tissue samples. Cellular phenotype experiments were then carried out to scrutinize the oncogenic role of *RAB10* in CRC *in vitro*. These experiments included the use of CCK-8, Transwell assay, and wound healing assay. Additionally, the activating influence of *RAB10* on the NF-κB signaling pathway was validated through PCR and WB analysis.

Data Acquisition and Processing

The COAD and READ datasets for *RAB10* were obtained from the GEPIA (Gene Expression Profiling Interactive Analysis) online application (http://gepia.cancer-pku.cn/). GEPIA serves as a web server to analyze RNA sequencing expression data from tumors and normal samples sourced from the TCGA and the GTEx projects. The Ethical Review Board at Fujian Cancer Hospital approved all protocols employed in this study, aligning with the principles of the Declaration of Helsinki.

Samples Collection

The three CRC tissue samples were sourced from Fujian Cancer Hospital. Our research focused exclusively on patients who underwent surgical resection alone, excluding those subjected to alternative treatments to avoid interference. None of the patients received chemotherapy or radiotherapy before surgery. All subjects included in the study had confirmed diagnoses through pathological and histological examinations. Tumor staging adhered to the Seventh Edition of the Union for International Cancer Control's tumor-node-metastasis (TNM) staging system. Histologic grading followed the criteria set by the World Health Organization.

Cell Culture

The CRC cell lines, HCT116 and SW480, were procured from the American Type Culture Collection (ATCC, Manassas, VA, USA). HCT116 cells were cultured in McCoy's 5A complete medium, while SW480 cells were cultured in Leibovitz's L-15 complete medium, both maintained at 37°C with 5% CO_2 and saturated humidity. Both culture media were supplemented with 10% fetal bovine serum, 100 U/mL penicillin, and 100 μg/mL streptomycin.

Cell Transfection

Lipofectamine® 3000 transfection reagent (Thermo Fisher, USA) facilitated the transfection of shRNAs or control (NC) into HCT116 and SW480 cells. AC010970.2 (pcDNA-AC010970.2) was employed to transfect *RAB10* into HCT116 and SW480 cells (MOI value = 10). Following 6-12 hours, 1 mL of complete culture medium per well was added. Cells were cultured at 37°C for 12-24 hours, replaced with a conventional culture medium, and continued to be cultured. The transfection efficiency of HCT116 and SW480 cells was observed using a fluorescence microscope after 48h and 72h, respectively. The shRNAs used for transfection are as follows: (1) *RAB10* shRNA1: 5'- CCTCACGTTAGCTGAAGATAT-3'; (2) *RAB10* shRNA2: 5'-GCCTTCAATACTACCTTTATT-3'; (3) *RAB10* shRNA3: 5'-TTGCAAGGGAGCATGGTATTA-3'

qRT-PCR Analysis

RNAiso Plus (Cat#9109, Takara, Dalian, China) facilitated total RNA extraction. The NovoScript® Plus All-in-one 1st Strand cDNA Synthesis SuperMix (QIAGEN, China) was employed for the preparation of mRNA cDNA samples, while the HiScript® 1st Strand cDNA Synthesis Kit (Cat# R111-02, Vazyme, China) was used for miRNA cDNA samples. The expression levels of specific genes were quantified using the NovoStart® SYBR qPCR SuperMix Plus (Cat# E096-01B Novoprotein, China). The relative mRNA content was calculated using the $2^{-\triangle\triangle Ct}$ method.

The sequences of the primers, synthesized by Fuzhou Shangya Biosynthesis (Fuzhou, China), are as follows: (1) *GAPDH* Forward: 5'-GGTGTGAACCATGAGAAGTATGA-3'; (2) *GAPDH* Reverse: 5'-GAGTCCTTCCACGATACCAAAG-3'; (3) *RAB10* Forward: 5'-TGCTCCTGATCGGGGATTC-3'; (4) *RAB10* Reverse: 5'-TGATGGTGTGAAATCGCTCCT-3'; (5) *NF-κB p65* Forward: 5'-TCACCAAAGACCCACCTCACCG -3'; (6) *NF-κB p65* Reverse: 5'- GGACCGCATTCAA GTCATAGTCCC -3'.

Western Blot Analysis

The lysis buffer (Meilunbio, China) was utilized to lyse HK2 cells with various treatments on ice for protein extraction. Protein samples were electrophoresed on polyacrylamide gel (PAGE) and transferred to PVDF. Following blocking, corresponding antibodies were applied for labeling, and the Chemiluminescence imaging system (BIO-RAD, ChemiDoc Touch) was employed to detect the expression of the target protein.

The antibodies used are as follows: The antibodies used are as follows: (1) Beta-actin (1:8000, proteintech, cat# 66009-1-Ig, China); (2) *RAB10* (1:3000, proteintech, cat#11808-1-AP, China); (3) *NFKB* (1:2000, proteintech, cat#60004-I-Ig, China); p-NF-κB (1:2000, Affinity, cat#AF2006, China); (4) HRP-conjugated IgG (proteintech, cat# SA00001-2, China). Each experiment was independently repeated three times.

CCK-8 Assay

HCT116 and SW480 cells were cultured in a 96-well plate at 8 × 104 cells/mL density. Each group comprised 8 composite

wells, and cells were cultured until HCT116 and SW480 cells adhered to the wall. Complete culture media containing different concentrations of drugs according to the specified groups were prepared. HCT116 and SW480 cells were then exposed to the drugs and continued to be cultured. CCK-8 solution (10 μL per well) (Beyotime Biotechnology, Shanghai, China) was added, and the mixture was incubated for 1 hour. The absorbance of each sample at 450 nm was measured using a microplate reader (BIOTEK, Vermont, USA). Each experiment was independently repeated three times.

Transwell Assay

For substrate adhesion, Matrigel was diluted and applied to the upper chamber of the Transwell apparatus. The lower chamber of a 24-well plate was filled with 500 μL of culture media containing 10% FBS. HCT116 and SW480 cells, in a good growth state with a confluence of 70%-80%, were prepared into cell suspensions and inoculated in the upper chamber of the Transwell. After a 24-hour incubation, cells were fixed with 4% paraformaldehyde for 20-30 minutes. The fixative was discarded, and 0.1% crystal violet was added to the chamber for 5-10 minutes of staining. Five visual fields were selected under a 10× microscope to observe and count the cells. Each experiment was independently repeated three times.

Scratch Assay

Post-transfection, cells were cultured under optimal conditions until they reached a confluence of 80% to 90%. Mitomycin C at a 10 μg/mL concentration was applied during the assay to inhibit cell proliferation. The migratory capacity of HCT116 and SW480 cells was assessed by observing their movement into the cell-free zone created by a sterile insert. The closure of this gap was then monitored after a 24-hour duration. Each experiment was independently repeated three times.

Statistical Analysis

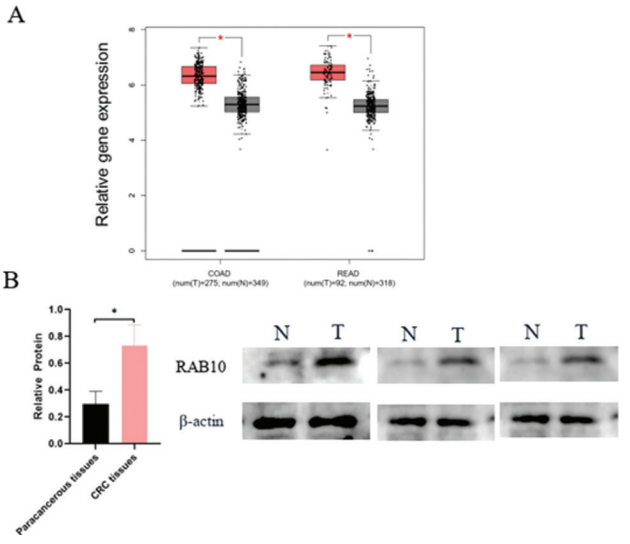
Quantitative data were subjected to statistical analysis using SPSS 20.0 software (IBM Corp., Armonk, N.Y., USA). Each experiment was independently repeated three times. The *t* test analysis was employed to calculate the differences between the two groups. A significance level of $P < .05$ was considered statistically significant.

RESULTS

CRC Exhibits Significant RAB10 Expression

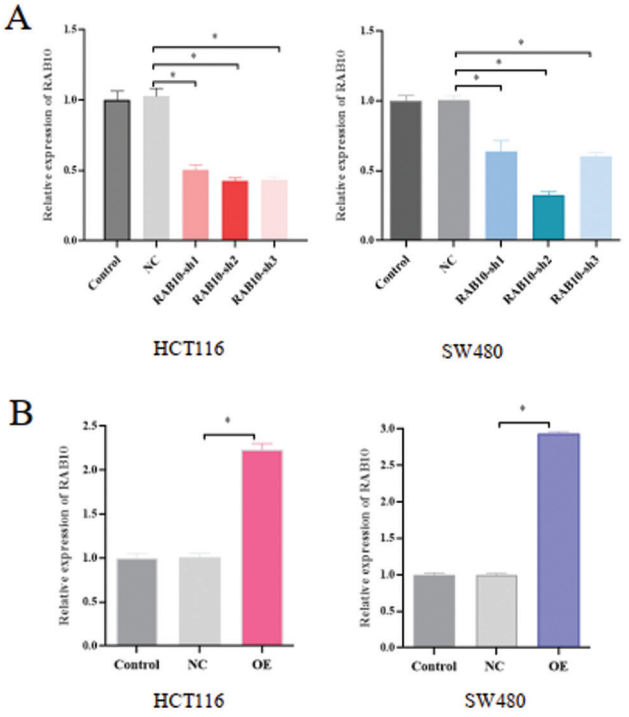
Firstly, we investigated and detected *RAB10* expression in CRC. As depicted in Figure 1A, *RAB10* exhibited considerable overexpression in CRC tissues compared to normal tissues, as observed in the GEPIA database ($P < .05$). Additionally, three pairs of CRC tissue samples and their corresponding paracancerous tissues were collected for WB validation. Figure 1B demonstrates that the protein level of *RAB10* was significantly higher in the CRC tissues than in the paracancerous tissues ($P < .05$), consistent with the expression trend observed in TCGA. These results indicate a significant overexpression of *RAB10* in CRC.

Figure 1. Elevated Expression of *RAB10* in Colorectal Cancer (CRC). (A) The expression level of *RAB10* in COAD and READ datasets in the TCGA database. (B) Protein expression level of *RAB10* in three pairs of paracancerous tissues (N) and colorectal cancer tissues (T). Beta-actin served as the internal reference (n = 3).



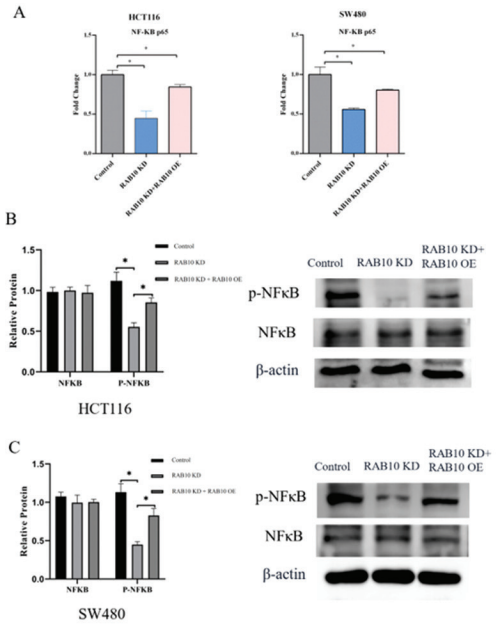
*$P < .05$ between the two groups. The data signifies a statistically significant increase in *RAB10* expression in CRC tissues compared to paracancerous tissues.

Figure 2. Efficiency of *RAB10* Knockdown and Overexpression in CRC Cells. (A) Knockdown efficiency of *RAB10* in CRC cell lines HCT116 and SW480. (B) Overexpression efficiency of *RAB10* in CRC cell lines HCT116 and SW480 (n = 3)



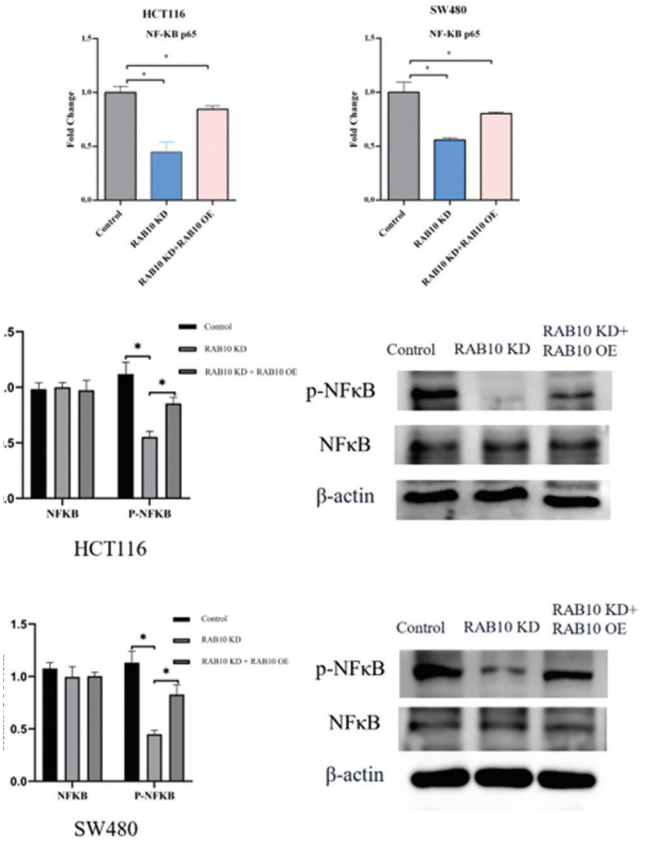
*$P < .05$ between the two groups. The data demonstrates a statistically significant alteration in *RAB10* expression, confirming successful knockdown and overexpression in CRC cell lines.

Figure 3. *RAB10* Drives Colorectal Cancer (CRC) Progression *In Vitro*. (A) The CCK-8 assay illustrating the cell survival rate of CRC cell lines HCT116 and SW480 with *RAB10* knockdown (KD) or *RAB10* knockdown + *RAB10* overexpression (OE) treatments. (B) The transwell assay showcases the migration of HCT116 and SW480 cell lines with *RAB10* knockdown or *RAB10* knockdown + *RAB10* overexpression treatments. (C) Transwell assay presenting the invasion of HCT116 and SW480 cell lines with *RAB10* knockdown or *RAB10* knockdown + *RAB10* overexpression treatments. (D) The wound healing assay demonstrating the migration of HCT116 and SW480 cell lines with *RAB10* knockdown or *RAB10* knockdown + *RAB10* overexpression treatments (n = 3).



*$P < .05$ between the two groups. The data signifies a statistically significant impact of *RAB10* on the proliferation, migration, and invasion of CRC cells *in vitro*.

Figure 4. Figure 4. *RAB10 I*nduces NF-κB Activation in Colorectal Cancer (CRC). (A) mRNA expression level of NF-κB in HCT116 and SW480 cell lines treated with *RAB10* knockdown or *RAB10* knockdown + *RAB10* overexpression. (B-C) Protein expression level of NF-κB in HCT116 (B) and SW480 (C) cells treated with *RAB10* knockdown or *RAB10* knockdown + *RAB10* overexpression (n = 3).



*$P < .05$ between two groups. The data illustrates a statistically significant impact of *RAB10* on the activation of NF-κB in CRC cells.

The Knockdown and Overexpression Efficiency of RAB10 in CRC Cell Lines

In the subsequent step, we explored the function of *RAB10* using HCT116 and SW480 cells. The knockdown efficiency of three types of *RAB10*-shRNAs is depicted in Figure 2A, with RAB10-shRNA2 exhibiting the most effective knockdown ($P < .05$). Therefore, RAB10-shRNA2 was selected for subsequent experiments. Additionally, to investigate the function of *RAB10* further, pcDNA was utilized for the overexpression (OE) of *RAB10* in CRC cell lines. As observed in Figure 2B, the overexpression efficiency of *RAB10* was significantly higher than that in the control or NC groups ($P < .05$). The effective knockdown and overexpression of *RAB10* in the HCT116 and SW480 cell lines establish the groundwork for the subsequent cellular experiments.

RAB10 Promotes the Progression of CRC *In Vitro*

We investigated the oncogenic role of *RAB10* in HCT116 and SW480 cells. As represented in Figure 3A, the cell survival rate decreased in the *RAB10* knockdown (KD) treated group compared to the control group, while it was reversed in the *RAB10* OE group compared with the *RAB10* KD group ($P < .05$). The Transwell assay demonstrated reduced migration and invasion when *RAB10* was knocked down. Interestingly, *RAB10* OE enhanced migration and invasion ($P < .05$) (Figure 3B-3C). Similarly, the wound healing assay also exhibited decreased migration with *RAB10* KD treatment, which was subsequently reversed by *RAB10* OE ($P < .05$) (Figure 3D). These findings prove that the oncogene *RAB10* promotes the progression of CRC *in vitro*.

RAB10 Triggers NF-κB Activation

We also investigated the underlying mechanism of *RAB10* in CRC. In a previous study, *RAB10* was reported to regulate tumor progression,[20] and the NF-κB signaling pathway also regulates cancer progression.[21] Therefore, we subsequently investigated the impact of *RAB10* on NF-κB in CRC. As illustrated in Figure 4A, after knocking down

RAB10 in HCT116 and SW480 cells, the level of NF-κB p65 significantly decreased ($P < .05$).

However, with *RAB10* OE, the level of NF-κB p65 was higher compared to the *RAB10* KD group. Consistently, the protein expression level of pNF-κB in HCT116 and SW480 cell lines significantly decreased in the *RAB10* KD group and increased in the *RAB10* overexpressed group ($P < .05$) (Figure 4B – 4C). These findings suggest that *RAB10* induces the activation of NF-κB in CRC *in vitro*.

DISCUSSION

CRC is a significant malignancy with profound health implications; however, its etiology and pathogenesis remain incompletely understood.[22] The past two decades have witnessed a gradual increase in incidence, with a notable trend towards affecting a younger demographic due to changes in dietary patterns.[1, 23] This has inspired academic interest in understanding the formation and spread of colon cancers.

In our study, *RAB10* emerged as highly expressed in CRC datasets and tissue samples. Moreover, the oncogenic role of *RAB10* was confirmed in the CRC cell lines HCT116 and SW480, where it promoted the growth and migration/invasion of CRC cells. Additionally, *RAB10* was found to induce the activation of NF-κB in CRC *in vitro*. These findings present *RAB10* as a novel genetic biomarker/target with potential implications for diagnosing and treating CRC.

RAB10, a protein-coding gene, falls under the RAS superfamily of small GTP enzymes.[24] Primarily localized in exocytosis and endocytosis compartments, it plays a pivotal role in regulating intracellular vesicular transport.[25] With implications in signal transduction and apoptosis, *RAB10* significantly influences cell proliferation and tumor progression.[26] Notably, different studies have highlighted its upregulation in several cancer types, including breast cancer[29] and ovarian cancer.[27, 28] These findings align with our observations in colorectal cancer.

Furthermore, *RAB10* has been demonstrated to promote malignant proliferation and metastasis in various tumors. For instance, Wang et al.[11] established a link between *RAB10* and hepatocellular carcinoma, highlighting its role in tumor growth and poor prognosis. Additionally, Gang et al.[12] uncovered the involvement of the miR-574-5p/*RAB10* axis in promoting cell proliferation in glioma. Our cellular experiments provided novel evidence that *RAB10* promotes CRC cells' proliferation, migration, and invasion, marking the first verification of its oncogenic role in colorectal cancer.

NF-κB plays an important role in cancer development.[30] Ongoing research highlights its heightened expression in CRC, where NF-κB orchestrates the occurrence, growth, and metastasis of tumor cells by regulating the transcription of corresponding genes.[31, 32] The sustained expression of NF-κB is implicated in promoting COX-2 expression, leading to excessive intestinal mucosal cell proliferation, an early event in CRC development critical for invasion and metastasis.[33]

Among NF-κB›s diverse physiological functions is the inhibition of apoptosis-inhibiting genes' transcription, preventing the onset of cell apoptosis.[34, 35] In our research, a novel finding emerges as we identify, for the first time, that *RAB10* induces the activation of NF-κB in CRC. This groundbreaking finding positions *RAB10* as a potential treatment target in CRC, offering a promising avenue for therapeutic interventions in malignancies.

Study Limitations

While our study provides valuable insights into the role of *RAB10* in colorectal cancer and its impact on NF-κB activation, it is essential to acknowledge certain limitations. Firstly, our investigation primarily relied on *in vitro* cellular experiments, and extrapolating these findings to *in vivo* scenarios requires caution. Additionally, our study focused on specific cellular behaviors, such as proliferation, migration, and invasion, and did not delve into the broader systemic effects in a living organism. Furthermore, the complex molecular interaction within the CRC microenvironment is complex, and our study does not cover the multifaceted dynamics involved. Addressing these limitations in future research will contribute to a more nuanced understanding of the implications and potential applications of *RAB10* as a treatment target in CRC.

CONCLUSION

In conclusion, our study has revealed a significant elevation of *RAB10* in colorectal cancer. Furthermore, this study demonstrated the oncogenic role of *RAB10* through the activation of NF-κB in CRC. This identification positions *RAB10* as a novel genetic biomarker, holding potential implications for the diagnosis and treatment of CRC. However, it is crucial to acknowledge certain study limitations. Including an animal model for validation and exploring the prognostic value of *RAB10* are imperative aspects that warrant further investigation. These avenues for future research will undoubtedly enhance the depth and applicability of our findings in the context of CRC.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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