Original Article

DOI: 10.5582/ddt.2025.01022

Trpa1 knockout favors colon tumorigenesis in dextran sulfate sodium (DSS)-induced colitis mice

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SUMMARY: Chronic inflammation in the colon has been recognized as a key pathogenic mechanism driving colorectal cancer development. TRPA1 (transient receptor potential ankyrin 1), a key member of the TRP cation channel superfamily, is closely implicated in inflammatory processes and has emerged as a promising therapeutic target for anti-inflammatory drug development. However, the precise role of TRPA1 in colorectal carcinogenesis and its potential as a therapeutic target for colorectal cancer (CRC) remain incompletely understood. In this study, we demonstrate that *Trpa1* knockout significantly exacerbates DSS-induced colitis-associated tumorigenesis in murine models, a phenomenon mechanistically linked to *Trpa1* deficiency-mediated aggravation of inflammatory bowel pathology. RNAseq and gene knockout effect analysis revealed a consistently low expression pattern of *TRPA1* across colorectal cancer cell lines (n = 58, median log2(TPM+1) = 0.025), with limited impact on cell viability upon *TRPA1* knockout. Notably, analysis of human clinical specimens revealed substantial downregulation of TRPA1 expression in CRC compared to adjacent normal tissues. Kaplan-Meier survival analysis further indicated that patients with TRPA1-low tumors exhibited significantly poorer overall survival outcomes. These collective data suggest a tumor-suppressive role for TRPA1 in colorectal carcinogenesis, potentially through its immunomodulatory functions within the colitis-cancer transformation axis.

Keywords: TRPA1, colitis, colon cancer, CRC, carcinogenesis, DSS

1. Introduction

Colorectal cancer (CRC), a gastrointestinal malignant tumor, poses a severe threat to global human health. Epidemiological studies reveal CRC currently ranks as the third most commonly diagnosed cancer and the second leading cause of cancer-related mortality worldwide (*1,2*). According to the 2020 Global Cancer Statistics report, approximately 1.93 million new CRC cases and 0.94 million related deaths were recorded globally, accounting for nearly 10% and 9.4% of total cancer incidence and fatalities respectively (*3,4*). These epidemiological patterns underscore the critical need for elucidating the underlying pathogenesis of CRC, which holds paramount importance for developing effective prevention strategies and therapeutic interventions.

The pathogenesis of CRC stems from a complex interplay between genetic susceptibility, modifiable lifestyle factors (particularly alcohol use, red meat consumption, and obesity), and comorbidities including inflammatory bowel disease (IBD) and diabetes mellitus (*3,5,6*). Compelling epidemiological evidence indicates a particularly strong association between IBD and CRC susceptibility, with IBD patients (encompassing both ulcerative colitis and Crohn's disease) exhibiting 2-3-fold elevated CRC risk compared to the general population (*7-9*). Emerging evidence reveals that the persistent inflammatory milieu facilitates carcinogenesis through dysregulated activation of cytokine/chemokine networks and immune cell populations, collectively orchestrating tumor initiation, progression, and metastasis – a pathological continuum formally designated as the "inflammation-cancer transformation" (*10*). Systematic investigation into the molecular mechanisms underlying chronic inflammation-driven malignant transformation of colonic epithelial cells is imperative for advancing our understanding of CRC tumorigenesis and progression.

TRPA1 (transient receptor potential ankyrin 1), a pivotal member of the TRP cation channel superfamily, exhibits distinctive homotetrameric architecture with six transmembrane domains, enabling its remarkable capacity to integrate multimodal exogenous stimuli ranging from thermal fluctuations to chemical irritants and mechanical stress (*11,12*). This polymodal

receptor demonstrates endogenous activation through inflammatory mediators such as bradykinin and trypsin (*13*). Mechanistically, TRPA1 drives calcium influx to potentiate the release of neuropeptides (*e.g.*, substance P) and pro-inflammatory cytokines (*e.g.*, IL-6, TNF-α), thereby enhancing nociceptor sensitization through autocrine/paracrine signaling pathways (*14*). These pathophysiological insights not only underscore the central regulatory role of TRPA1 in inflammatory pain transduction but also identify it as a promising therapeutic target for the development of analgesic and anti-inflammatory drugs (*15-17*). However, the precise role of TRPA1 in colorectal carcinogenesis remains incompletely understood, and its potential as a therapeutic target for colon cancer requires further validation.

In this study, we utilized *Trpa1* knockout ($Trpa1^{-/-}$) mice to investigate the role of this molecule in inflammation-driven colorectal carcinogenesis and assessed the impact of *TRPA1* genetic ablation on colorectal cancer cell survival. Additionally, by analyzing TRPA1 expression in human CRC tissues and its correlation with patient prognosis, we comprehensively analyzed the role of this molecule in the pathology of CRC.

2. Materials and Methods

2.1. Agents and animals

DSS (molecular weight: 40,000) and azoxymethane (AOM) were purchased from Shanghai Aladdin Biochemical Technology Co., Ltd. (Shanghai, China). $Trpa1^{+/-}$ C57BL/6N mice were purchased from Cyagen Biosciences Co., Ltd. (Jiangsu, China). The $Trpa1^{-/-}$ and wild type C57BL/6N mice used in the experiment were bred from the above-mentioned heterozygous mice. All experimental animals were housed in a specific pathogen-free environment, and the mice had free access to water and food. All experimental procedures strictly adhered to international guidelines for the care and use of laboratory animals.

2.2. The model of inflammation-tumor transformation

Female wild-type and $Trpa1^{-/-}$ C57BL/6N mice (7-8-week-old) were utilized in this study. Animals were divided into three groups based on genotype and treatment protocols: (1) wild-type control group (NC group, n = 5), receiving intraperitoneal injection of an equivalent volume of saline; (2) wild-type DSS-treated group (WT+DSS group, n = 11); and (3) $Trpa1^{-/-}$ DSS-treated group ($Trpa1^{-/-}$+DSS group, n = 9). The latter two groups were intraperitoneally injected with 10 mg/kg body weight of azoxymethane (AOM) for chemical induction on day 0 of the experiment. Starting from day 5, the WT+DSS and $Trpa1^{-/-}$+DSS groups were subjected to cyclic intervention with 1% DSS solution and sterile drinking water (Figure 1A), establishing a chronic colitis model through intermittent DSS exposure. The NC group received sterile drinking water throughout the experimental period. Body weight was monitored every 3 days, and the characteristics of the feces and the presence of blood in the stool were recorded regularly.

At the experimental endpoint, mice were sacrificed, and colonic tissues were fully dissected. The length from the anorectal junction to the cecal base was measured, and macroscopic tumor nodules were counted under a dissecting microscope. Colon tissue samples were fixed in 4% paraformaldehyde, followed by paraffin embedding, sectioning, and hematoxylin-eosin (HE) staining for histopathological analysis.

2.3. The model of subacute colitis

This study utilized 7-8-week-old female C57BL/6N mice, including wild-type and $Trpa1^{-/-}$ strains. Animals were divided into three groups based on genotype and treatment protocols: wild-type control group (NC group, n = 8), wild-type DSS-treated group (WT+DSS group, n = 8), and $Trpa1^{-/-}$ DSS-treated group ($Trpa1^{-/-}$+DSS group, n = 8). The experimental protocol comprised two phases: 1% DSS solution was administered *via* free drinking water from days 0-30, followed by 1.5% DSS solution from days 31-42. Control animals received sterile drinking water throughout the 42-day period.

Systematic monitoring was conducted every three days, encompassing body weight measurement and fecal consistency assessment, with disease severity quantified using the Disease Activity Index (DAI). Post-sacrificed, colonic specimens were collected. Colon length was measured from the anorectal junction to the cecal base, and histopathological analyses were performed on colonic tissues, including HE staining, Alcian blue (AB) staining, and periodic acid-Schiff (PAS) staining.

2.4. Histopathological analyses

Histochemical staining of murine colonic tissues, including HE, AB, and PAS, was performed using Solarbio (Beijing, China) kits. Tissue sections were dewaxed in xylene and rehydrated through a graded ethanol series (100%, 95%, 80%, 70%) prior to staining. For HE, sections were stained with Mayer's hematoxylin for 5 min, differentiated in 0.5% acid-alcohol for 2-5 sec, rinsed in running water for 20 min for nuclear bluing, and counterstained with 1% aqueous eosin Y for 1 min. AB staining involved 3% acetic acid pretreatment (3 min), incubation with 1% Alcian blue 8GX (in 3% acetic acid) in a humid chamber (30 min, RT), followed by three 1-min distilled water rinses and Nuclear Fast Red counterstaining (5 min). PAS staining protocol comprised

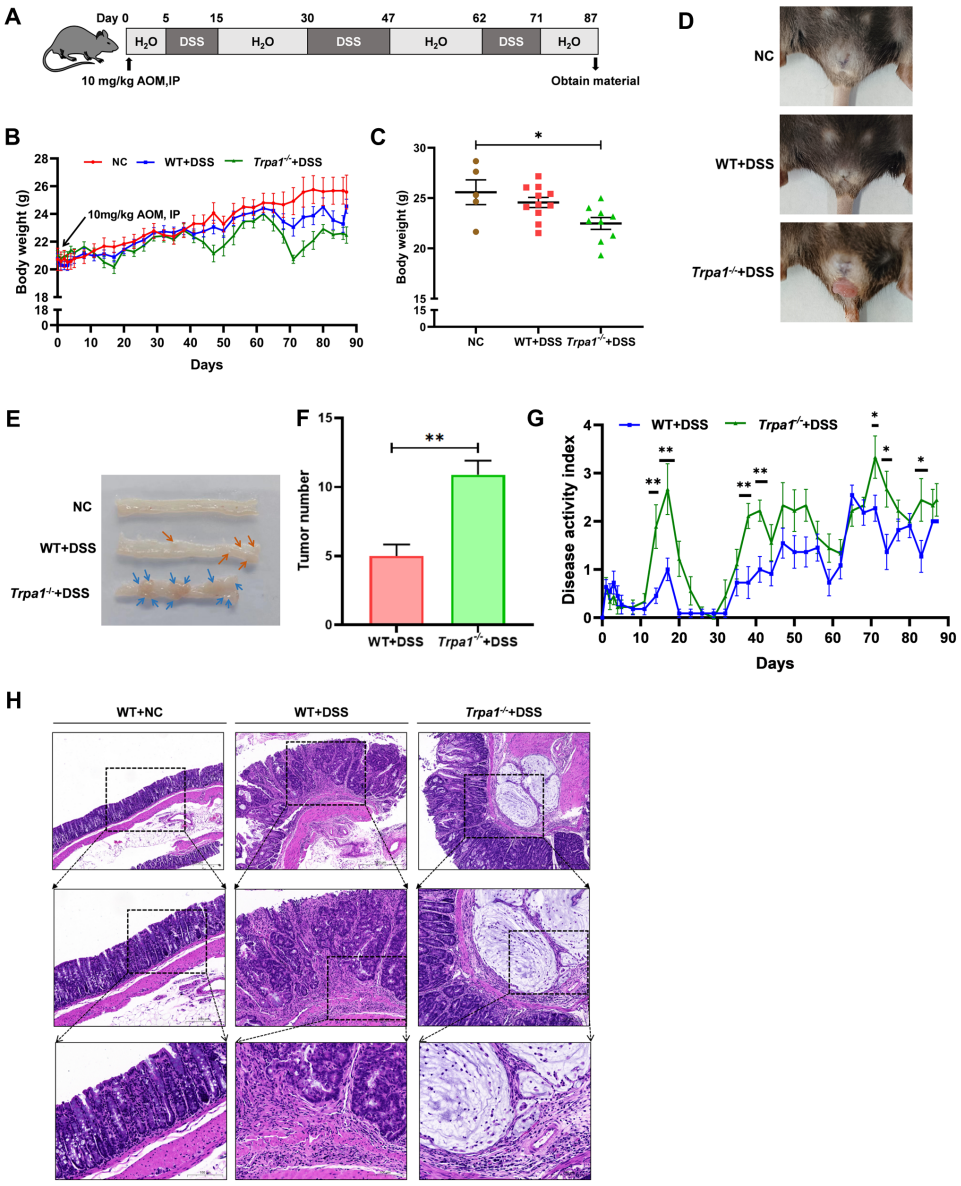

Figure 1. ***Trpa1*** **deficiency promotes colitis-associated tumorigenesis in mice.** Colitis-associated tumorigenesis model was established by intraperitoneal injection of 10 mg/kg AOM followed by DSS induction. The NC group received saline injection and drank sterile drinking water, while the WT+DSS and *Trpa1*$^{-/-}$+DSS groups were injected with AOM and alternately administered 1% DSS and drinking water. (**A**) Schematic diagram for the establishment of the AOM/DSS-induced colitis-associated tumorigenesis model. (**B**) Body weight changes of mice in each group during the experiment. (**C**) Comparison of body weight differences among groups before sacrifice. (**D**) Representative images of anal changes in mice from each group. (**E** and **F**) The number of colonic tumors in each group. (**G**) DAI scores of model mice. (**H**) HE staining of colonic tissues from the AOM/DSS-induced tumorigenesis model, with magnifications of 100×, 200×, and 400× from top to bottom. *$p < 0.05$, **$p < 0.01$.

oxidation with 1% periodic acid (5-8 min), Schiff reagent incubation (15 min, dark), and Gill's hematoxylin nuclear staining (1-2 min) with acid-alcohol differentiation. All sections were dehydrated through an ethanol-xylene gradient, mounted with neutral resin, air-dried, and digitally imaged using a 3DHISTECH (Hungary) panoramic scanner at 20× magnification.

2.5. Analysis of TRPA1 expression and gene knockout effects in CRC cells

This study leveraged the DepMap Public 24Q2 dataset to analyze RNA-seq profiles and CRISPR-Cas9 knockout screening data targeting TRPA1, with cell viability metrics quantified from CRC cell lines (*18*). Utilizing Python (v3.12.2), data preprocessing and integration were performed with pandas, followed by matrix operations executed *via* numpy. Pearson correlation coefficients and their statistical significance between TRPA1 expression levels and post-knockout cell viability scores were calculated using scipy.stats. Data visualization was implemented through matplotlib.pyplot to generate scatter plots illustrating gene expression-phenotypic effect correlations.

2.6. Analysis of TRPA1 expression in CRC tissues and prognosis of patients

TCGA database was utilized for RNA sequencing data and clinical information about CRC. R-4.4.3-win were employed for the following data analysis. Analysis was performed using the limma package to identify differential expression of TRPA1 between cancer tissues and matched adjacent normal tissues. Visualization of TRPA1 expression patterns was achieved through ggplot2 and ggpubr packages, generating scatter plots and paired boxplots comparing tumor-normal pairs. The CRC cohort was stratified into high- and low-expression subgroups based on median TRPA1 expression levels. Kaplan-Meier survival analysis with log-rank testing (implemented *via* survival and survvminer packages) evaluated the correlation between TRPA1 expression and overall survival (OS).

2.7. Statistical analyses

The animal experimental data were visualized using GraphPad Prism 8.0. Pathological section images were captured and exported *via* SlideViewer software after scanning with a panoramic tissue cell scanner, and colonic goblet cells were counted using ImageJ. Statistical differences were analyzed *via* One-way ANOVA or *t*-test in SPSS. Data are shown as the mean ± standard error of the mean (Mean ± SEM). Statistical significance was defined as $p < 0.05$.

3. Results

3.1. *Trpa1* knockout favors colorectal tumorigenesis in mice with colitis

As outlined in Figure 1A, we successfully established an AOM/DSS-induced mouse model of colitis-associated tumorigenesis. During the experimental period, both WT+DSS and *Trpa1*$^{-/-}$+DSS groups exhibited body weight reduction compared to the control group, with *Trpa1*-knockout mice demonstrating a more pronounced weight loss trend (Figure 1B). Pre-sacrificed body weight measurements revealed that *Trpa1*$^{-/-}$+DSS mice showed 12.1±2.3% reduction compared to the NC group ($p < 0.05$) and 8.5 ± 2.4% reduction relative to the WT+DSS group (Figures 1C). Notably, severe diarrhea was observed in the *Trpa1*$^{-/-}$+DSS group as early as day 9 of the experiment, while only occasional soft stools were detected in WT+DSS group counterparts during the same period. Prolonged DSS intervention led to gradual manifestation of intestinal hemorrhage symptoms in both groups. By the experimental endpoint, rectal prolapse was observed in 22% of *Trpa1*$^{-/-}$+DSS mice, a pathological phenotype completely absent in the WT+DSS group (Figure 1D). Anatomical analysis demonstrated a significantly increased tumor burden in *Trpa1*-deficient mice, with the mean tumor count (10.9 ± 1.0 *vs* 5.0 ± 0.8) being markedly higher than that in the wild-type model group ($p < 0.01$) (Figures 1E-1F). Additionally, these animals exhibited colonic dilation and cecal atrophy. Quantitative DAI assessment indicated significantly elevated scores in *Trpa1*$^{-/-}$+DSS group throughout the induction period, suggesting intensified colonic inflammatory responses compared to WT+DSS group (Figure 1G).

Pathological evaluation through HE staining of colonic tissues from three experimental groups further validated differential progression in inflammation-tumor transformation. NC group maintained intact mucosal architecture with orderly arranged crypts and no pathological alterations (Figure 1H). AOM/DSS model groups universally exhibited tumor characteristics, including crypt structural destruction, glandular structural disorganization, and substantial inflammatory cell infiltration. Notably, *Trpa1*-deficient mice displayed exacerbated pathological progression. Histological analysis revealed mucinous vacuole formation in 44.4% of *Trpa1*$^{-/-}$+DSS specimens, suggesting the potential formation of mucinous adenocarcinoma (Figure 1H). These pathological features indicate that *Trpa1* gene deletion accelerates malignant progression in inflammation-associated colorectal tumor.

3.2. *TRPA1* is a non-essential gene for CRC cell survival

The above findings suggest that TRPA1 plays a critical role in tumor initiation suppression. Based on this phenotypic characteristic, we further investigated its regulatory effects on cancer cell-autonomous proliferation. Utilizing the DepMap database (2024Q2 release), we identified 58 human colorectal cancer cell lines with both whole-transcriptome sequencing data and genome-wide CRISPR-Cas9 loss-of-function screening data. Results revealed a consistently low expression pattern of *TRPA1* across colorectal cancer cell lines (median log2(TPM+1) = 0.025), with limited impact on cell viability upon *TRPA1* knockout (CRISPR scores ranging from -0.3 to 0.3, Figure 2). Furthermore, no

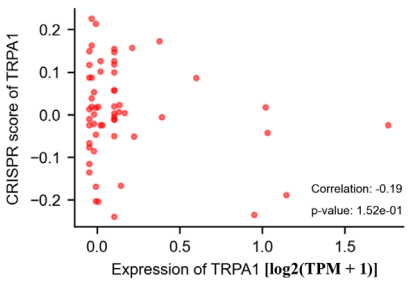

Figure 2. Correlation analysis between TRPA1 expression levels and CRISPR scores in colorectal cancer cells. Pearson correlation coefficients and their statistical significance between TRPA1 expression levels (log2(TPM+1)) and post-knockout cell viability scores were calculated.

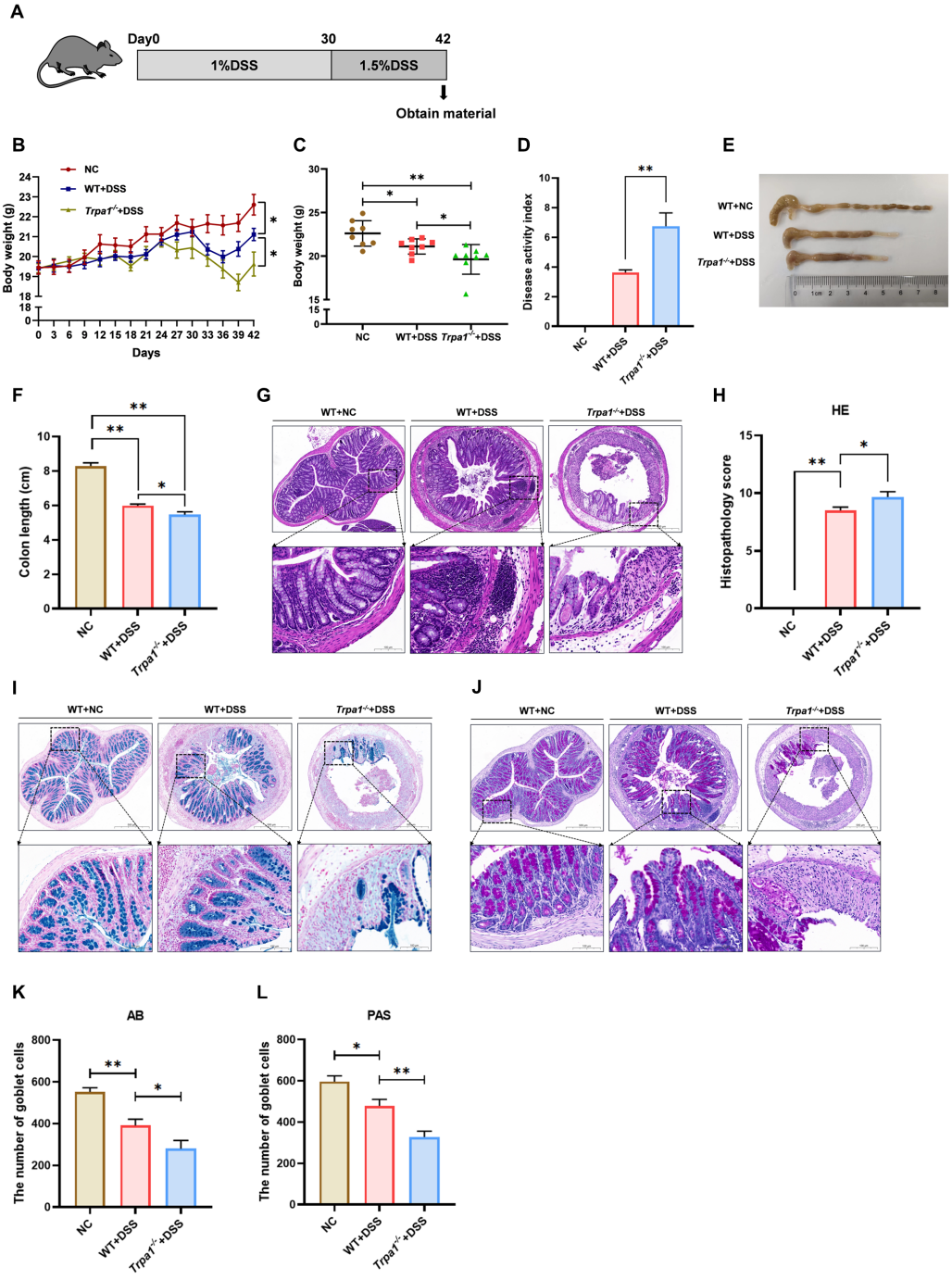

Figure 3. *Trpa1* deficiency exacerbates colitis in mice. Colitis was induced by 1%-1.5% DSS. The NC group was allowed free access to sterile drinking water, while the WT+DSS and *Trpa1*$^{-/-}$+DSS groups were given free access to 1%-1.5% DSS to induce colitis. (**A**) Schematic diagram of the DSS-induced subacute colitis model in mice. (**B**) Changes in body weight of mice in each group over time. (**C**) Comparison of body weight differences among groups before sacrifice. (**D**) Comparison of DAI scores among groups before sacrifice. (**E** and **F**) Representative images of colons in each group, as well as colon length measurement and comparison. (**G**) HE staining of colonic cross-sections from each group, with images shown at 100× and 400× magnification. (**H**) Histopathological scoring of HE-stained colonic tissues in each group. (**I and J**) Representative images of AB (I) and PAS (J) staining of colonic cross-sections from each group (100× and 400× magnification). (**K** and **L**) Quantification of goblet cells in colonic cross-sections stained with AB (K) and PAS (L) in each group. *$p < 0.05$, **$p < 0.01$.

significant correlation was observed between TRPA1 expression levels and knockout-mediated viability changes ($r = 0.19$, $p = 0.15$, Figure 2). These data indicate that *TRPA1* is unlikely to function as a core essential gene for colorectal cancer cell survival, and its tumor-suppressing effects may arise through non-cell-autonomous mechanisms, potentially involving the regulation of immune-epithelial interactions within the tumor microenvironment.

3.3. TRPA1 deficiency exacerbates DSS-induced colitis in mice

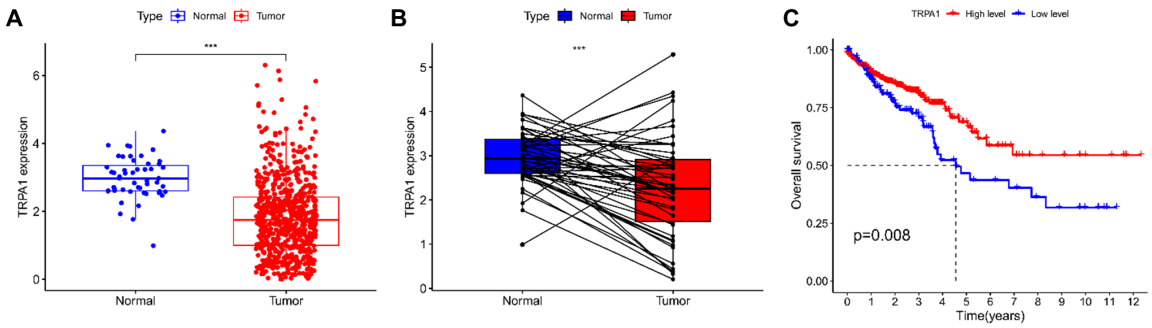

Figure 4. Clinical relevance of TRPA1 expression in CRC patients Differential expression analysis of TRPA1 in unpaired (**A**) and paired (**B**) samples from the TCGA-COAD/READ cohort. (C) Overall survival analysis between high- and low-TRPA1 expression groups. ***$p < 0.001$.

Our previous findings suggested a potential suppressive role of TRPA1 in colitis-associated tumorigenesis, while its lack of direct impact on CRC cell proliferation implies that its anti-tumorigenic effects may be mediated through inflammatory regulation. To elucidate the role of TRPA1 in colitis, we established a subacute colitis model using 1.0%-1.5% DSS-induced ulcerative colitis, following the protocol outlined by Li *et al.* (*19*) (Figure 3A). During the experimental period, NC group mice exhibited steady weight gain, normal feeding/drinking behaviors, and maintained fecal consistency. In contrast, both WT+DSS and *Trpa1*$^{-/-}$+DSS groups developed diarrhea by day 15, with *Trpa1*-deficient mice displaying earlier onset of hematochezia, reduced locomotor activity, and accelerated weight loss (Figure 3B). Terminal measurements revealed significantly lower body weight ($p < 0.05$) and elevated DAI scores ($p < 0.01$) in *Trpa1*$^{-/-}$+DSS mice compared to WT+DSS controls (Figures 3C-3D). Colonic length analysis demonstrated significant colon shortening in DSS-treated groups (Figure 3E), with *Trpa1*$^{-/-}$+DSS mice exhibiting a 8.3% greater reduction in colon length than WT+DSS counterparts (5.5±0.2 cm *vs.* 6.0±0.1 cm, $p < 0.05$; Figure 3F).

Histopathological evaluation *via* HE staining (Figure 3G) revealed distinct mucosal stratification and intact crypt architecture in NC mice. DSS-challenged groups exhibited severe epithelial damage, including crypt distortion, marked goblet cell depletion, and dense submucosal lymphocytic infiltration. Notably, *Trpa1*$^{-/-}$+DSS mice displayed exacerbated pathology characterized by near-complete epithelial denudation, lymphoid follicle formation, and a 1.2-fold increase in histological severity scores ($p < 0.05$; Figure 3H). AB/PAS staining (Figures 3I-3J) confirmed goblet cell loss across experimental groups, with *Trpa1* deficiency amplifying DSS-induced depletion (Figures 3K-3L).

These collective findings demonstrate that *Trpa1* ablation significantly aggravates DSS-driven ulcerative colitis. The amplified inflammatory milieu in *Trpa1*-deficient mice provides a mechanistic link between enhanced colitis severity and accelerated neoplastic transformation observed in prior experiments.

3.4. Clinical relevance of TRPA1 expression in CRC patients

To establish the clinical significance of TRPA1 in human colorectal carcinogenesis, we systematically analyzed its expression patterns and prognostic value using the TCGA-COAD/READ cohort ($n = 647$ tumor tissues *vs.* $n = 51$ matched adjacent normal tissues). RNA sequencing data revealed significant downregulation of TRPA1 in malignant tissues compared to non-tumor counterparts ($p < 0.001$; Figures 4A-4B). Stratification of patients by median TRPA1 expression demonstrated striking survival disparities. Kaplan-Meier analysis showed that the high-TRPA1 subgroup ($n = 324$) had significantly prolonged overall survival compared to the low-expression cohort ($n = 323$) ($p = 0.008$; Figure 4C).

These findings align with our preclinical models, collectively indicating that TRPA1 functions as a tumor suppressor in colorectal cancer pathogenesis, with its loss correlating with aggressive disease progression and poor clinical outcomes.

4. Discussion

The role of TRPA1 in CRC remains controversial. Some studies propose that TRPA1 promotes colon cancer cell proliferation by coupling with the Na^+/Ca^{2+} exchanger 1 (NCX1) to maintain calcium homeostasis (*20*). However, other research suggests that TRPA1 activation-induced Ca^{2+} influx may trigger apoptosis under specific conditions. For instance, in metastatic colorectal cancer cells, oxidative stress-activated TRPA1 mediates mitochondrial dysfunction and apoptosis (*21*). Our study investigated the role of TRPA1 in tumor initiation and progression from the perspective of inflammation-cancer transformation. Our findings demonstrated that *Trpa1* knockout exacerbated colon tumor development, with both tumor number and size increased compared to wild-type mice. Despite the limited impact of TRPA1 deletion on colorectal cancer survival, we hypothesize

that TRPA1 may indirectly suppress tumorigenesis by mitigating inflammatory responses.

The role of TRPA1 in inflammatory processes is complex. While TRPA1 is generally considered pro-inflammatory in acute settings—where its knockout or inhibition attenuates inflammation—our observations in a three-month chronic inflammation-tumor transformation model indicated more severe colonic inflammation in *Trpa1*-knockout mice compared to wild-type counterparts. This suggests a potential dichotomy in TRPA1 functionality between acute and chronic inflammatory contexts. To further clarify, we established a subacute colitis model and confirmed that TRPA1 retains its anti-inflammatory role in this system. Our previous data indicated that *Trpa1* knockout increased the proportion of Th1 cells in subacute colitis mice, thereby exacerbating inflammatory progression (data not shown). Consistent with our findings, Samuel Bertin *et al*. demonstrated that dual knockout of *IL-10* and *Trpa1* in mice resulted in significantly aggravated spontaneous colitis compared to single *IL-10* knockout controls, a phenomenon mechanistically linked to *Trpa1* deletion-driven enhancement of Th1 cell differentiation (*22*). Thus, TRPA1 may exert opposing roles in acute versus chronic colitis pathology. The tumor-promoting effects of TRPA1 deficiency likely operate indirectly by amplifying pro-inflammatory pathways that facilitate inflammation-tumor transformation in colonic epithelium.

Previous studies suggest that TRPA1 exerts a direct tumor-suppressive role in colon cancer cells, wherein its activation promotes Ca^{2+} influx, leading to tumor cell death *via* mitochondrial dysfunction and apoptosis (*21*). Thus, an alternative explanation proposes that *Trpa1* knockout exacerbates inflammatory responses (which drive inflammation-to-tumor transformation) while simultaneously eliminating TRPA1-mediated tumor cell cytotoxicity, collectively promoting colorectal tumorigenesis. However, our study revealed notably low TRPA1 expression in CRC cells, implying that its direct tumor-suppressive effects may be minimal. Instead, TRPA1 likely suppresses tumorigenesis primarily through attenuating chronic colonic inflammation.

These collective data suggest a tumor-suppressive role for TRPA1 in colorectal tumorigenesis, potentially through its immunomodulatory functions within the colitis-tumor transformation axis. The inverse relationship between TRPA1 expression and malignant features across experimental systems underscores its potential as both a prognostic biomarker and a therapeutic target for inflammation-associated colorectal malignancies.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received March 11, 2025; Revised May 19, 2025; Accepted May 27, 2025.

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Released online in J-STAGE as advance publication June 20, 2025.