Original Article

TRIM29 is differentially expressed in colorectal cancers of different primary locations and affects survival by regulating tumor immunity based on retrospective study and bioinformatics analysis

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Background: In colorectal cancer (CRC) patients, different primary tumor locations caused distinct prognosis and clinicopathological features. It is necessary to identify specific tumor markers according tumor site. Our previous work has identified differentially expressed genes between CRC and adjacent normal tissues, in which only TRIM29 was differently expressed between right colon cancer (RCC) and left colon cancer (LCC) patients. Rectal cancer (RECC) was not included in this latter study and the effects of TRIM29 on the survival with RCC and LCC patients were not investigated. This study further verified TRIM29 expression through Gene Expression Omnibus (GEO) database and our retrospective study. The role of TRIM29 on survival according tumor sites was also explored. Furthermore, the molecular mechanisms of TRIM29 were explored.

Methods: The GEO dataset was used to confirm the differential expression of TRIM29 in proximal and distal cancers. Moreover, TRIM29 were assess using immunohistochemistry (IHC) in 227 cases to observe the correlation between TRIM29 and tumor site. The relationship between TRIM29 and the clinicopathologic features was investigated according tumor sites. Furthermore, the disease-free survival (DFS) and overall survival (OS) was analyzed using the Kaplan-Meier method to assess the prognostic value of TRIM29. Finally, bioinformatics analysis was used to explore the molecular mechanisms. The Tumor-Immune System Interactions and Drug Bank database (TISIDB) was used to analyze the correlations between TRIM29 expression and tumor immune functions. The correlation of TRIM29 with tumor infiltrating lymphocytes or mismatch-repair-proficient/mismatch-repair-deficient (pMMR/dMMR) status was also investigated.

Results: TRIM29 expression was significantly higher in patients with RCC ($P<0.001$). RCC patients with high TRIM29 tended to be older, male, in stage III–IV, with N+ staging, and intestinal obstruction ($P<0.001$, $P<0.001$, $P<0.001$, $P<0.001$, and $P=0.010$, respectively). High TRIM29 expression was associated with an increased risk of recurrence/metastasis and death, only in RCC patients ($P=0.020$ and $P<0.001$). Functional annotations and immune activity analysis showed that TRIM29 is related to tumor infiltrating lymphocytes and immune dysfunction.

Conclusions: TRIM29 plays varying roles in patients with different tumor sites. TRIM29 is correlated with the clinicopathological features and prognosis in RCC patients. Indeed, TRIM29 may serve as a new biomarker for RCC patients.

Keywords: TRIM29; colorectal cancer (CRC); primary tumor location; tumor immunity; survival

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Introduction

Colorectal cancer (CRC) ranks third in incidence and death rate among all malignant tumors (1). The location of CRC has become an important topic. Since proximal and distal CRC arises through different embryonic layers, Bufill *et al.* suggested that these are two distinct types of cancers (2). Furthermore, rectal cancer (RECC) differs from colon cancer in anatomy, aetiology, clinical manifestation, biological features, treatment response, and clinical outcomes (3,4). Therefore, dividing CRC into left colon cancer (LCC) and right colon cancer (RCC) may be overly simplistic and most specialists now classify CRC into LCC, RCC, and RECC. There are obvious differences in clinicopathologic features and survival depending on the location of the tumors. These differences were first observed between LCC and RCC in metastasis CRC patients (5). The differences in survival between patients with different primary tumor locations may be due to various sensitivities to target drugs, as suggested in the FIRE-3 and CALGB/SWOG 80405 trials (6). A study has also shown that primary tumor location may be predictive of early stage and locally advanced CRC (7). We hypothesize that the differences not only result from various sensitivities to target drugs, but may be due to the molecular mechanisms involved (8). Papagiorsis' study showed that there were different chromosomal variations and epigenetic changes in LCC and RCC patients, with at least 1,000 genes in the major signaling pathways significantly differentially expressed (9). The key oncogenes and tumor suppressors were differentially expressed, including APC, TP53, KRAS, and EGFR (9-11). In recent years, novel biomarkers were found to be differentially expressed between LCC and RCC, including G protein subunit gamma 4 (GNG4), Transcobalamin 1 (TCN1), and dual-specificity phosphatase-2 (DUSP2) (12,13). However, to date, the driver gene and the mechanisms underlying the differences observed in patients with different tumor locations remain unclear. Our previous study identified an upregulated gene (TRIM29) in RCC patients compared to LCC patients (14). TRIM29 has verified as an oncogene in many kinds of cancers, and our previous study has confirmed it play an important role in the tumorigenesis and development of CRC. More interestingly, we also found it differently expressed between LCC and RCC. However, the sample size in the latter study was small and the expression of TRIM29 was not investigated in RECC patients. Furthermore, the effects of TRIM29 on the survival of patients with different tumor locations were not examined. This current study further confirmed that TRIM29 expression is highly expressed in proximal CRCs compared to distal CRCs by using a large dataset from the GEO database. The differing roles of TRIM29 were examined in patients with tumors in three different sites. More importantly, the potential molecular mechanisms of TRIM29 were investigated. Reactome/Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of the hub genes related to TRIM29 was conducted using the String database. Combined with the KEGG pathway enrichment analyses in our previous study (15), we hypothesized that TRIM29 is significantly correlated to immune activity. Interestingly, it has been reported that the immune microenvironment is different in patients with different tumor locations (16,17). Thus, the correlation between TRIM29 expression and immune function was assessed using the Tumor-Immune System Interactions and Drug Bank database (TISIDB). The findings herein may reveal the potential molecular mechanisms of CRC according to tumor site. TRIM29 may be a prognostic marker of RCC and a predictive marker of immunotherapy. We present the following article in accordance with the REMARK reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-365/rc).

Methods

This study mainly includes four steps. Firstly, we proved TRIM29 were highly expressed in RCC patients. A GEO database was used to analyze TRIM29 expression in proximal and distal CRCs. Reverse transcription polymerase chain reaction (RT-PCR), IHC and Western blotting were used testing TRIM29 expression level to

classify TRIM29 was significantly highly expressed in RCC patients. Secondly, a retrospective analysis of 227 patients was conducted to analyze the value of TRIM29 in RCC, LCC and RECC patients respectively. The relationship between TRIM29 and clinicopathological parameters was also explored. Kaplan-Meier analysis was used to discuss the relationship between TRIM29 expression/clinicopathological features and survival. Thirdly, Bioinformatics analysis were used to explore the potential molecular mechanisms and the results focused that TRIM29 may modulate tumor-associated immunity. At last, GEO database and TISIDB were used to explore the relationship between TRIM29 and tumor-associated immunity. H&E staining was applied to observe the tumor infiltrating lymphocytes

Access to public data

An expression profiling dataset [GSE39582(GPL570 platform)], containing 233 proximal colorectum samples and 350 distal colorectum samples, was obtained from the GEO database (http://www.ncbi.nlm.nih.gov/geo). The TRIM29 expression level, tumor location, and the mismatch-repair-proficient/mismatch-repair-deficient (pMMR/dMMR) status of each sample in the dataset was recorded and analyzed.

Patient characteristics

The medical records of 227 patients with CRC, who were treated at the Hebei Medical University Fourth Affiliated Hospital between January 2008 and January 2015, were retrospectively reviewed. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The collection of samples in this study was approved by ethics board of Hebei Medical University Fourth Affiliated Hospital (No. 2017MEc089). Informed consent was obtained from all patients. The following inclusion criteria were applied: (I) patients with pathologically confirmed CRC; and (II) patients who had undergone curative surgical resection (primary tumor and all metastases were excised together). The following patients were excluded: (I) patients with two or more primary tumors; (II) patients with adenocarcinoma and other types of malignancies affecting the appendix; (III) patients with tumors of unknown location; and (IV) patients with incomplete information. Disease staging was performed according to the seventh edition of the American Joint Committee on Cancer's TNM classification. The patients' demographic and clinicopathological characteristics were collated from a medical data platform by trained staff, who used standardized data collection and quality-control procedures. Patients were followed up by hospital visits for regular review or followed up by telephone visits every 2 months. The end of the follow-up time was January 2021, and the median follow-up time was 48.2 months. Disease-free survival (DFS) was defined as the time from surgery to the tumor recurrence and metastasis, overall survival (OS) was defined as the time from surgery to death of any cause or the loss of follow-up.

Among all patients enrolled, 35.24% (n=80) had RCC, 37.00% (n=84) presented with LCC, and 27.75% (n=63) had RECC. Among the RCC patients, 44 (55.00%) were men and 36 (45.00%) were women. There were 16 patients (20.00%) under the age of 60 years and 64 patients (80.00%) were 60 years or older. Among the LCC patients, 60 (71.43%) were male and 24 (28.57%) were female. There were 32 patients (38.10%) under the age of 60 years and 52 patients (61.90%) aged 60 years or older. Among the RECC patients, 25 (39.68%) were male and 38 (60.32%) were female. There were 39 (61.90%) patients aged 60 years and 24 (38.10%) patients aged 60 years or older.

Six clinicopathological features (gender, age, intestinal obstruction, TNM stage, T stage, N stage) are important in clinical treatment and may relate to prognosis. So the relationship between TRIM29 and these six clinical covariates was analyzed.

Fresh-frozen tissue samples from human CRC

A total of 68 fresh-frozen human CRC tissues were obtained from Hebei Medical University Fourth Affiliated Hospital, including 4 LCC tissues, 24 RCC samples, and 20 RECC tissues. All samples were pathologically confirmed as either colorectal adenocarcinoma tissues or normal colorectal tissues.

Paraffin sectioning and immunohistochemical staining

CRC tissues and matched normal tissues were obtained from the 227 patients. Paraffin sections were prepared and deparaffinized in xylene and dehydrated in a graded series of ethanol. Endogenous peroxidase activity was blocked using 3% H_2O_2 solution, followed by point antigen retrieval using a 20-minute heat-induced antigen retrieval procedure in pH 9.0 TRIS-EDTA buffer (zsbio). The slides

were probed with an anti-TRIM29 antibody (Signalway Antibody). Protein expression was measured using a 3,3-diaminobenzidine (DAB) peroxidase substrate (zsbio).

Interpretation of the histology and immunohistochemical staining results

The IHC staining results of TRIM29 were independently evaluated by two pathologists who were not aware of the patients' clinical outcomes. A consensus decision was made through consultation when they had an interobserver discrepancy. The staining intensity was scored according to the following criteria: 0, no staining; 1+, weak staining; 2+, moderate staining; and 3+, strong staining. High IHC expression was defined as a staining intensity of 3+ in over 25% of tumor cells.

Hematoxylin and eosin staining and tumor lymphocytic infiltration

Tissue specimens were stained with hematoxylin and eosin (H&E) and the tumor lymphocytic infiltration was evaluated. Tumor lymphocytic infiltration greater than 50% was defined as high tumor lymphocytic infiltration.

RNA extraction, RT-PCR, and quantitative real-time PCR (qPCR)

Total RNA was extracted from 68 tissue samples (including 20 RCC samples, 24 LCC samples, and 24 RECC samples) with TRIzol reagent (Invitrogen). The cDNA was synthesized with OneScript Plus Reverse Transcriptase (abm). The qPCR was conducted with the OneScript Plus cDNA Synthesis kit (abm). Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as an internal normalization reference.

The qPCR primers used are listed as follows:
TRIM29 forward: AGCATCAGCGACTCTGTGTTG;
TRIM29 reverse: GAAGTTGCCTAGTGACTGTCC;
GAPDH forward: GAGAAGGCTGGGGCTCATTT;
GAPDH reverse: AGTGATGGCATGGACTGTGG.

Western blot analysis

All fresh-frozen tumor samples were lysed using RIPA lysis buffer (Applygen, China) containing a protease inhibitor cocktail. Thereafter, 30 μg of protein lysate per sample was separated by sodium dodecyl-sulfate polyacrylamide gel electrophoresis (SDS-PAGE) using a 10% gel and transferred to polyvinylidene fluoride membranes (Millipore, Billerica, MA, USA). The membranes were blocked with 5% skim milk for at least 1 hour at 37 ℃, followed by incubation with primary antibodies overnight at 4 ℃. The primary antibodies employed were anti-TRIM29 (Signalway Antibody) and anti-β-actin (Santa Cruz Biotechnology). Then, the membranes were probed with the corresponding secondary antibodies (Promega, USA) and incubated with a chemiluminescent substrate to form the protein bands. Images were taken using an Image Reader LAS-4000 (Fuji Ltd., 120 Japan).

Construction of a protein-protein interaction (PPI) network and determining the functional annotations of TRIM29

The Search Tool for the String application (http://string.embl.de/), an open-source online tool, was used to identify the proteins which closely correlated with TRIM29 and a PPI network was constructed. A local clustering coefficient greater than 0.875 was considered as significantly related hub genes. Subsequently, gene ontology (GO) analysis, including biological processes (BP), molecular function (MF), and cellular component (CC), and Reactome/KEGG pathways analysis were performed for the hub genes associated with TRIM29.

Construction of the relationship between TRIM29 and immune infiltration

An integrated repository portal for tumor-immune system interactions (TISIDB, http://cis.hku.hk/TISIDB/) was used to examine the correlation between TRIM29 expression and tumor infiltrating lymphocytes, as well as immunomodulators and chemokines.

Statistical analyses

All statistical analyses were performed using the IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA). Figures were prepared using GraphPad Prism 5 software. Categorical variables were analyzed using the chi-square test. Continuous variables were analyzed using the Student's *t*-test. DFS and OS was analyzed using the Kaplan-Meier method, and comparisons were performed using the log-rank test. The Cox proportional-hazards model was performed for multivariate analyses to identify the

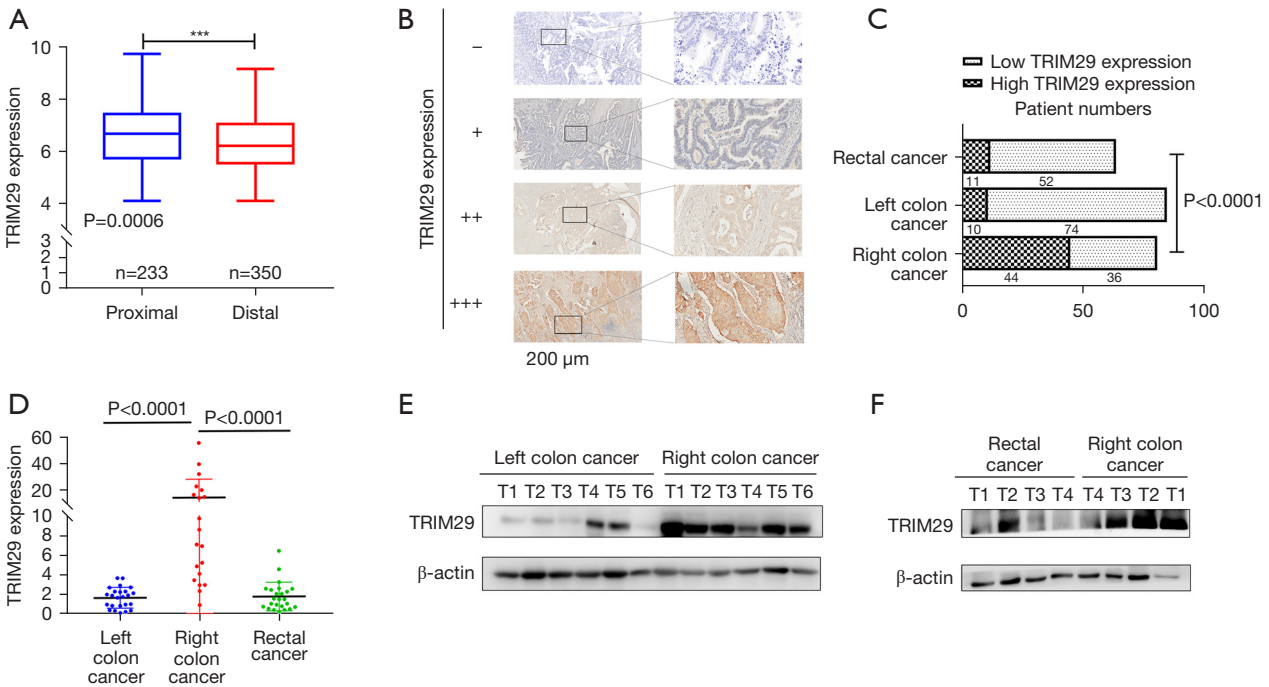

Figure 1 Immunohistochemical analysis showed that TRIM29 is highly expressed in RCC compared to LCC and RECC patients. (A) The GEO database was used to compare TRIM29 expression in proximal and distal colorectal cancer patients. (B) Representative IHC images staining by DAB of TRIM29 expression. (C) A graph showing the TRIM29 expression levels in RCC, LCC, and RECC patients. The results showed that TRIM29 expression was higher in RCC patients (P<0.0001). (D) The relative expression levels of TRIM29 in RCC, LCC, and RECC were assessed by qPCR. TRIM29 expression was significantly higher in RCC patients compared to both LCC and RECC patients (P<0.0001). (E,F) Western blotting was used to compare TRIM29 expression in 6 RCC samples and 6 LCC samples, and to compare TRIM29 expression in 4 RCC samples and 4 RECC. TRIM29 expression was higher in RCC samples compared to than LCC samples (E) and RECC samples (F). Statistical analysis was performed using two-tailed Student's *t*-tests (A,D). The statistical analysis was performed using the chi-square test. The error bars represent the SEM (C). ***, P<0.001. IHC, immunohistochemistry; RCC, right colon cancer; LCC, left colon cancer; RECC, rectal cancer; GEO, Gene Expression Omnibus; qPCR, quantitative polymerase chain reaction; SEM, standard error of the mean.

prognostic factors for DFS and OS. The other clinical covariates were corrected as confounding factors by using Cox proportional-hazards model, when analyzing the independent prognostic role of TRIM29. Spearman's test was used to measure correlations between TRIM29 and immune functions. All statistical tests were two-sided, and a P value less than 0.05 was considered statistically significant.

Results

TRIM29 is highly expressed in proximal CRC patients compared to distal CRC patients

The GSE39582 dataset [GPL570(HG-U133_Plus_2) Affymetrix Human Genome U133 Plus 2.0 Array] was downloaded from the GEO database. A total of 583 samples, consisting of 233 proximal colorectum samples and 350 distal colorectum samples, were analyzed for TRIM29 expression levels. The results showed that proximal colorectum cancer patients expressed higher TRIM29 levels than distal CRC patients (see *Figure 1A*, P=0.0006).

TRIM29 expression is significantly higher in RCC than in LCC and RECC

To further determine the TRIM29 expression in tumors at different locations, qPCR, Western blotting, and IHC was used to detect the TRIM29 mRNA and protein levels.

IHC was used to detect TRIM29 protein levels in 227 paraffin sections of CRC. Among them, 80 of the

Table 1 A comparison of the clinicopathological parameters between patients with high TRIM29 expression and low TRIM29 expression in left colon cancer

Factor	N	High TRIM29 expression (n=10)	Low TRIM29 expression (n=74)	χ^2	P value
Gender				3.090	0.079
Male	60	10 (100%)	50 (67.57%)		
Female	24	0 (0%)	24 (32.43%)		
Age (years)				5.272	0.22
<60	32	0 (0%)	32 (43.24%)		
≥60	52	10 (100%)	42 (56.76%)		
Intestinal obstruction				7.599	0.006
No	66	4 (40%)	62 (83.78%)		
Yes	18	6 (60%)	12 (16.22%)		
TNM stage				0.009	0.923
Stage I–II	45	6 (60%)	39 (52.70%)		
Stage III–IV	39	4 (40%)	35 (47.30%)		
T stage (Serosa involved)				2.637	0.104
T1–T3 (no)	22	0 (0%)	22 (29.73%)		
T4 (yes)	62	10 (100%)	52 (70.27%)		
N stage				0.454	0.500
N0	42	6 (60%)	36 (48.65%)		
N+	42	4 (40%)	38 (51.35%)		

patients had RCC, 84 patients presented with LCC, and 63 had RECC. The results revealed that TRIM29 protein expression was significantly higher in RCC samples than in LCC and RECC samples (*Figure 1B,1C*, P<0.001).

The qPCR was used to detect the TRIM29 mRNA level in a cohort of 68 CRC tissues, including 20 RCC, 24 LCC, and 24 RECC samples. The qPCR results demonstrated that TRIM29 mRNA expression was significantly higher in RCC compared to LCC and RECC (*Figure 1D*, P<0.0001). Then, 16 of the 68 samples were subjected to Western blotting in which 6 RCC tumor tissues were compared with 6 LCC samples, and 4 of the 6 RCC tumor tissues were compared with 4 RECC tumor tissues. The results revealed that TRIM29 protein expression was significantly higher in RCC compared to LCC and RECC (*Figure 1E,1F*).

TRIM29 is associated with different clinicopathologic features in patients with different tumor sites

The relationship between the TRIM29 expression and clinicopathological parameters was analyzed separately in RCC, LCC, and RECC patients. Six main clinicopathological parameters may affect prognosis were included in the analysis. In LCC patients, high TRIM29 expression was associated with intestinal obstruction before surgery (P=0.006). In RECC patients, high TRIM29 expression was associated with more advanced stage and younger age (P=0.015 and P=0.000, respectively). In patients with RCC, high TRIM29 expression was associated with the male sex, older age, stage III–IV, N+ staging, and intestinal obstruction (P≤0.010) (*Tables 1-3*).

Table 2 A comparison of the clinicopathological parameters between patients with high TRIM29 expression and low TRIM29 expression in rectal cancer

Factor	N	High TRIM29 expression (n=11)	Low TRIM29 expression (n=52)	χ^2	P value
Gender				0.008	0.927
Male	25	5 (45.45%)	20 (38.46%)		
Female	38	6 (54.55%)	32 (61.54%)		
Age (years)				16.405	0.000
<60	39	11 (100%)	28 (53.85%)		
≥60	24	0 (0%)	24 (46.15%)		
Intestinal obstruction				1.818	0.178
No	51	11 (100%)	40 (76.93%)		
Yes	12	0 (0%)	12 (23.07%)		
TNM stage				5.950	0.015
I–II	49	5 (45.45%)	44 (84.62%)		
III–IV	14	6 (54.55%)	8 (15.38%)		
T stage (Serosa involved)				1.818	0.178
T1–T3 (no)	12	0 (0%)	12 (23.08%)		
T4 (yes)	51	11 (100%)	40 (76.92%)		
N stage				2.999	0.083
N0	45	5 (45.45%)	40 (76.92%)		
N+	18	6 (54.55%)	12 (23.08%)		

Cox univariate analysis of DFS in different tumor locations

The correlation between DFS and 7 clinicopathological factors (6 clinicopathological parameters and TRIM29) was assessed by Cox regression analysis separately in patients with RCC, LCC, and RECC (*Tables 4-6*). In LCC patients, Cox univariate analysis revealed that gender, age, N stage, and TNM stage were prognostic factors for DFS (*Table 4*, P=0.044, P=0.021, P=0.000, and P=0.000, respectively). In RECC patients, none of the seven clinicopathological factors were prognostic factors for DFS (*Table 5*). In RCC patients, Cox univariate analysis showed that N stage, TNM stage, and TRIM29 expression levels were prognostic factors for DFS (*Table 6*, P=0.000, P=0.000, and P=0.020, respectively). The relative ratio (RR) of DFS for the patients with low and high TRIM29 expression is shown in *Figure 2A-2C*. The results revealed that, only in the RCC group, patients with high TRIM29 expression had a significantly different risk of recurrence and metastasis compared to patients with low TRIM29 expression (P=0.020).

Cox univariate analysis of OS in different tumor locations

The correlation between OS and the upper 7 clinicopathological factors was assessed by Cox regression analysis separately in patients with RCC, LCC, and RECC (*Tables 7-9*). In LCC patients, Cox univariate analysis showed that age, T stage, N stage, and TNM stage were prognostic factors for OS (*Table 7*, P=0.021, P=0.022, P=0.009, and P=0.008, respectively). In RECC patients, age and N stage were identified as prognostic factors for OS (*Table 8*, P=0.017 and P=0.020, respectively). In RCC patients, N stage, TNM stage, TRIM29 expression level, and intestinal obstruction were prognostic factors for OS (*Table 9*, P=0.000, P=0.000, P=0.006, and P=0.040, respectively). The results revealed that, only in the RCC group, patients with high TRIM29 expression had a

Table 3 A comparisons of the clinicopathological parameters between patients with high TRIM29 expression and low TRIM29 expression in right colon cancer

Factor	N	High TRIM29 expression (n=44)	Low TRIM29 expression (n=36)	χ^2	P value
Gender				12.415	0.000
Male	44	32 (72.73%)	12 (33.33%)		
Female	36	12 (27.27%)	24 (66.67%)		
Age (years)				24.444	0.000
<60	16	0 (0%)	16 (44.44%)		
≥60	64	44 (100%)	20 (55.56%)		
Intestinal obstruction				6.599	0.010
No	32	12 (27.27%)	20 (55.56%)		
Yes	48	32 (72.73%)	16 (44.44%)		
TNM Stage				19.394	0.000
I–II	32	8 (18.18%)	24 (66.67%)		
III–IV	48	36 (81.82%)	12 (33.33%)		
T stage (Serosa involved)				2.566	0.109
T1–T3 (no)	28	12 (27.27%)	16 (44.44%)		
T4 (yes)	52	32 (72.73%)	20 (55.56%)		
N stage				19.394	0.000
N0	32	8 (8.18%)	24 (66.67%)		
N+	48	36 (81.82%)	12 (33.33%)		

significantly different risk of death compared to patients with low TRIM29 expression (*Figure 2D-2F*, P=0.006).

Kaplan-Meier analysis of the relationship between TRIM29 and DFS in patients with different tumor sites

To determine the effect of TRIM29 expression levels on prognosis in patients with different tumor sites, Kaplan-Meier survival curves and log-rank tests were performed. High TRIM29 expression was associated with poor DFS only in RCC patients, but not in LCC nor RECC patients (*Figure 3A-3C*). In RCC patients, the median DFS was 40 months in patients with low TRIM29 expression and 12 months in patients with high TRIM29 expression (P=0.017).

Kaplan-Meier analysis of the relationship between TRIM29 and OS in patients with different tumor sites

Kaplan-Meier survival curves and log-rank tests were conducted to investigate the relationship between OS and the levels of TRIM29 expression. The results suggested that high TRIM29 expression was associated with shorter OS only in RCC patients, but not in LCC nor RECC patients (*Figure 3D-3F*). In RCC patients, the median OS was 58 months in patients with low TRIM29 expression and 23 months in patients with strong TRIM29 expression (P=0.006).

Functional annotations and the predicted signaling Reactome/KEGG pathways

A network of TRIM29 and its co-expression genes is shown in *Figure 4A*. The Reactome pathway analysis of the genes related with TRIM29 was performed using the String database (http://string.embl.de/) (*Figure 4B*). The functional enrichment pathways are cytokine signaling in immune system, immune system, interferon signaling, and interferon gamma signaling. The annotated keywords of the hub genes associated with TRIM29 is shown in

Table 4 Univariate analyses of factors associated with disease-free survival in left colon cancer

Factor	Risk ratio	95% confidence interval	P value
Gender (males were used as a reference)			
Female	0.513	0.268–0.982	0.044
Age (less than 60 years was used as a reference)			
≥60 years old	0.518	0.296–0.907	0.021
Infiltration depth (T stage) (T1–3 was used as a reference)			
T4	0.563	0.310–1.022	0.059
N stage (N0 was used as a reference)			
N+	2.968	1.681–5.241	0.000
TNM stage (stage I–II was used as a reference)			
Stage III	3.392	1.927–5.968	0.000
TRIM29 expression level (low TRIM29 expression was used as a reference)			
High TRIM29 expression	0.948	0.633–1.421	0.797
Intestinal obstruction (no intestinal obstruction was used as a reference)			
Yes	0.892	0.456–1.744	0.739

Table 5 Univariate analyses of factors associated with disease-free survival in rectal cancer

Factor	Risk ratio	95% confidence interval	P value
Gender (males were used as a reference)			
Female	1.044	0.537–2.032	0.898
Age (less than 60 years was used as a reference)			
≥60 years old	0.655	0.331–1.298	0.225
Infiltration depth (T stage) (T1–3 was used as a reference)			
T4	0.779	0.340–1.780	0.553
N stage (N0 was used as a reference)			
N+	1.548	0.758–3.162	0.231
TNM stage (stage I–II was used as a reference)			
Stage III	1.073	0.469–2.456	0.868
TRIM29 expression level (low TRIM29 expression was used as a reference)			
High TRIM29 expression	0.982	0.408–2.361	0.967
Intestinal obstruction (no intestinal obstruction was used as a reference)			
Yes	0.931	0.386–2.241	0.872

Table 6 Univariate analyses of factors associated with disease-free survival in right colon cancer

Factor	Risk ratio	95% confidence interval	P value
Gender (males were used as a reference)			
Female	0.825	0.498–1.367	0.455
Age (less than 60 years was used as a reference)			
≥60 years old	1.023	0.553–1.891	0.942
Infiltration depth (T stage) (T1–3 was used as a reference)			
T4	1.443	0.837–2.485	0.187
N stage (N0 was used as a reference)			
N+	2.903	1.651–5.102	0.000
TNM stage (stage I–II was used as a reference)			
Stage III	1.704	1.285–2.259	0.000
TRIM29 expression level (low TRIM29 expression was used as a reference)			
High TRIM29 expression	1.849	1.104–3.096	0.020
Intestinal obstruction (no intestinal obstruction was used as a reference)			
Yes	0.647	0.233–1.796	0.403

Figure 4C. KEGG pathway analysis of the hub genes related to TRIM29 was performed using the String database (*Figure 4D*). The overlap between the Reactome/KEGG pathways enrichment and the annotated keywords analysis of the hub genes of TRIM29 suggested that TRIM29 is likely related to immune function. Considering that TRIM29 has a greater effect on RCC patients compared to either LCC or RECC patients, the correlation between TRIM29 expression and immune function was examined in colon adenocarcinoma (COAD) samples using TISIDB.

The correlation between TRIM29 expression and immune function

Analysis of the correlation between TRIM29 expression and tumor infiltrating lymphocytes using TISIDB

To clarify the correlation between TRIM29 expression and immune function, the correlation between TRIM29 expression and tumor infiltrating lymphocytes in COAD samples was examined using TISIDB (*Figure 5A*). Elevated TRIM29 expression was significantly associated with activated dendritic cells (Act DC), abundance of CD-56 dim cells, interdigitating dendritic cells (iDC), monocytes, neutrophils, natural killer (NK) cells, natural killer T cells (NKT), plasmacytoid dendritic cells (pDC), central memory CD4 T cells (Tcm CD4), central memory CD8 T cells (Tcm CD8), effector memory CD8 T (Tem CD8), and T-helper lymphocyte type-1 (Th1) cell infiltration in CRC (P<0.05), which was suggestive of a general increase in immune infiltration (*Figure 5B-5M*).

Analysis of the relationship between TRIM29 expression and chemokines using TISIDB

Chemokines play a key role in inducing immune cell infiltration, hence, the relationship between TRIM29 expression and chemokines was investigated (*Figure 5N*). Elevated TRIM29 was significantly associated with high expression of C-X-C motif chemokine receptor 1 (CXCR1), C-X-C motif chemokine receptor 2 (CXCR2), and C-X-C motif chemokine receptor 4 (CXCR4) (*Figure 5O-5Q*, P<0.05).

Analysis of the relationship between TRIM29 expression and immunostimulators using TISIDB

The correlation between TRIM29 and immunostimulators was assessed (*Figure 6A*). The results demonstrated that TRIM29 over-expression was significantly associated with V-Set immunoregulatory receptors (C10orf54), CD70, CD276, HERV-H LTR-associating 2 (HHLA2), and inducible T Cell costimulator ligand (ICOSLG), thereby causing immune imbalance (*Figure 6B-6F*, P<0.05).

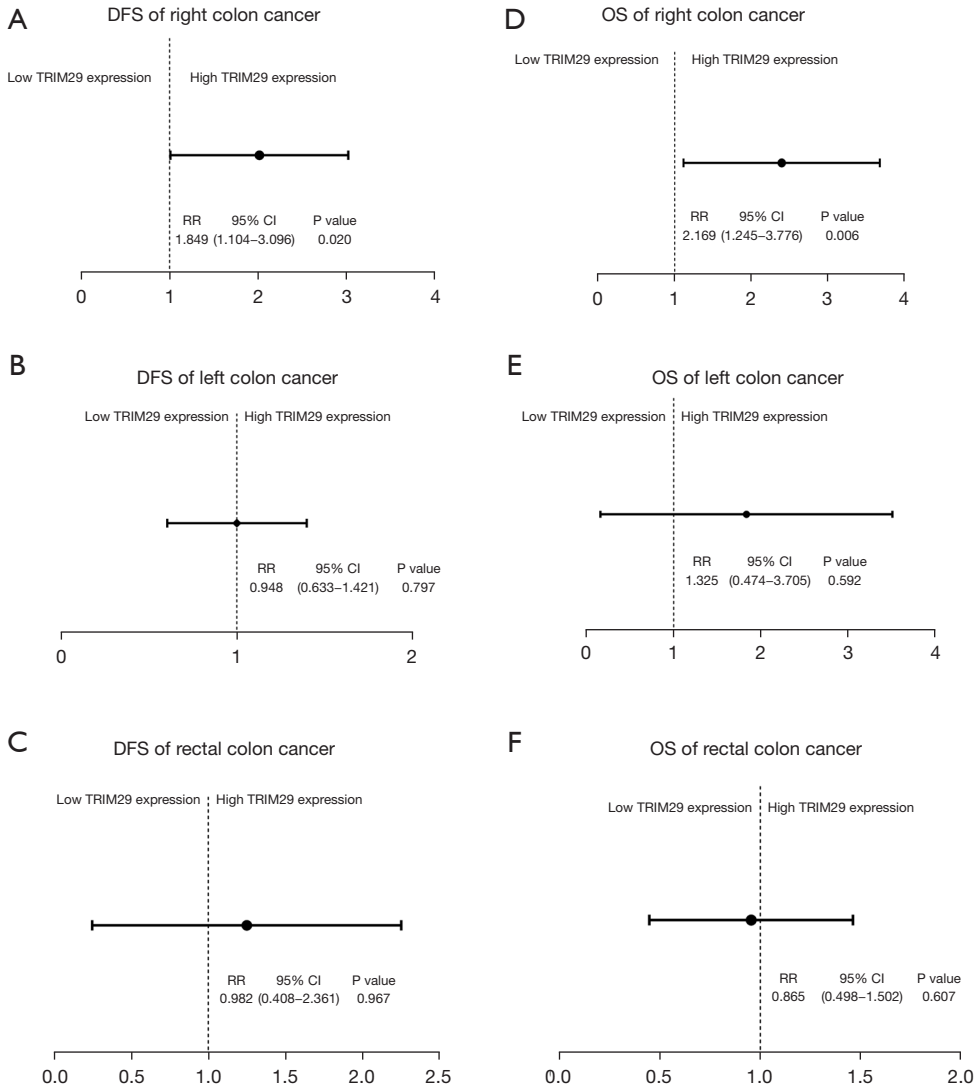

Figure 2 The risk ratio of disease-free survival and overall survival for the patients with different TRIM29 expression in the RCC, LCC, and RECC groups. (A) The RR of DFS for patients with different TRIM29 expression in RCC. (B) The RR of DFS for patients with different TRIM29 expression in LCC. (C) The RR of DFS for patients with different TRIM29 expression in RECC. (D) The RR of OS for patients with different TRIM29 expression in RCC. (E) The RR of OS for patients with different TRIM29 expression in LCC. (F) The RR of OS for patients with different TRIM29 expression in RECC. RCC, right colon cancer; LCC, left colon cancer; RECC, rectal cancer; RR, risk ratio; DFS, disease-free survival; OS, overall survival.

Analysis of the relationship between TRIM29 expression and immunoinhibitors using TISIDB

Immune checkpoint inhibitors are an important treatment for CRC, and thus their relationship with TRIM29 expression was explored (*Figure 6G*) to determine whether TRIM29 can be used as a molecular marker for the efficacy of immunotherapy. Elevated TRIM29 expression was significantly associated with CD274 (PD-L1), galectin 9 (LGALS9), programmed cell death 1 (PDCD1, PD-1), poliovirus receptor-related 2 (PVRL2), transforming growth factor beta receptor 1 (TGFBR1), T cell immunoreceptor with Ig and itim domains (TIGIT), V-set domain containing T cell activation inhibitor 1 (VTCN1), suggesting that tumors with high TRIM29 expression upregulated immune checkpoint molecules after immune stimulation to avoid immune damage (*Figure 6H-6N*, P<0.05).

Table 7 Univariate analyses of factors associated with overall survival in left colon cancer

Factor	Risk ratio	95% confidence interval	P value
Gender (males were used as a reference)			
Female	0.027	0.001–1.091	0.056
Age (less than 60 years was used as a reference)			
≥60 years old	0.372	0.160–0.863	0.021
Infiltration depth (T stage) (T1–3 was used as a reference)			
T4	0.373	0.161–0.866	0.022
N stage (N0 was used as a reference)			
N+	96.487	3.122–2,991.488	0.009
TNM stage (stage I–II was used as a reference)			
Stage III	120.600	3.499–4,156.624	0.008
TRIM29 expression level (low TRIM29 expression was used as a reference)			
High TRIM29 expression	1.325	0.474–3.705	0.592
Intestinal obstruction (no intestinal obstruction was used as a reference)			
Yes	0.999	0.389–2.565	0.999

Table 8 Univariate analyses of factors associated with overall survival in rectal cancer

Factor	Risk ratio	95% confidence interval	P value
Gender (males were used as a reference)			
Female	0.702	0.287–1.716	0.438
Age (less than 60 years was used as a reference)			
≥60 years old	0.222	0.064–0.766	0.017
Infiltration depth (T stage) (T1–3 was used as a reference)			
T4	0.650	0.216–1.955	0.443
N stage (N0 was used as a reference)			
N+	2.971	1.186–7.445	0.020
TNM stage (stage I–II was used as a reference)			
Stage III	2.351	0.868–6.366	0.093
TRIM29 expression level (low TRIM29 expression was used as a reference)			
High TRIM29 expression	0.865	0.498–1.502	0.607
Intestinal obstruction (no intestinal obstruction was used as a reference)			
Yes	1.820	0.650–5.093	0.254

Table 9 Univariate analyses of factors associated with overall survival in right colon cancer

Factor	Risk ratio	95% confidence interval	P value
Gender (male was used as a reference)			
Female	0.838	0.493–1.425	0.514
Age (less than 60 years were used as a reference)			
≥60 years old	1.023	0.538–1.948	0.944
Infiltration depth (T stage) (T1-3 were used as a reference)			
T4	1.598	0.892–2.861	0.115
N stage (N0 were used as a reference)			
N+	4.057	2.121–7.762	0.000
TNM stage (stage I-II were used as a reference)			
Stage III	4.057	2.121–7.762	0.000
TRIM29 expression level (low TRIM29 expression were used as a reference)			
High TRIM29 expression	2.169	1.245–3.776	0.006
Intestinal obstruction (no intestinal obstruction was used as a reference)			
Yes	1.782	1.026–1.782	0.040

Analysis of the correlation between TRIM29 expression levels and tumor infiltrating lymphocytes in clinical patients

H&E staining was applied to observe the tumor infiltrating lymphocytes in the above 227 formalin-fixed, paraffin-embedded CRC samples. The results revealed that high TRIM29 protein expression was correlated with high tumor-infiltrating lymphocytes (*Figure 7A-7C*, P=0.0053).

Analysis of the relationship between TRIM29 expression levels and pMMR/dMMR status using the GEO dataset

The GSE39582 dataset, consisting of 459 pMMR and 78 dMMR samples, was used to analyze the pMMR/dMMR status and TRIM29 expression level. The results revealed that dMMR patients expressed higher TRIM29 levels compared to dMMR patients (*Figure 7D*, P=0.0014).

Discussion

The difference in prognosis among RCC, LCC, and RECC patients is notable, with most studies confirming that RCC patients have poorer prognosis compared to patients with LCC and RECC (5,14,18-20). Furthermore, the intestinal flora, clinical manifestations, and treatment responses of patients with RCC, LCC, and RECC vary considerably (18,19). Several biomarkers, including genes, micro RNAs (miRNAs), and long non-coding RNAs (lncRNAs), have been shown to be differentially expressed and play different roles in the diagnosis and prognosis of patients with LCC and RCC. Such biomarkers include P53, excision repair cross-complementing 1 (ERCC1), forkhead box P3 (Foxp3), GNG4, and T-cell restricted intracellular antigen-1 (TIA-1) (12,21-25). However, to date, an accurate biomarker for malignancies at different tumor sites has not been identified. Our previous study was the first to demonstrated elevated expression of TRIM29 in RCC patients compared to LCC patients (14). However, this latter study did not include RECC patients. The present report is the first to analyze the prognostic value of TRIM29 in three groups of patients with different tumor locations, as well as the relationship between TRIM29 and clinicopathological features.

The current study demonstrated higher TRIM29 expression in RCC patients compared to either LCC or RECC patients. In addition, high TRIM29 expression was only associated with intestinal obstruction before surgery in LCC patients, and it was associated with higher frequency of stage TNM III–IV and younger age in RECC patients. In RCC patients, higher TRIM29 expression was associated

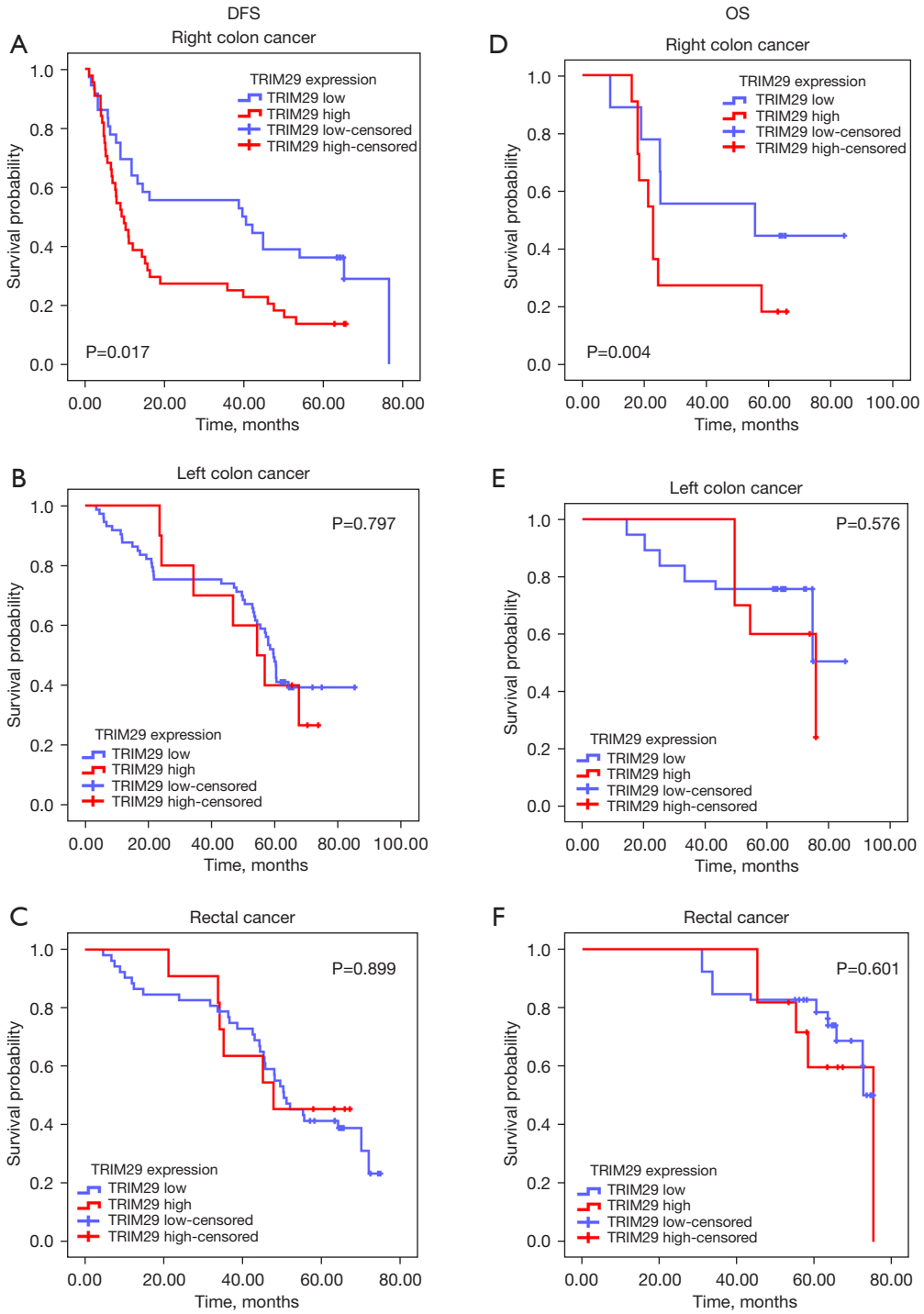

Figure 3 The disease-free survival and overall survival curves of patients with RCC, LCC, and RECC. The Kaplan-Meier curves of DFS in RCC (A), LCC (B) and RECC (C) patients according to TRIM29 expression levels. The Kaplan-Meier curves of OS in RCC (D), LCC (E), RECC (F) patients according to TRIM29 expression levels. Statistical analysis was performed using the chi-square test. RCC, right colon cancer; LCC, left colon cancer; RECC, rectal cancer; RR, risk ratio; DFS, disease-free survival; OS, overall survival.

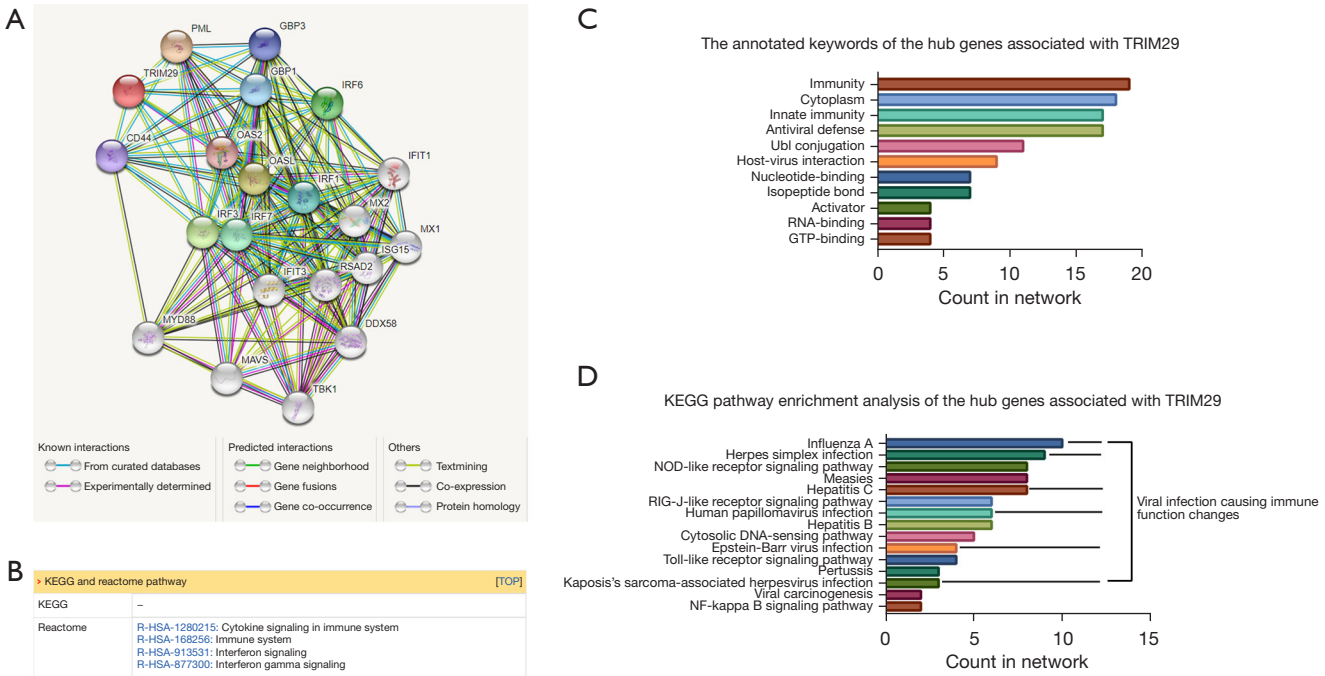

Figure 4 Functional annotations and predicted signaling pathways. (A) The PPI network of TRIM29 was constructed. A network of TRIM29 and its co-expression genes was set up visually. (B) The Reactome pathway analysis of TRIM29 and its co-expression genes. (C) The association between the annotated keywords of the hub genes and TRIM29. (D) The KEGG pathway enrichment analysis of the hub genes associated with TRIM29. PPI, protein-protein interaction; KEGG, Kyoto Encyclopedia of Genes and Genomes.

with more clinical features (the male sex, older age, stage III–IV tumor, N+ staging, and intestinal obstruction). Furthermore, high TRIM29 expression was significantly associated with an increased risk of recurrence/metastasis and death only in RCC patients.

TRIM29 is a number of the TRIM family that plays an important regulatory role in immune functions (26,27). Indeed, TRIM29 has been reported to act as an oncogene in many cancers, such as CRC, breast cancer, and lung cancer (28-31). It has been shown to affect immune function by regulating interferon levels and ubiquitination (26,27,32). Bioinformatics analysis suggested that TRIM29 may regulate tumor immunity in CRC. Therefore, this study examined the relationship between TRIM29 expression and tumor immune function in COAD patients by using TISIDB. The results revealed that TRIM29 may be involved in a general increase in immune infiltration and overexpression of chemokines. A report has suggested that the immune microenvironment in patients with CRC on the right side is characterized by increased infiltration of immune cells and higher interferon-γ signatures (33). In agreement with previous literature (26,27), our results suggested that RCC patients are more likely to overexpress TRIM29, leading to increased immune infiltration and overexpression of chemokines. Furthermore, certain immunostimulators were overexpressed with upregulated TRIM29 expression. Interestingly, certain immunoinhibitors were also upregulated with TRIM29 overexpression. It is plausible that tumors with high TRIM29 expression upregulate immune checkpoint molecules after immune stimulation to avoid immune damage.

The above data verified that TRIM29 plays a significant role in RCC patients, resulting in a general increase in immune infiltration that may lead to immune imbalance. TRIM29 may act as a novel biomarker and a potential therapeutic target in RCC patients. However, larger prospective studies are warranted to confirm these results.

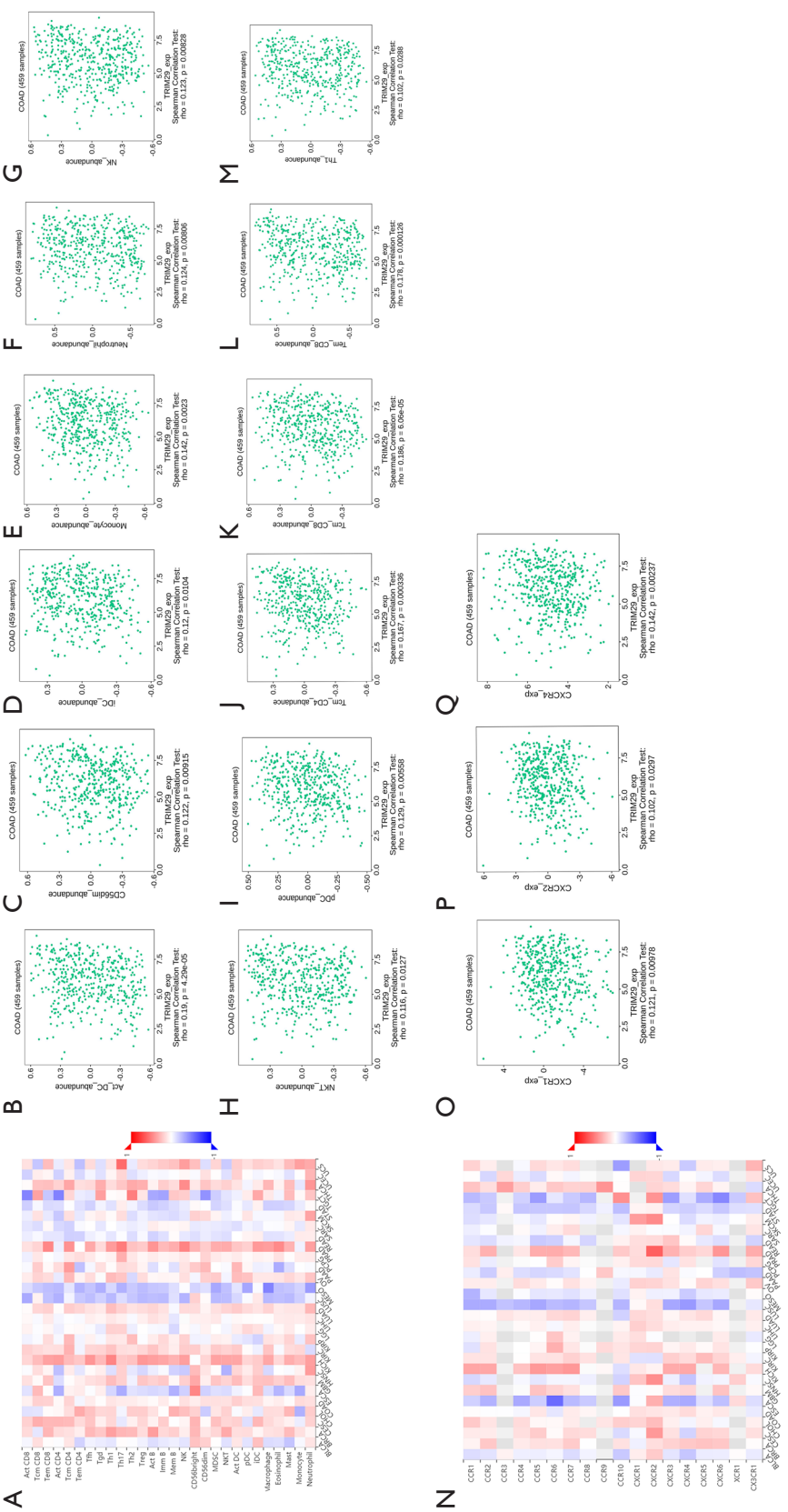

Figure 5 The correlations between TRIM29 expression and tumor infiltrating lymphocytes (TILs) and chemokine receptors. (A) The relations between TRIM29 expression and 28 types of TILs across human cancers. (B-M) TRIM29 was significantly correlated with certain infiltrating lymphocytes in COAD. (N) The relationship between TRIM29 expression and the expression of 18 chemokine receptors across human cancers. (O-Q) TRIM29 was significantly correlated with C-X-C motif chemokine receptor 1 (CXCR1), C-X-C motif chemokine receptor 2 (CXCR2), and C-X-C motif chemokine receptor 4 (CXCR4) in COAD samples. TIL, tumor infiltrating lymphocytes; BLCA, Bladder Urothelial Carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; KICH, Kidney Chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LGG, Brain Lower Grade Glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, Pheochromocytoma and Paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, Skin Cutaneous Melanoma; STAD, stomach adenocarcinoma; TGCT, Testicular Germ Cell Tumors; THCA, thyroid carcinoma; UCEC, Uterine Corpus Endometrial Carcinoma; UCS, Uterine Carcinosarcoma.

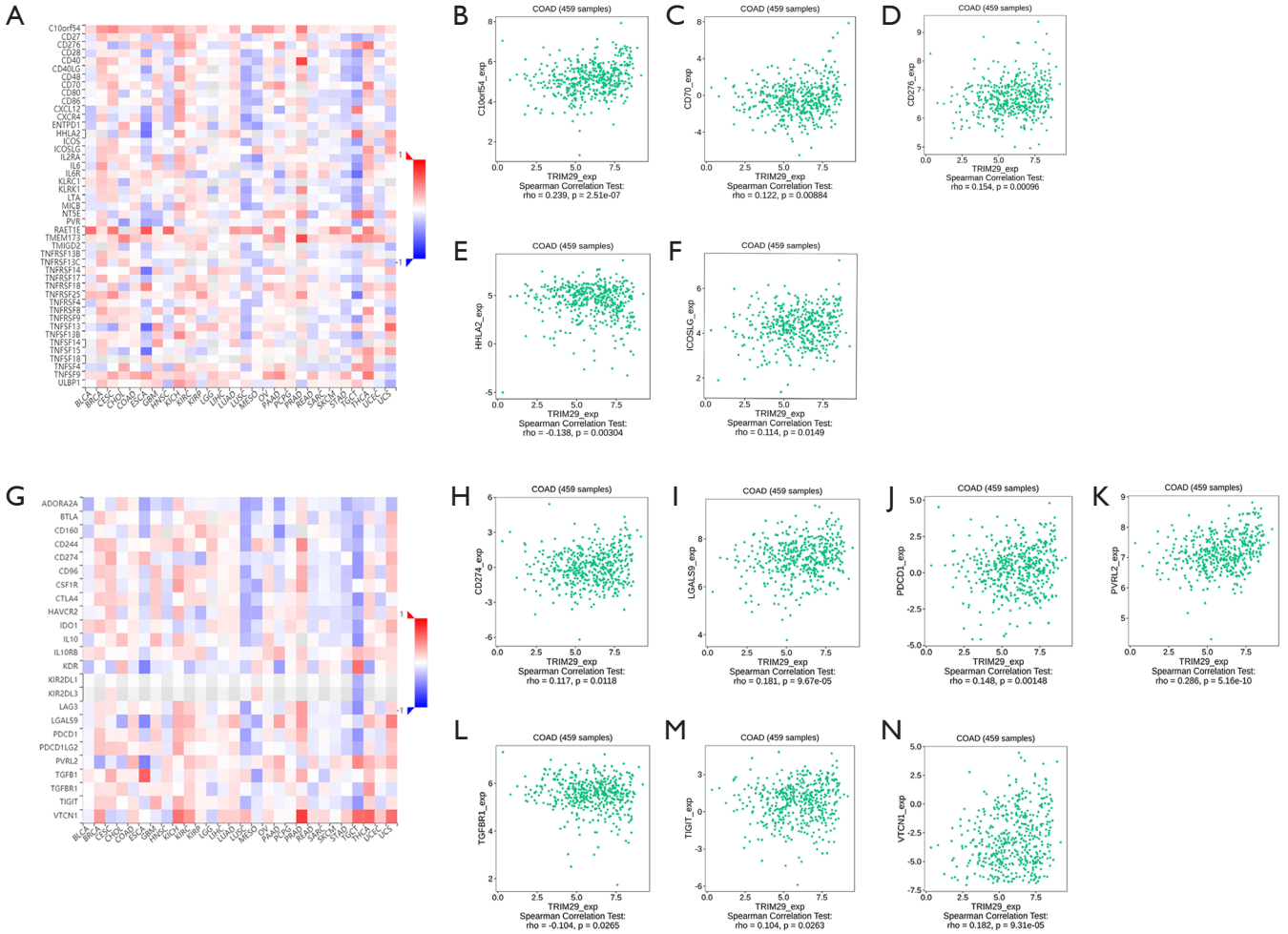

Figure 6 The correlation between TRIM29 expression and immunostimulator and immunoinhibitor. (A) The relationship between TRIM29 expression and 45immunostimulators across human cancers. (B-F) TRIM29 significantly correlated with certain immunostimulators in COAD. (G) The relationship between expression of TRIM29 and 24 immunoinhibitors across human cancers. (H-N) TRIM29 significantly correlated with certain immunoinhibitors in COAD. BLCA, Bladder Urothelial Carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LGG, Brain Lower Grade Glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, Pheochromocytoma and Paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, Skin Cutaneous Melanoma; STAD, stomach adenocarcinoma; TGCT, Testicular Germ Cell Tumors; THCA, thyroid carcinoma; UCEC, Uterine Corpus Endometrial Carcinoma; UCS, Uterine Carcinosarcoma.

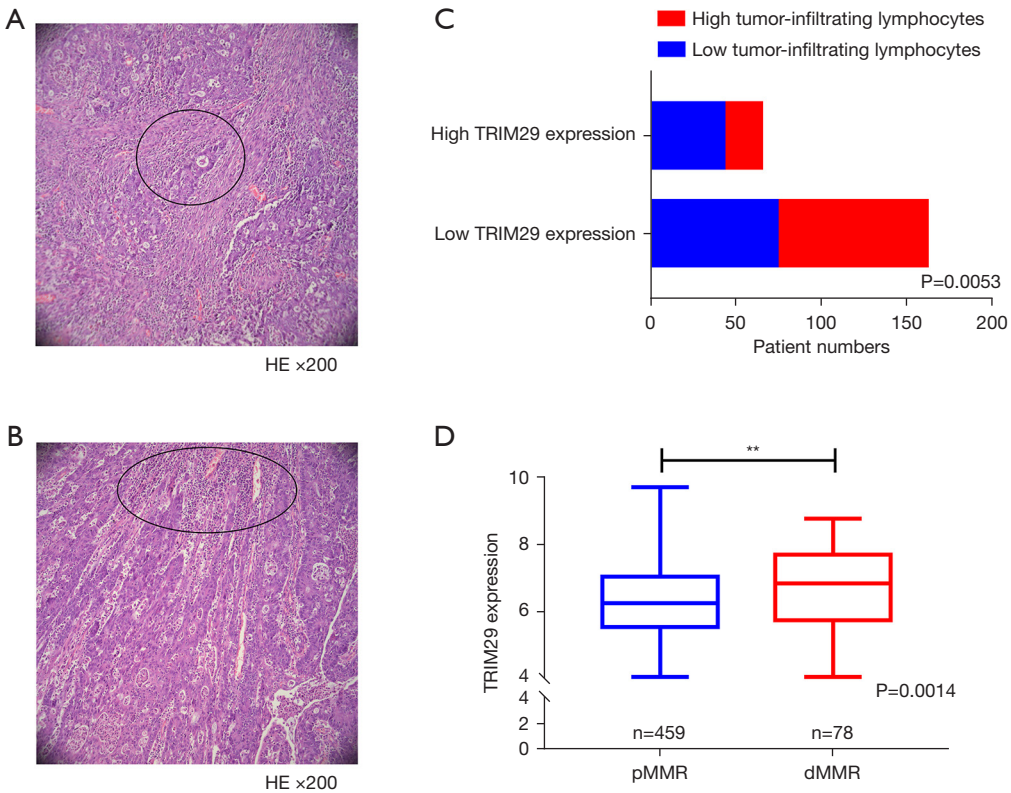

Figure 7 The correlation between TRIM29 expression and tumor infiltrating lymphocytes and pMMR/dMMR status. (A,B) Representative hematoxylin and eosin images of (A) low and (B) high levels of tumor infiltrating lymphocytes. (C) Statistical representation of the relationship between TRIM29 expression and tumor infiltrating lymphocytes. Statistical analysis was performed using the chi-square test. (D) The relationship between TRIM29 expression and MMR status. Statistical analysis was performed using the two-tailed Student's *t*-test. Error bars represent the SEM. **, P<0.01. pMMR, mismatch-repair-proficient; dMMR, mismatch-repair-deficient.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-365/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-365/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-365/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The collection of all human samples in this study was approved by ethics board of Hebei Medical University Fourth Affiliated Hospital (No. 2017MEc089). Informed consent was obtained from all patients.

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