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ORIGINAL ARTICLE

Bioinformatics Analysis Identified the Diagnostic, Prognostic, and Immunological Roles of TRIM17 in Pan-Cancer

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Abstract

Background. The process of carcinogenesis and cancer progression is intricate and influenced by various factors. Tripartite motif 17 (TRIM17), a member of the TRIM family of E3 ubiquitin ligases, plays a significant role in regulating a range of pathological and physiological processes. Recent research has highlighted its involvement in the initiation and advancement of human cancers. This study seeks to enhance our understanding of the role of TRIM17 in the development and progression of multiple malignancies by analyzing its presence in cancer tissues.

Methods. The study investigated the involvement of TRIM17 in cancer by utilizing data from The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) database. Various web platforms and software tools such as R, Cytoscape, HPA, Archs4, TISIDB, cBioPortal, STRING, GSCALite, and CancerSEA were employed for data analysis. In addition, the function of TRIM17 in glioblastoma was further validated by in vitro experiments.

Results. The expression of TRIM17 is dependent on the type of tumor. In several cancers, TRIM17 is highly expressed and associated with a poor prognosis, while in others it may act as a protective factor. Furthermore, TRIM17 has been linked to molecular or immune subtypes across a wide range of cancers, although there may be no significant difference in overall survival within these cancer types. Additionally, TRIM17 plays a role in regulating various tumor processes and is correlated with immune status. TRIM17 is able to inhibit the ability of growth and metastasis in glioblastoma.

Conclusions. Our study provides insight into the role of TRIM17 in the promotion, inhibition, and treatment of various cancers. We have identified TRIM17 as a potential biomarker for cancer diagnosis and prognosis, with therapeutic value in immune-based, targeted, or cytotoxic treatments. This research is essential for the clinical validation and treatment of TRIM17 in cancer patients.

Keywords. TRIM17; Pan-cancer; Anti-tumor; Bioinformatics; Carcinogenesis; Tumor immunity.

Introduction

Cancer is the most common cause of death in humans, accounting for about a quarter (22.8%) of global noncommunicable diseases (NCDs) deaths, resulting in significant health, economic, and social problems[1, 2]. Despite the fact that tumor evolution involves multiple and complex mechanisms of action, the exploration of the mechanisms of tumorigenesis and development has never ceased.

In recent years, with the application of new technologies such as transcriptomics and single-cell genomics, more powerful tools have been made available for the discovery and

identification of cancer markers[3, 4]. With the huge amount of sequencing data, it is also possible to use efficient bioinformatics methods to analyze biomarkers and cancers in order to clarify the predictive value of specific molecular markers in tumors or to help screen effective molecular markers for specific cancers[5].

Tripartite motif 17 (TRIM17) is a RING-type E3 ubiquitin ligase that belongs to the TRIM family and is involved in the regulation of a variety of pathological activities. For example, TRIM17 plays an important role in central nervous system disorders by mediating neuronal death and regulating α-synuclein expression[6, 7]. In tumors, TRIM17 has been shown to promote gastric cancer progression as well as the development of chemotherapeutic resistance in non-small cell lung cancer and has been associated with hepatitis B-related liver cancer progression[8-10]. These studies have provided some insight into the possible role of TRIM17 in tumors, but its expression and predictive value at the pan-cancer level remain unknown.

Therefore, in this study, we performed an integrated and comprehensive bioinformatics analysis of TRIM17 expression, diagnostic and prognostic value, functional enrichment, and immune infiltration at the pan-cancer level. The results showed that TRIM17 has significant diagnostic and prognostic value in a wide range of cancers and exhibits different modes of action in different cancers. Meanwhile, our study further revealed the relationship between TRIM17 and immunostimulatory factors, immunosuppressive factors, MHC molecules, chemokines and their receptors in a variety of tumors, which was rarely reported in previous studies. We believe that these studies will help to further clarify the importance of TRIM17 as a molecular marker and target in tumor diagnosis, prognosis, immunomodulation, and immunotherapy.

Materials and Methods

Gene Expression Analysis of C1ORF112

Utilizing the Human Protein Atlas (HPA) database (https://www.proteinatlas.org/), we generated a plot depicting the mRNA and protein levels of TRIM17. For insights into the tissue and cell line expression of TRIM17, we referred to the Harmonizome database (https://maayanlab.cloud/Harmonizome/). Data on TRIM17 mRNA expression in both tumor and normal samples were sourced from The Cancer Genome Atlas (TCGA) (https://cancergenome.nih.gov) and the Genotype-Tissue Expression (GTEx) (https://gtexportal.org/) project.

We excluded samples with “0” values for gene expression and retained paired samples for comparative analysis. RNA-seq data, initially in Fragments Per Kilobase of transcript per Million mapped reads (FPKM) format, were processed through the Toil pipeline to be converted into transcripts per million (TPM) and subjected to log2 transformation for subsequent analysis. Statistical analyses were conducted using R (version 3.6.3), and the ggplot2 package (version 3.3.3) was employed to visualize TRIM17 gene expression as bar graphs across various cancer patient cohorts. The median expression value was chosen as the threshold for dichotomizing gene expression levels. To assess group differences, the Wilcoxon rank-sum test was applied.

Receiver Operator Characteristic (ROC) Curve of TRIM17 in Cancers

Receiver Operating Characteristic (ROC) curves were employed to assess the diagnostic efficacy of TRIM17 across various malignancies. The mRNA expression data for TRIM17, extracted from both neoplastic and adjacent normal tissues within the TCGA and GTEx databases, served as the foundation for these curves. The computation of ROC curves was facilitated by the pROC package (version 1.18.0) in R, while the visualization was accomplished using the ggplot2 package.

Survival Prognosis Analysis

Kaplan-Meier (K-M) survival curves, which include Overall Survival (OS) and Disease-Free Survival (DFS), along with a survival significance map for TRIM17 across all tumor types in TCGA, were constructed utilizing the "Survival Analysis" feature of the Gene Expression Profiling Interactive Analysis version 2 (GEPIA2) (http://gepia2.cancer-pku.cn/) platform.

HELLS Expression in Different Molecular and Immune Subtypes of Cancers

The correlation between TRIM17 expression levels and distinct molecular or immune phenotypes in various cancers was examined using the “subtype” module of the TISIDB

database. This database integrates diverse datasets to assess the interplay between cancer and the immune system. Our analysis focused on the mRNA expression patterns of TRIM17 across several immune subtypes, encompassing C1 (characterized by wound healing), C2 (dominated by IFN-g), C3 (inflammatory), C4 (lymphocyte-depleted), C5 (immunologically inactive), and C6 (TGF-b dominant).

Genetic Alteration Analysis of TRIM17

The genetic alterations of the TRIM17 gene were examined through the cBioPortal (https://www.cbioportal.org/) database. This resource was leveraged to analyze the frequency of somatic mutations and to gather genomic data on TRIM17 mutations across various cancer types, utilizing the "cancer types summary and mutations" and "mRNA vs. study" modules. Detailed mutation sites were identified through the "mutations" module of the portal.

Protein-Protein Interaction (PPI) Network Analyses and Functional Enrichment Analysis of TRIM17

Protein-protein interaction data for TRIM17 were retrieved from the STRING database (https://string-db.org/). A confidence score threshold of greater than 0.7 was applied to filter significant interactions. The identified interacting genes were subjected to a Protein-Protein Interaction (PPI) network analysis using Cytoscape for graphical representation. Key modules within the network were identified with the cytoHubba plugin in Cytoscape, and the top 10 nodes, as determined by the Maximum Connectivity (MCC) criterion of cytoHubba, were designated as hub genes. The pathlinker plugin was utilized to map out the signaling pathways based on these hub genes. Subsequently, the relationships between these hub genes and various cancers were investigated.

For genes with significant interactions with TRIM17, as identified by STRING, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed using the "clusterProfiler" and "org.Hs.eg.db" R packages. The outcomes of these analyses were visualized as bubble charts employing the "ggplot2" package.

Gene Set Enrichment Analysis

Gene set enrichment analysis (GSEA) was conducted using the "clusterProfiler" R package to identify differential biological pathways between cohorts with high and low TRIM17 expression levels. Pathways with significant changes were identified based on a false discovery rate (FDR) threshold of less than 0.25 and an adjusted p-value below 0.05. The top five enriched pathways were depicted as mountain plots. Visualization of the GSEA outcomes was achieved using the "ggplot2" R package.

CancerSEA

The role of TRIM17 in various cancers was assessed at the single-cell resolution using the CancerSEA database (http://biocc.hrbmu.edu.cn/CancerSEA/). The criteria for establishing a significant correlation between TRIM17 expression and cancer-associated functional states were set to a correlation coefficient greater than 0.3 and a statistical significance level of p-value < 0.05.

Immunogenomic Analyses of TRIM17 in Cancers

Our investigation focused on analyzing the relationships between TRIM17 expression levels and the expression of immunoinhibitory and immunostimulatory molecules, major histocompatibility complex (MHC) proteins, chemokines, and chemokine receptors across various cancer types. This analysis was conducted using the "immunomodulator" and "chemokine" modules within the TISIDB database.

In vivo and in vitro functional validation

Cell proliferation was measured employing the CCK8 assay. Initially, cells were plated into 96-well plates, and the culture medium was refreshed post-adhesion. To each well, 100 µl of complete growth medium and 10 µl of CCK8 solution were introduced, followed by incubation at 37°C for 2 hours. The optical density at 450 nm was recorded using a spectrophotometer, with absorbance changes monitored at intervals of 0, 12, 24, 36, 48, and 72 hours. To evaluate cell migration, both transwell migration and wound healing assays were utilized. For the transwell migration assay, approximately 20,000 cells were placed in the upper chamber in serum-free medium, while the lower chamber contained medium supplemented with 10% FBS. After 24 hours, cells were fixed, stained, and enumerated. In the wound healing

assay, cells were also cultured for 24 hours in serum-free medium and medium with 10% FBS in the lower chamber. The cells were grown to confluence in a 6-well plate, then a wound was created using a 1250 μl pipette tip. After washing with PBS and capturing images at the 0-hour mark under a microscope, the cells were maintained in serum-free DMEM. Migration was assessed by comparing the images taken at 24 hours post-wounding with those at the initial time point.

Statistical Analysis

Data analysis was conducted using R (version 4.2.2) and GraphPad Prism (version 9.0), with statistical significance defined as $p<0.05$. For categorical data, we employed analysis of variance (ANOVA) for comparisons, while t-tests were applied to assess differences in continuous variables. The relationship between continuous variables was explored using either Spearman or Pearson correlation coefficients, depending on the data's characteristics. In addition to parametric tests, nonparametric assessments were conducted: the Wilcoxon rank sum test was utilized for comparing two independent samples, and the Kruskal-Wallis H test was applied for analyzing differences among multiple samples.

Results

Gene expression analysis and pan-cancer expression of TRIM17

The results of gene expression analysis have showed that the mRNA and protein expression of TRIM17 was detected in multiple tissues and organs (Figure 1A). Based on datasets of the HPA, GTEx, and FANTOM5 (function annotation of the mammalian genome), we found that TRIM17 expressed primarily in the cerebellum, testis, basal ganglia, cerebral cortex, hippocampal formation, spleen, hypothalamus, amygdala and salivary gland (Figure 1B-E). Protein expression data from the HPA database on 44 tissues and organs indicated that the protein of TRIM17 is mainly expressed in the cerebral cortex, cerebellum, thyroid gland, adrenal gland, nasopharynx, bronchus, lung, oral mucosa, and salivary gland (Figure 1F). Furthermore, single-cell RNA-seq data showed that TRIM17 was highly expressed in early and late spermatids (Figure 1G).

The mRNA expression level of TRIM17 in different tumors was then investigated. We evaluated 18,102 unpaired samples covering 33 clinically common tumor types. Compared with normal tissues, high TRIM17 mRNA expression was observed in the bladder urothelial carcinoma (BLCA), cholangiocarcinoma (CHOL), acute myeloid leukemia (LAML), ovarian serous cystadenocarcinoma (OV), pancreatic adenocarcinoma (PAAD), uterine corpus endometrial carcinoma (UCEC) (all $p < 0.001$), lung squamous cell carcinoma (LUSC) (all $p < 0.001$), and pheochromocytoma and paraganglioma (PCPG) ($p < 0.05$). Tumor tissue of Adrenocortical Carcinoma (ACC), breast invasive carcinoma (BRCA), colon adenocarcinoma (COAD), Lymphoid Neoplasm Diffuse Large B-cell Lymphoma (DLBC), glioblastoma multiforme (GBM), Kidney chromophobe (KICH), Kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), Brain Lower Grade Glioma (LGG), Prostate adenocarcinoma (PRAD), Rectum adenocarcinoma (READ), Skin Cutaneous Melanoma (SKCM), Testicular Germ Cell Tumors (TGCT), Thyroid carcinoma (THCA) (all $p < 0.001$) and Thymoma (THYM) (all $p < 0.001$) had significantly lower TRIM17 mRNA expression when compared to corresponding normal tissue (Figure 1H). Analysis of another dataset containing 11,123 samples showed that TRIM17 was highly expressed in BLCA, CHOL, liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), LUSC, stomach adenocarcinoma (STAD), THCA, UCEC (all $p < 0.001$), PCPG and READ ($p < 0.05$), and lowly expressed in GBM, KICH (all $p < 0.001$), KIRP, PRAD (all $p < 0.01$), as compared to normal tissue. ACC, DLBC, LAML, LGG, mesothelioma (MESO), OV, TGCT, uterine carcinosarcoma (UCS), and uveal melanoma (UVM) could not be analyzed due to lack of sufficient normal tissue samples (Figure 1I). The expression of TRIM17 in paired samples was also explored. Twenty-three tumor types with paired samples were screened in 11,123 samples. Further analysis showed that compared to paired paracancerous tissues, TRIM17 expression was elevated in BLCA, LIHC, LUAD, LUSC, THCA (all $p < 0.001$), CHOL, STAD, UCEC (all $p < 0.01$), READ ($p < 0.05$), and decreased in KICH, PRAD (all $p < 0.001$), KIRC, KIRP (all $p < 0.01$), and had difference in BRCA, cervical squamous cell

carcinoma, and endocervical adenocarcinoma (CESC), COAD, esophageal carcinoma (ESCA), head and neck squamous cell carcinoma (HNSC), PAAD, PCPG (all $p > 0.05$) (Figure 1J).

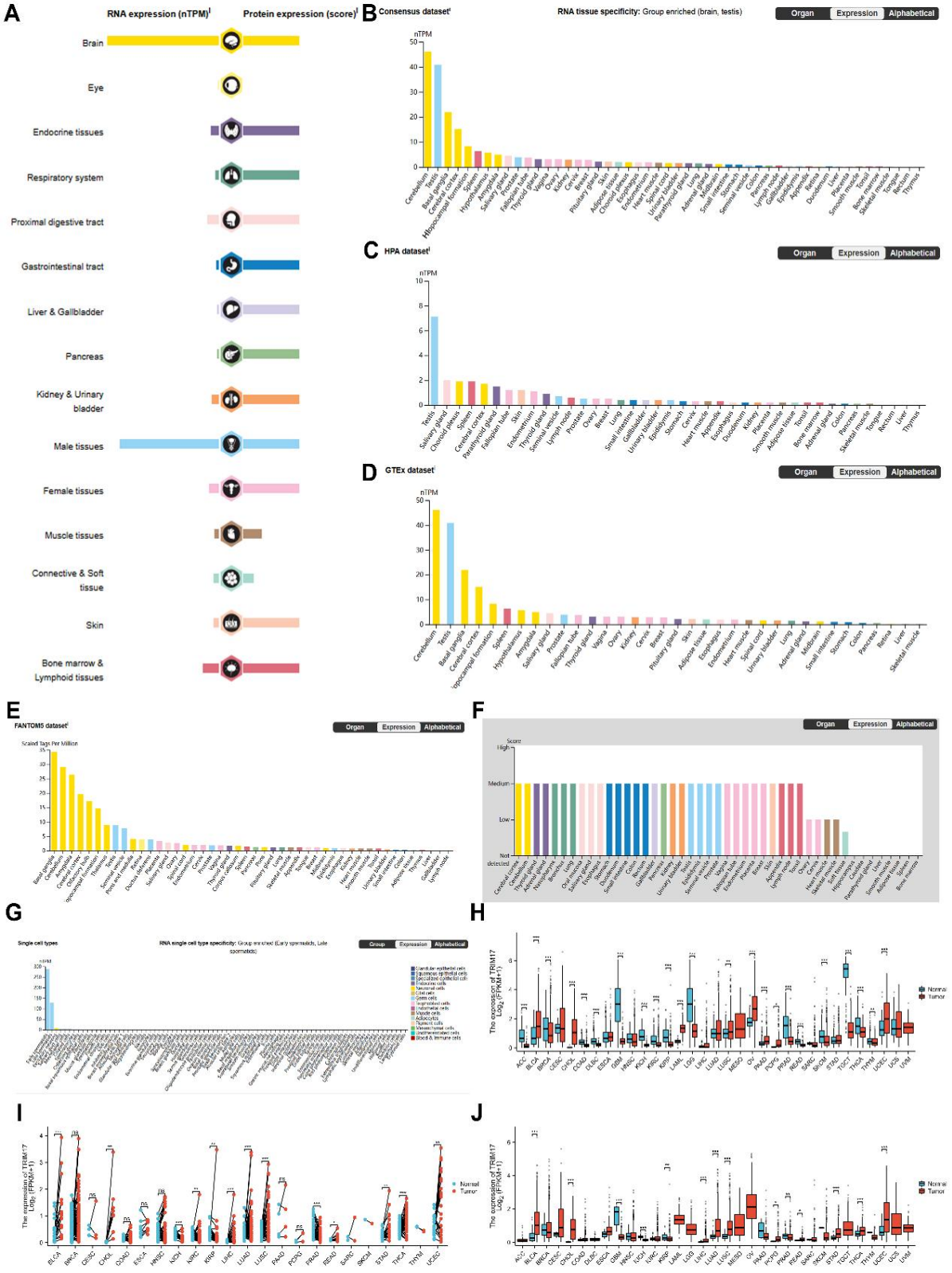

Figure 1 RNA and protein expression profile of TRIM17 in human organs and tissues. (A) The summary of TRIM17 mRNA and protein expression in human organs and tissues; (B) TRIM17 mRNA expression summary in different human organs and tissues based on consensus dataset; (C) TRIM17 protein expression summary in different human organs and tissues; (D) TRIM17 expression in various cell types; (E-G) TRIM17

tissue expression based on datasets of the HPA (Human protein atlas), GTEx, and FANTOM5 (Function annotation of the mammalian genome 5); (H) Expression of TRIM17 between the 33 cancers and normal tissues in unpaired sample analysis; (I) Expression of TRIM17 between the 33 cancers and paracancerous tissues in unpaired sample analysis; (J) Paired sample analysis of TRIM17 mRNA expression between 23 cancers and paracancerous tissues in BLCA, BRCA, CESC, CHOL, COAD, ESCA, HNSC, KICH, KIRC, KIRP, LIHC, LUAD, LUSC, PAAD, PCPG, PRAD, READ, SARC, SKCM, STAD, THCA, THYM and UCEC. ∗p < 0:05, ∗∗p < 0:01, ∗∗∗p < 0:001. ns, Not Significant.

The diagnostic and prognostic value of TRIM17

In a number of tumors, TRIM17 has a good predictive value. Thirteen tumors had an AUC greater than 0.7, of which nine tumors had an AUC greater than 0.8, which were ACC (0.899), CHOL (0.994), GBM (0.968), KICH (0.911), LAML (0.980), PCPG (0.839), SKCM (0.860), TGCT (0.974) and THYM (0.863) (Figure 2A-I).

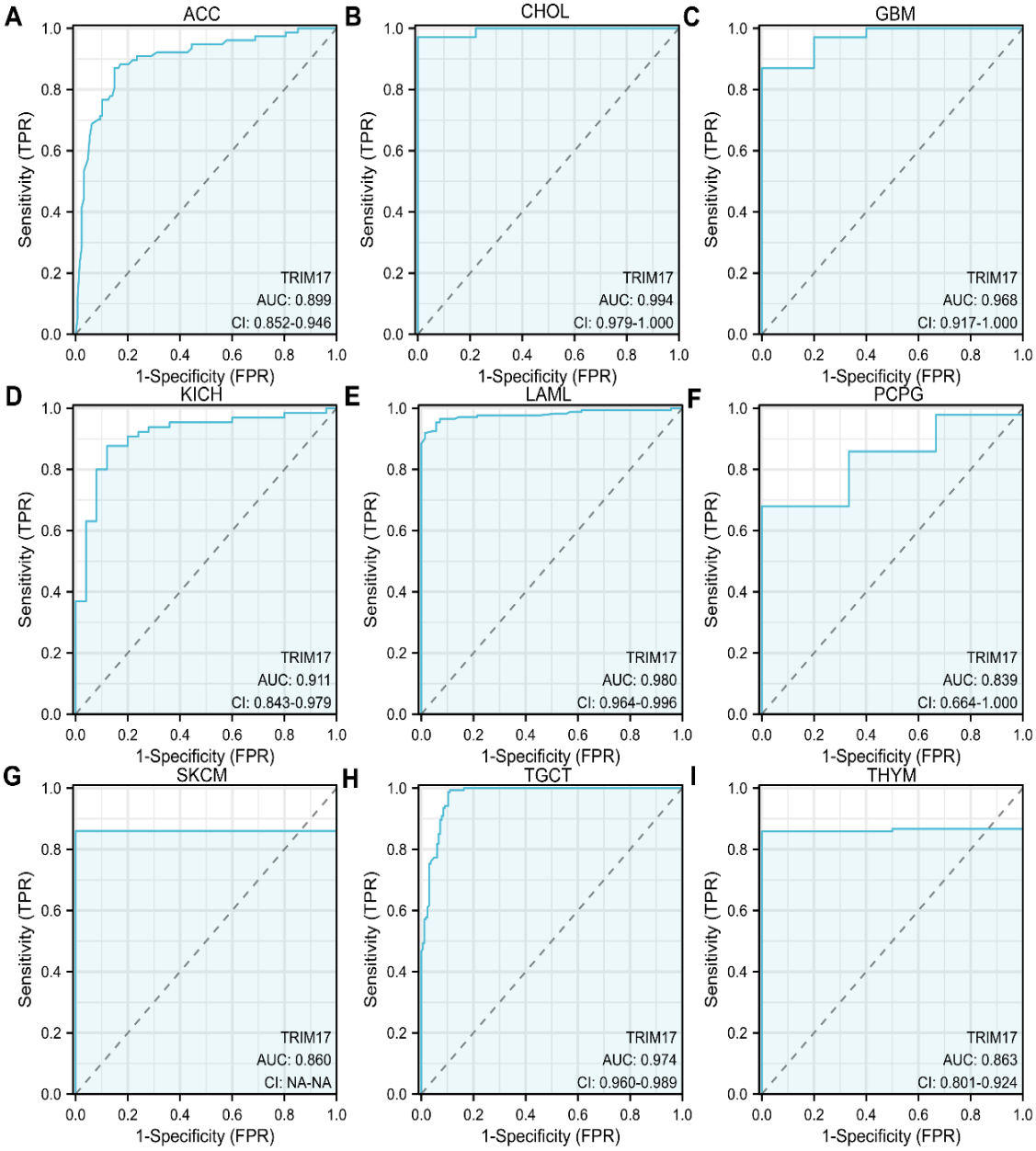

Figure 2 Receiver Operator Characteristic (ROC) curve of TRIM17 in 9 Cancers. (A) ACC, (B) CHOL, (C) GBM, (D) KICH, (E) LAML, (F) PCPG, (G) SKCM, (H) TGCT, (I) THYM.

To further explore the potential prognostic value of TRIM17, we analyzed the correlation between TRIM17 expression levels and the prognosis of patients with different tumors based on the TCGA dataset. For overall survival (OS), high TRIM17 expression was associated with shorter OS in KIRC and longer OS in LGG and READ (Figure 3A-D). This suggests that TRIM17 may be a poor prognostic factor for KIRC, but may portend a good prognosis for LGG and READ. For disease free survival (DFS), high TRIM17 expression was associated with shorter DFS in PRAD and STAD and longer DFS in LGG and SARC. This suggests that TRIM17 may portend a favorable prognosis for LGG and SARC and a poor prognosis for PRAD and STAD (Figure 3E-I).

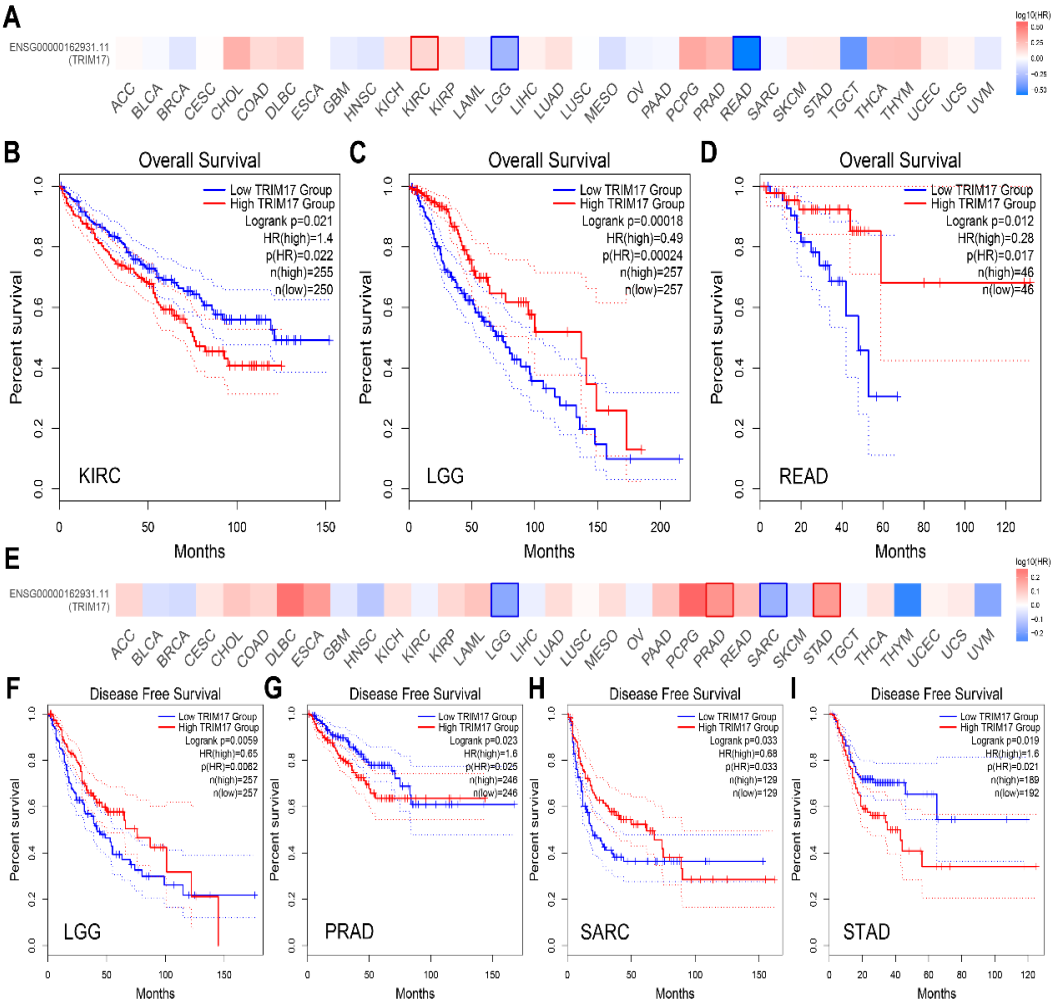

Figure 3 Correlation between TRIM17 expression and overall survival and disease-free survival in patients with different TCGA tumor types. (A) GEPIA2 was used to build an overall survival map (A) and conduct overall survival analyses (B–D); GEPIA2 was used to build a disease-free survival map (E) and conduct disease-free survival analyses (F-I).

TRIM17 expression in different molecular and immune subtypes of the cancers

Next, we further analyzed the correlation of TRIM17 expression with different tumor molecular subtypes and immune subtypes. For molecular subtypes, TRIM17 expression was significantly different in 12 tumors, including BRCA (five subtypes), GBM (five subtypes), HNSC (four subtypes), KIRP (four subtypes), LGG (six subtypes), LIHC (three subtypes), LUSC (four subtypes), OV (four subtypes), PCPG (four subtypes), PRAD (eight subtypes), STAD (five subtypes) and UCEC (four subtypes) (Figure 4A-L).

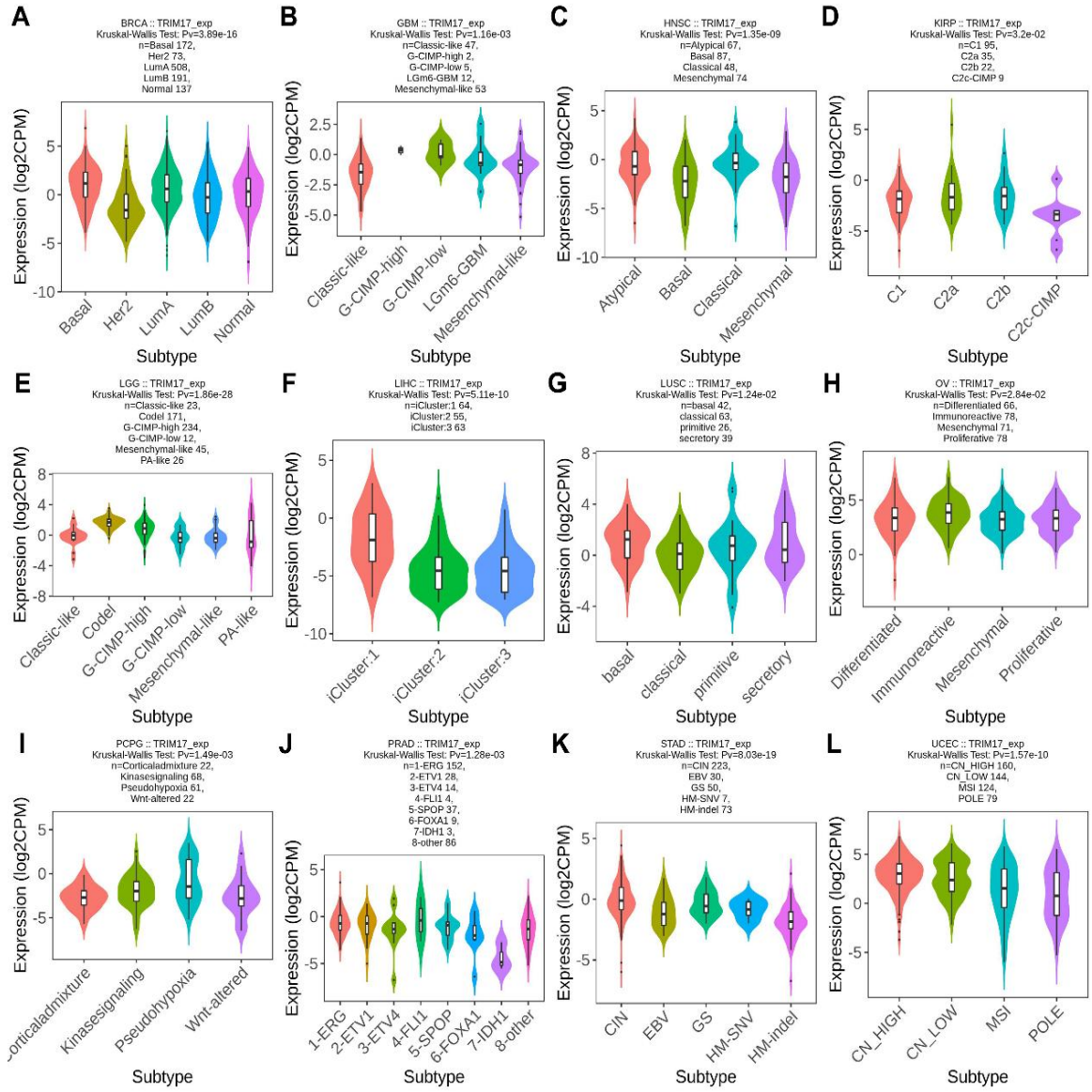

Figure 4 Correlations between TRIM17 expression and molecular subtypes in 12 cancers. (A) BRCA, (B) GBM, (C) HNSC, (D) KIRP, (E) LGG, (F) LIHC, (G) LUSC, (H) OV, (I) PCPG, (J) PRAD, (K) STAD, (L) UCEC.

For immune subtypes, TRIM17 expression was significantly different in nine tumors, including BRCA (five subtypes), HNSC (five subtypes), LGG (four subtypes), LIHC (five subtypes), PRAD (five subtypes), SKCM (five subtypes), STAD (five subtypes), UCEC (five subtypes) and UCS (three subtypes) (Figure 5A-I).

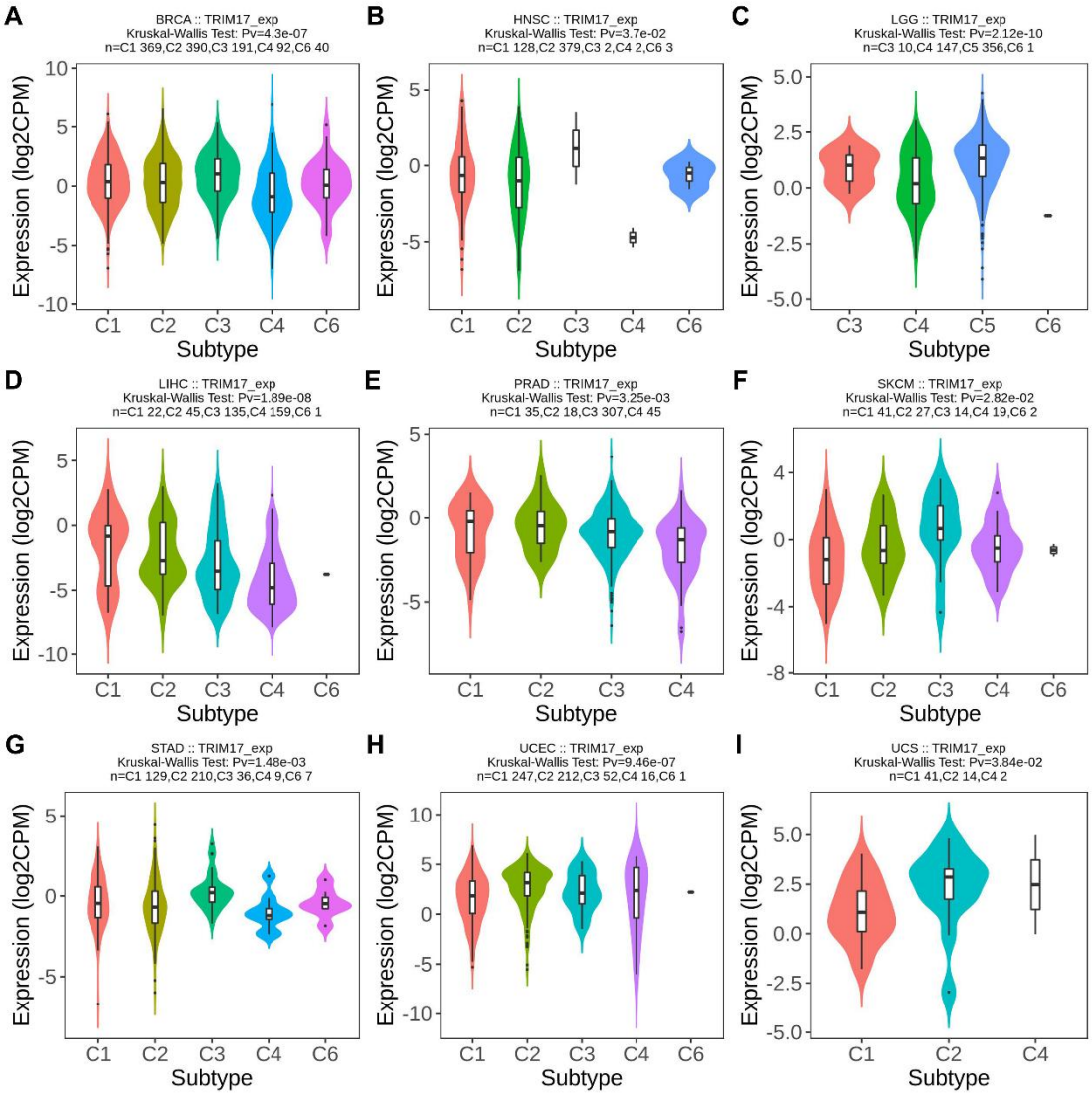

Figure 5 Correlations between TRIM17 expression and immune subtypes in 9 cancers. (A) BRCA, (B) HNSC, (C) LGG, (D) LIHC, (E) PRAD, (F) SKCM, (G) STAD, (H) UCEC, (I) UCS.

The genetic alteration llandscape of TRIM17 in different cancers

The genetic alteration of TRIM17 in various tumor types in TCGA datasets was then investigated using cBioPortal online tool. A total of 86 mutation sites were identified between amino acids 0-477, including 74 missense mutations, 7 truncatings, 4 splices and an inframe mutation. R376Q/W was the most frequent mutation site (Figure 6A). Mutations in TRIM17 are most commonly found in BRCA, LIHC, OV, CHOL, UCEC, and UCS, and missense mutations, amplifications, and deep deletions are the predominant mutation types (Figure 6B). Shallow deletion in TRIM17 mRNA expression in 33 tumor types were mainly seen in ACC, BLCA, GBM, HNSC, KICH, KIRC, KIRP, LGG, PRAD, SARC, and amplification were mainly seen in BRCA, LIHC, LUAD, OV (Figure 6C).

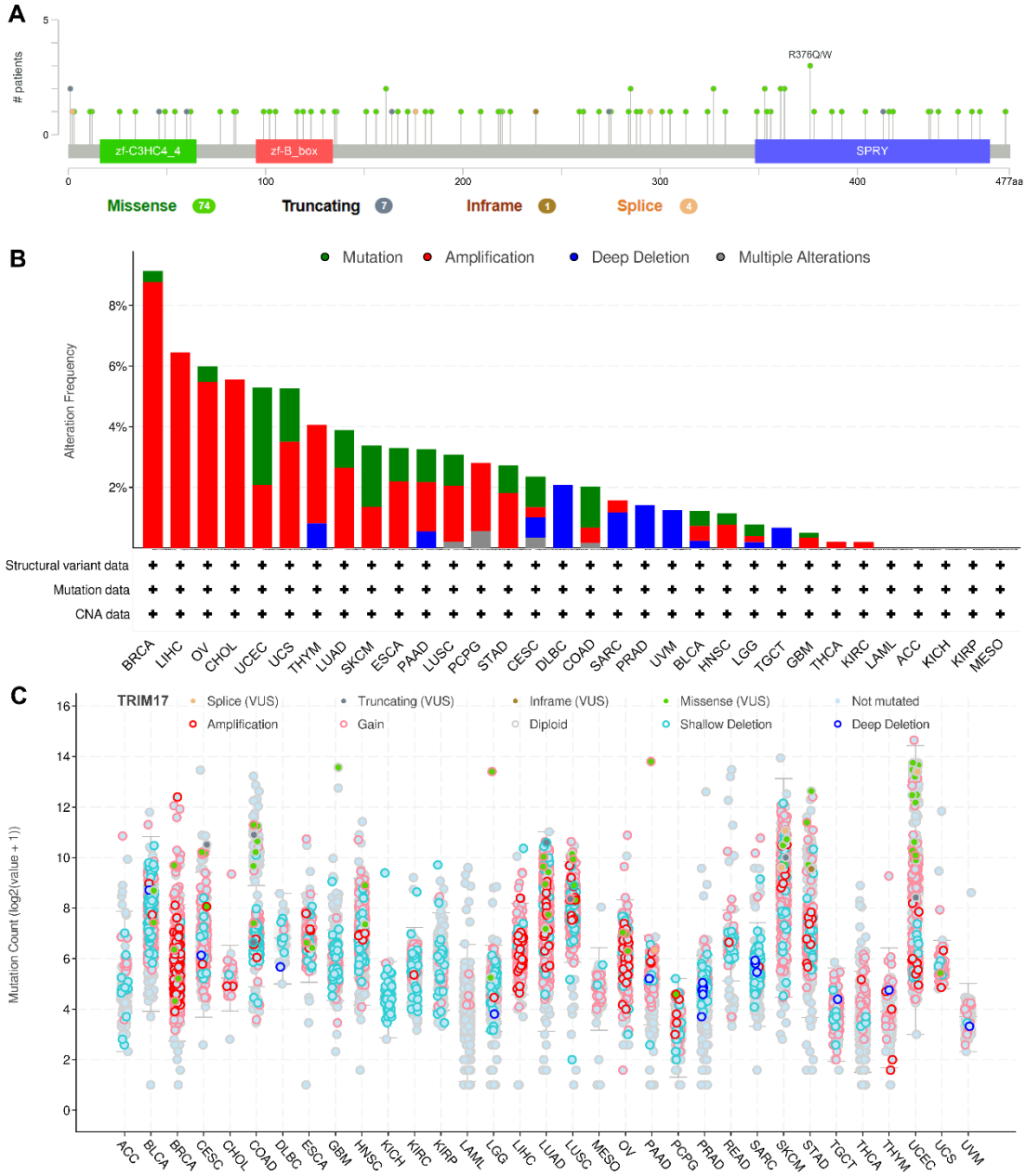

Figure 6 Genetic alteration of TRIM17 in different cancers. (A) Mutation diagram of TRIM17 across protein domains; (B) Bar chart of TRIM17 mutations in cancer studies based on TCGA pan-cancer atlas studies; (C) Mutation counts and types of TRIM17 in cancers.

The PPI, GO/KEGG functional enrichment of TRIM17 in cancers

In the string database, we screened 16 genes closely related to TRIM17 and established a PPI network (Figure 7A). The first ten hub genes are BBOX1, UBE2D1, TRIM17, TRIM9, TMLHE, TRAT1, TRIM24, TRIM28, TRIM33, and TRIM39 (Figure 7B). With the exception of UBE2D1, which is not correlated, the other genes are correlated to varying degrees in different cancers (Figure 7C).

These genes were next analyzed for GO/KEGG enrichment. RNA function was categorized in GO enrichment analysis into the biological process (BP), cellular component (CC), and molecular function (MF). The top GO terms of BP were amino-acid betaine metabolic process, suppression of viral release by host, carnitine metabolic process. The top GO terms of CC were nuclear matrix, heterochromatin, and euchromatin. The top GO terms of MF were ubiquitin-like protein transferase activity, ubiquitin-protein transferase activity and ubiquitin protein ligase activity. The top KEGG pathways were shigellosis, ubiquitin mediated proteolysis and lysine degradation. (Figure 7D).

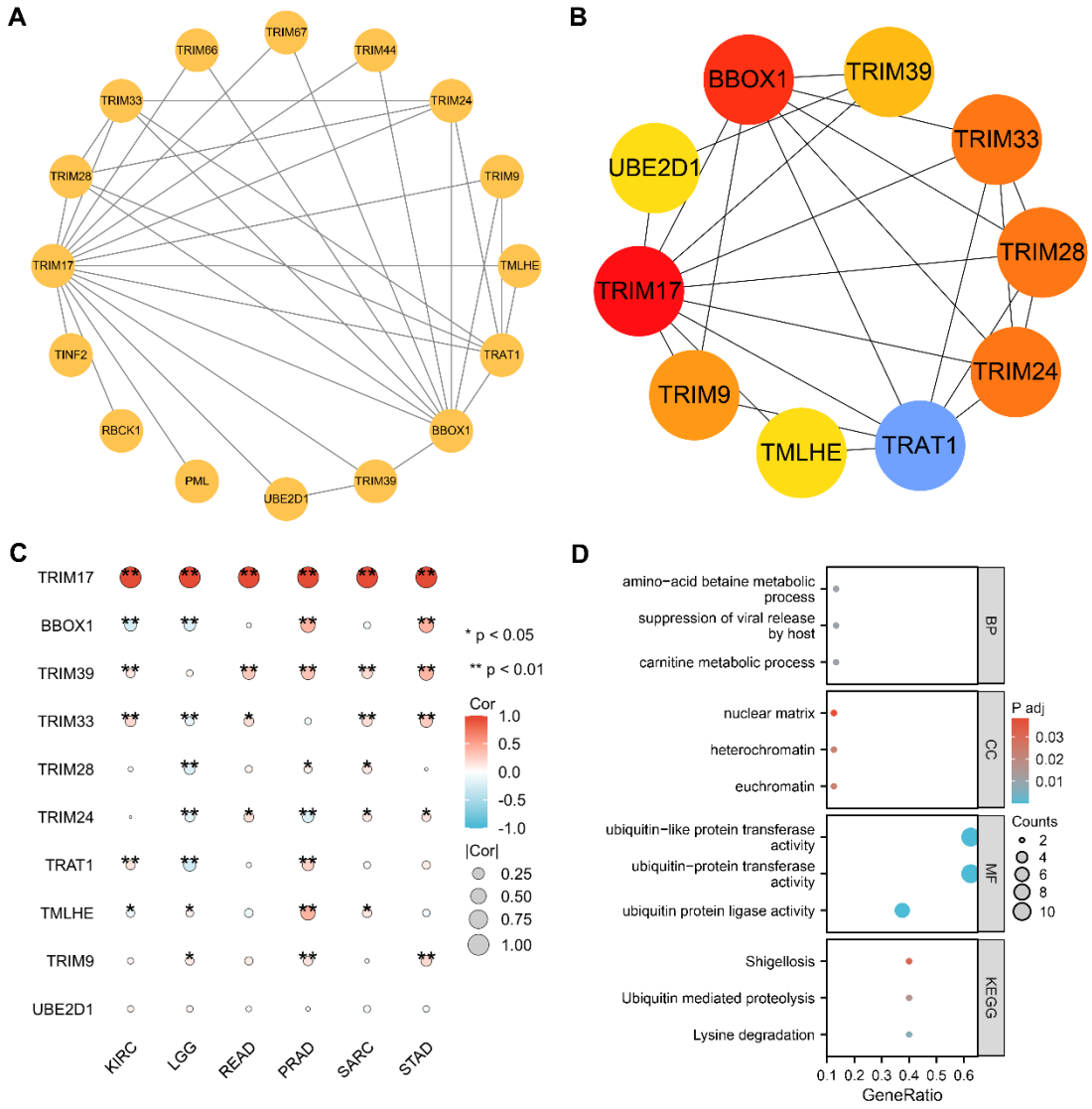

Figure 7 The PPI network and functional enrichment analysis of TRIM17. (A) The PPI network of TRIM17, (B) The top ten hub genes of PPI network, (C) The association hub gene with TRIM17 in 6 cancers present as heatmap. ∗p < 0:05, ∗∗p < 0:01, (D) GO/KEGG pathway enrichment for TRIM17.

Gene set enrichment of TRIM17 in cancers Figures 8A–I The GSEA results of 9 cancers are shown in .

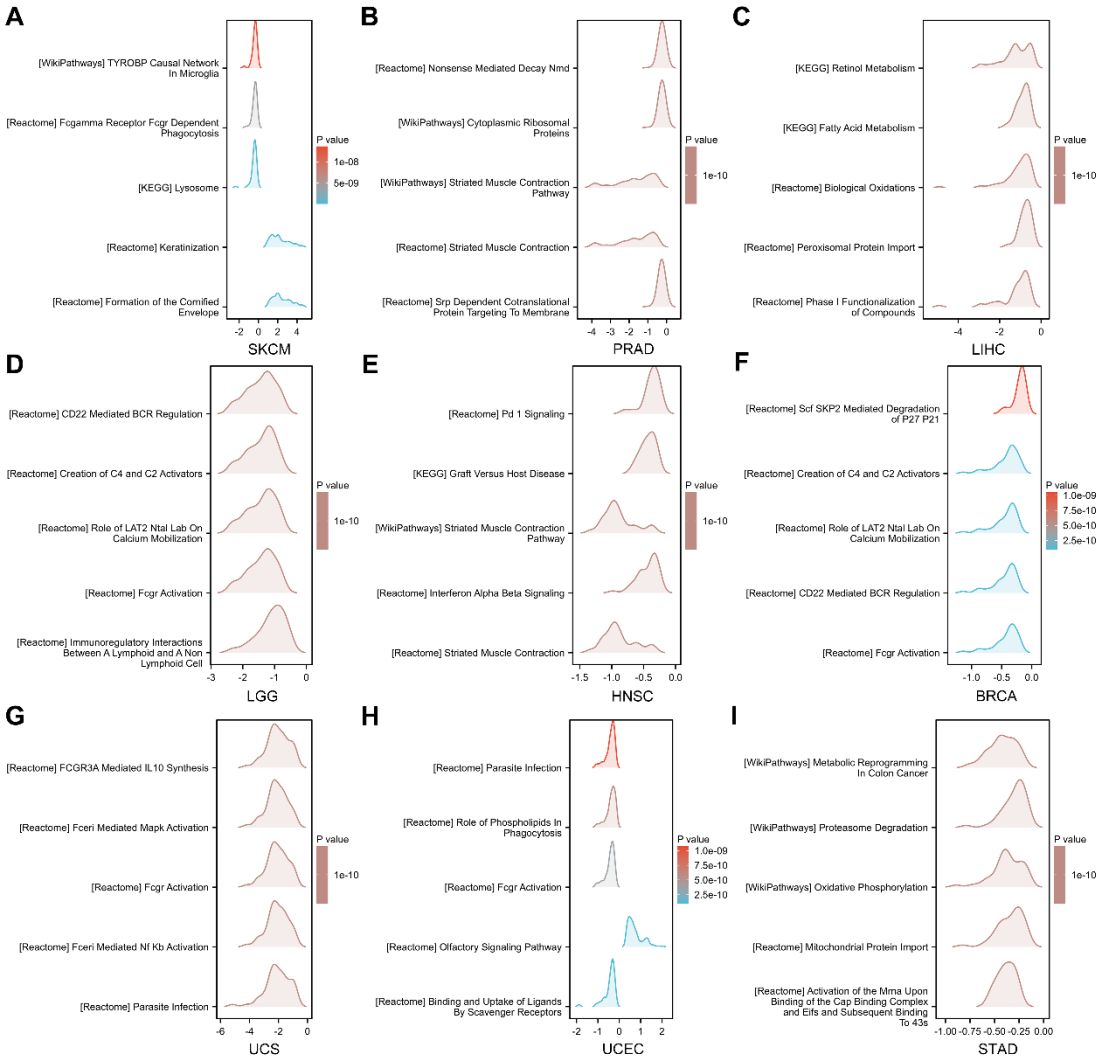

Figure 8 GSEA functional enrichment analysis of TRIM17 expression in 9 cancers. The top 5 GSEA functional enrichment pathways of TRIM17 in (A) SKCM, (B) PRAD, (C) LIHC, (D) LGG, (E) HNSC, (F) BRCA, (G) UCS, (H) UCEC, (I) STAD.

Although these results vary across cancer types, overall, the enriched pathways are mainly involved in: 1) inflammatory and immune-related functions, including FCGR3A mediated IL-10 synthesis, Fceri mediated MAPK activation, Fcgr activation, Fceri mediated NFκB activation, paradise infection, Fcgamma receptor Fcgr dependent phagocytosis, CD22 mediated BCR regulation, creation of C4 and C2 activators, immunoregulatory interactions between A lymphoid and A non- lymphoid cells, PD1 signaling, graft versus host disease, and interferon alpha beta signaling; 2) protein formation, transportation and degradation-related functions, including proteasome degradation, lysosome, mitochondrial protein import, peroxisomal protein import, cytoplasmic ribosome proteins, srp-dependent co-translational protein targeting to membrane, and scf SKP2 mediated degradation of P27 and P21; 3) functions related to substance metabolism and oxidative phosphorylation, including role of phospholipids in phagocytosis, metabolic reprogramming in colon cancer, oxidative phosphorylation, retinol metabolism, fatty acid metabolism, and biological oxidations. These results suggest that TRIM17 function is primarily associated with inflammation and immunity, regulation of protein function, and substance metabolism.

Functional States of TRIM17 in scRNA-Seq Datasets

Next, we further explored the correlation between TRIM17 expression in multiple tumor types and functional status at the single-cell level through the CancerSEA database. The results showed that TRIM17 expression had a positive correlation with angiogenesis, differentiation, inflammation

and stemness. Negative correlation was observed between the expression of TRIM17 and apoptosis, DNA damage, DNA repair and invasion (Figure 9A). The relationship between TRIM17 expression and functional status in specific tumor types was further investigated. In retinoblastoma (RB), TRIM17 positively correlated with angiogenesis, differentiation, inflammation and stemness and negatively correlated with apoptosis, DNA damage, DNA repair (Figure 9B). The expression of TRIM17 negatively correlated with invasion in GBM (Figure 9C). In uveal melanoma (UVM), TRIM17 had a negative correlation with apoptosis, DNA damage, DNA repair (Figure 9D). These results suggest that TRIM17 is involved in the regulation of multiple functional states in various tumors.

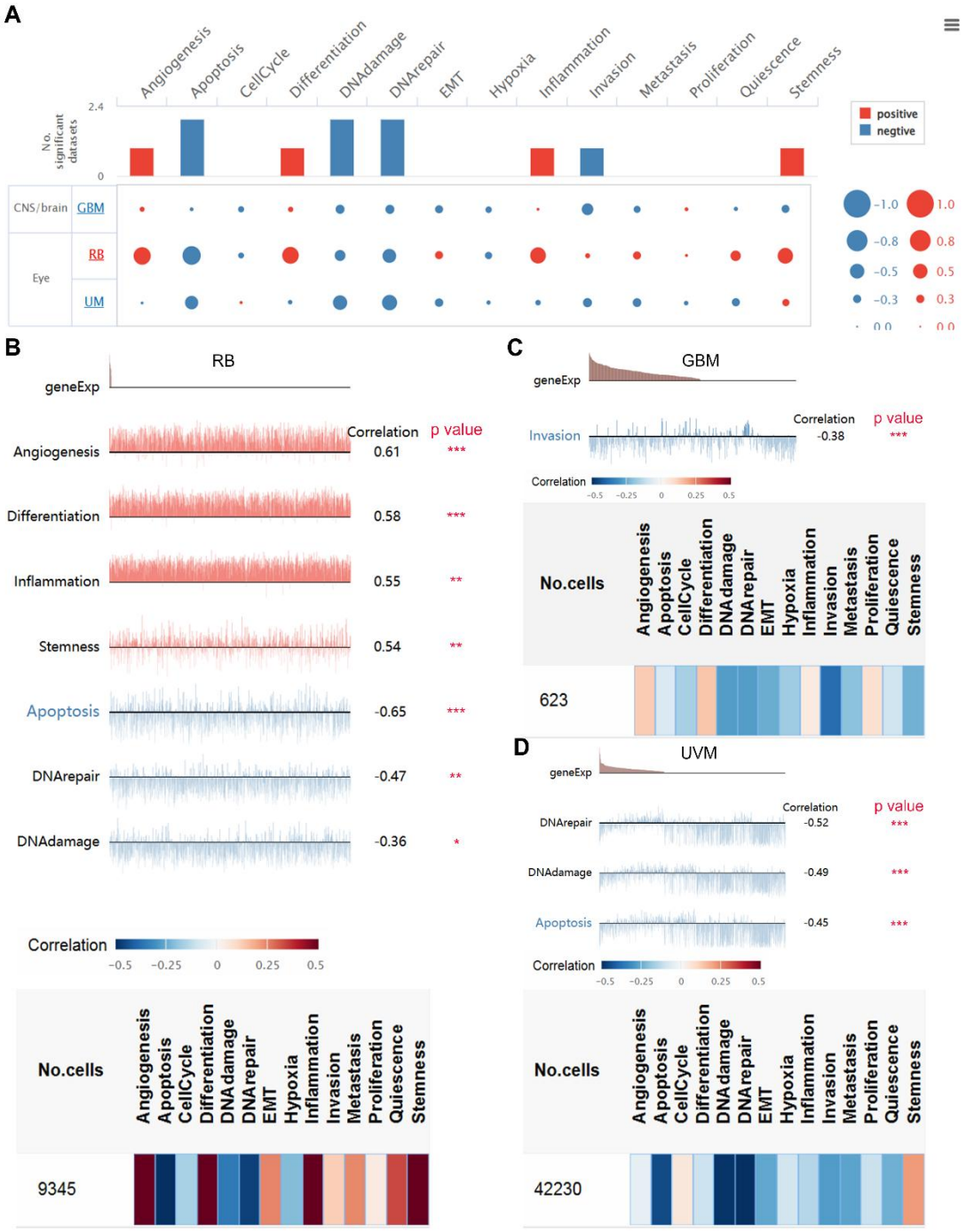

Figure 9 The correlation of TRIM17 with functional state in cancers. (A) The interactive bubble chart present correlation of TRIM17 with functional state in cancers. The correlation of TRIM17 with functional state in (B) RB, (C) GBM, (D) UVM; ***p < 0.001, **p < 0.01, *p < 0.05.

Immunogenomic analyses of TRIM17 in cancers

In order to further explore the relationship between TRIM17 and tumor immune regulation, we established a heat map of TRIM17 expression with immune cell markers or cytokines. The positive correlation of TRIM17 with most of the immunoinhibitors was observed in CESC, PRAD, TGCT, THCA, while the negative correlation was observed mainly in LGG, UVM (Figure 10A). In terms of immunostimulators, TRIM17 was positively correlated with most immunostimulators in the CESC, KIRC, LIHC, OV, PAAD, PRAD, TGCT and THCA, and negatively correlated with most immunostimulators in the LGG and UVM (Figure 10B). In addition, TRIM17 demonstrated a positive correlation with most MHCs in CESC, OV, PAAD, PRAD, TGCT, THCA, UCEC and a negative correlation with most MHCs in KIRP. LGG, MESO, SARC, STAD, UVM (Figure 10C). The majority of cytokines in CHOL, LIHC, PRAD and THCA showed a positive correlation with TRIM17, while in MESO and SARC there were negative correlations (Figure 10D). As for cytokine receptors, TRIM17 showed a positive correlation with most of them in CESC, LIHC, PRAD, TGCT, THCA, and a negative correlation in LGG (Figure 10E). These results suggest that TRIM17 has an immunomodulatory role in a wide range of tumors, but may play different regulatory roles in different tumor types.

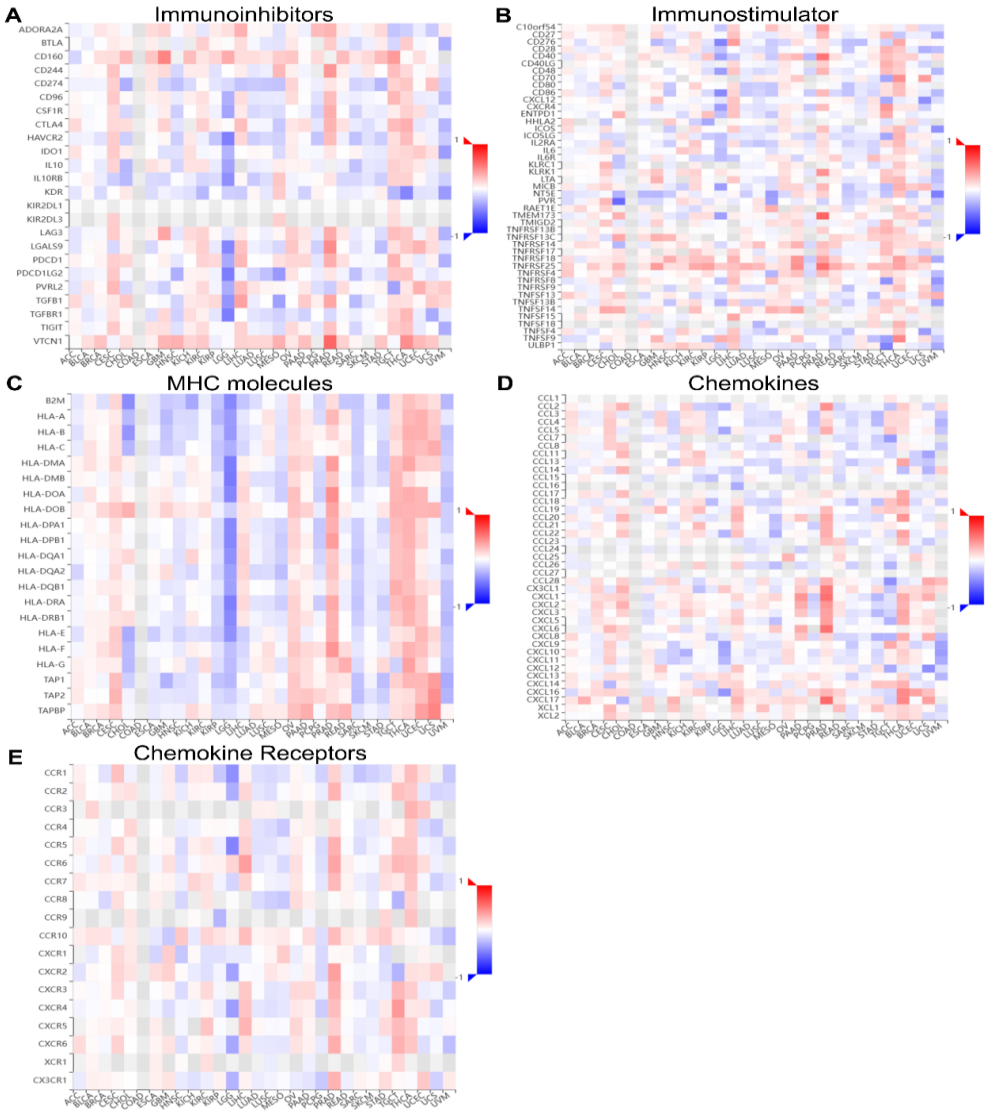

Figure 10 Correlation of TRIM17 with immunoregulation-related genes in cancers. Correlations between TRIM17 expression and (A) Immunoinhibitors, (B) Immunostimulators, (C) MHC molecules, (D) Chemokines, (E) Chemokine receptors. ⁎p < 0:05, ⁎⁎p < 0:01, ⁎⁎⁎p < 0.001.

TRIM17 is involved in the regulation of GBM cell proliferation, migration capacity

Taken together, we found that TRIM17 was involved in regulating multiple functions in a variety of tumors, especially in GBM. Thus, we further verified the role played by TRIM17 in GBM by in vitro experiments. Transwell migration assay showed that overexpression of TRIM17 significantly inhibited the migration ability of LN229 cells, whereas knockdown of TRIM17 resulted in an elevated level of LN229 migration (Figure 11A-B). Consistent with this, trauma healing assays further demonstrated that the migratory ability of LN229 cells was elevated with increasing levels of TRIM17 expression, while knockdown vice versa (Figure 11C-D). In addition, CCK8 cell proliferation assays demonstrated that overexpression of TRIM17 inhibited the proliferation of LN229 cells, whereas knockdown significantly promoted cell growth (Figure 11E-F). These results suggest that TRIM17 inhibits the growth and metastatic ability of GBM cells and may be a valuable tumor suppressor.

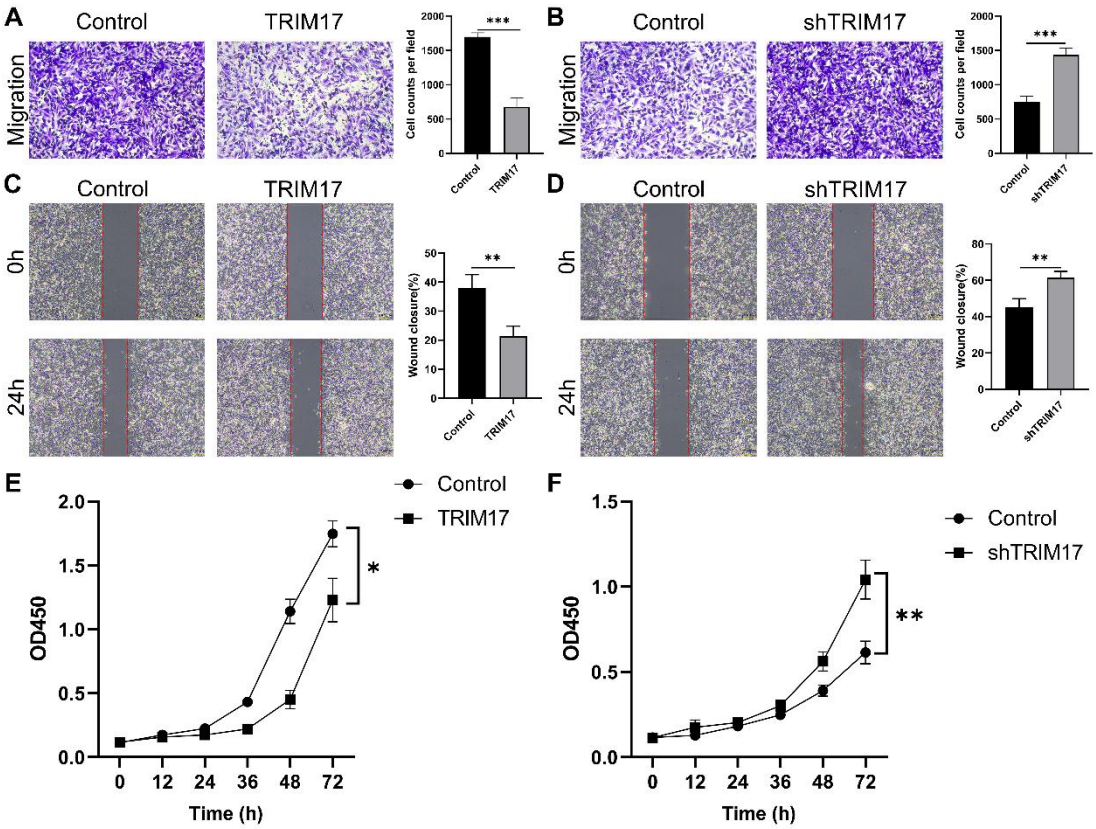

Figure 11 TRIM17 is involved in the regulation of GBM cell proliferation, migration capacity. Transwell migration assay of LN229 cell line with overexpression (A) and knockdown (B) of TRIM17. Wound healing experiments of LN229 cell line with overexpression (C) and knockdown (D) of TRIM17. CCK8 cell proliferation assay of LN229 cell line with overexpression (C) and knockdown (D) of TRIM17∗p < 0:05, ∗∗p < 0:01, ***p < 0.001.

Conclusion

Tumor development is a complex process involving multiple signaling pathways and dynamic regulation driven by the involvement of multiple genes[11, 12]. Among them, some key genes may play irreplaceable roles, including oncogenes and tumor-suppressor genes [13, 14]. Benefiting from the continuous development of bioinformatics, we can easily obtain massive tumor sequencing data and use updated algorithms to screen molecules that play important roles in pan-cancer and specific tumors and predict their mechanisms of action[15, 16]. These technologies are undoubtedly driving oncology research forward.

TRIM17 is an important member of the TRIM family, which contains over 80 known TRIM proteins in humans[17]. Due to the presence of the

RING-finger domain and a zinc finger structural domain named B-BOX, TRIM17 is defined as an E3 ubiquitin ligase that activates the proteasomal degradation pathway[18]. Previous studies have shown that, in addition to the above functions, TRIM17 can perform a "dual function" by binding to other TRIM proteins, such as TRIM28, TRIM39, and TRIM41, inhibiting their E3 ubiquitin ligase activity, preventing ubiquitination and stabilizing other proteins[7, 19, 20]. On this basis, TRIM17 is involved in regulating the stability of transcription factors[7], apoptosis[6] and autophagy[21]-associated factors, and further regulates cell proliferation and mitosis[22], mediating the development of numerous diseases such as Parkinson's disease[23], autism[23, 24], and cognitive disorders[25].

In tumors, current studies also support the important regulatory role played by TRIM17 as an E3 ubiquitin ligase. For example, in gastric cancer, high expression of TRIM17 was significantly associated with poor prognosis. Further mechanistic studies suggest that TRIM17 promotes gastric cancer progression by regulating BAX protein stability and antagonising apoptosis[8]. In non-small cell lung cancer, TRIM17 is closely associated with the development of Cisplatin resistance, which is mainly generated by promoting RBM38 ubiquitination and degradation[9]. These results imply that TRIM17 may be a valuable molecular marker and therapeutic target for tumors, but there is still a need to explore its value in other tumors. Therefore, in present study, we explored the role of TRIM17 in pan-cancer using a bioinformatics approach. Our results showed that TRIM17 expression was significantly higher in the nervous system and testis than in other tissues, which may imply its unique role in mediating neurological disorders as well as in regulating life activities such as cell division (Figure 1). The expression of TRIM17 was not the same in different tumors. We found that TRIM17 expression was significantly higher in some tumors than in normal tissues, while in others the opposite was true (Figure 2). This suggests that TRIM17 may play different or even opposite roles in different tumors.

The diagnostic and prognostic value of TRIM17 has also been further explored. We demonstrated tumor types with AUC greater than 0.8, including ACC, CHOL, GBM, KICH, LAML, PCPG, SKCM, TGCT and THYM, suggesting that TRIM17 has good diagnostic value in these cancers (Figure 3). Interestingly, high TRIM17 expression for LGG implied a better prognosis for both OS and DFS (Figure 4), which is consistent with the results in Fig. 1. TRIM17 expression did not have a significant impact on survival in some tumors, but this does not mean that it is of no value in these cancers. In fact, TRIM17 is abnormally expressed in a particular cancer subtype, and the results may not be reflected in the overall population of that cancer. Therefore, analysis of TRIM17 expression in different tumor molecular subtypes and immune subtypes is necessary (Figure 5 and 6). We also observed that TRIM17 was mutated frequently in different cancers, especially in BRCA, LIHC, OV, CHOL with the alteration frequency up to about 6% (Figure 7).

To further elucidate the role of TRIM17 in tumors, we next explored its protein interaction network, functional enrichment, and correlation with cancer status and immune status. We identified 10 hub genes and explored their relationship with TRIM17 expression in various cancers. The expression of TRIM17 is closely associated with these genes, suggesting that they have complementary biological roles in cancer. Interestingly, most of these genes are E3 ubiquitin ligases, suggesting that TRIM17 may act synergistically with other E3 ubiquitin ligases to exert ubiquitination regulation (Figure 8). Although GSE enrichment analyses revealed that the functions of TRIM17 varied in different tumors, overall, these functions can be grouped into three main categories, including inflammatory and immune-related functions, protein formation, transportation and degradation-related functions, and functions related to substance metabolism and oxidative phosphorylation (Figure 9). This was further confirmed by subsequent analyses of cancer functional status and immune status (Figure 10-11).

In conclusion, our study elucidated the role of TRIM17 in pan-cancer from multiple perspectives, including its expression profile, associated functions, mutation sites, and relationship with immune status. TRIM17 has potential diagnostic and prognostic potential, and is expected to be a therapeutic target for a number

of tumors. However, these studies are limited to comprehensive analyses of existing data, and we still need to further validate these findings in in vitro and in vivo experiments in the future. We believe that these findings can provide a reference for revealing the clinical application value of TRIM17.

Data Availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

References

1. Sung, H., et al., Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin, 2021. **71**(3): p. 209-249.
2. Bray, F., et al., The ever-increasing importance of cancer as a leading cause of premature death worldwide. Cancer, 2021. **127**(16): p. 3029-3030.
3. Wang, Q., et al., Spatially Resolved Transcriptomics Technology Facilitates Cancer Research. Adv Sci (Weinh), 2023. **10** (30): p. e2302558.
4. Ahmed, R., et al., Single-Cell RNA Sequencing with Spatial Transcriptomics of Cancer Tissues. Int J Mol Sci, 2022. **23**(6).
5. Cortes-Ciriano, I., et al., *Computational analysis of cancer genome sequencing data.* Nat Rev Genet, 2022. **23**(5): p. 298-314.
6. Magiera, M.M., et al., Trim17-mediated ubiquitination and degradation of Mcl-1 initiate apoptosis in neurons. Cell Death Differ, 2013. **20**(2): p. 281-92.
7. Lassot, I., et al., The E3 Ubiquitin Ligases TRIM17 and TRIM41 Modulate alpha-Synuclein Expression by Regulating ZSCAN 21. Cell Rep, 2018. **25**(9): p. 2484-2496 e9.
8. Shen, J., et al., The E3 ubiquitin ligase TRIM17 promotes gastric cancer survival and progression via controlling BAX stability and antagonizing apoptosis. Cell Death Differ, 2023. **30**(10): p. 2322-2335.
9. Zhong, T., et al., TRIM17-mediated ubiquitination and degradation of RBM38 promotes cisplatin resistance in non-small cell lung cancer. Cell Oncol (Dordr), 2023. **46**(5): p. 1493-1507.
10. Hu, W., et al., Comprehensive Analysis of TRIM Family Genes in Hepatitis Virus B-Related Hepatoma Carcinoma. Front Genet, 2022. **13**: p. 913743.
11. Peng, W., et al., Improving cancer driver gene identification using multi-task learning on graph convolutional network. Brief Bioinform, 2022. **23**(1).
12. Graham, T.A. and A. Sottoriva, *Measuring cancer evolution from the genome.* J Pathol, 2017. **241**(2): p. 183-191.
13. Petroni, G., et al., Targeting oncogene and non-oncogene addiction to inflame the tumour microenvironment. Nat Rev Drug Discov, 2022. **21**(6): p. 440-462.
14. Kontomanolis, E.N., et al., Role of Oncogenes and Tumor-suppressor Genes in Carcinogenesis: A Review. Anticancer Res, 2020. **40**(11): p. 6009-6015.
15. Jimenez-Santos, M.J., et al., *Bioinformatics roadmap for therapy selection in cancer genomics.* Mol Oncol, 2022. **16**(21): p. 3881-3908.
16. Jiang, P., et al., *Big data in basic and translational cancer research.* Nat Rev Cancer, 2022. **22**(11): p. 625-639.
17. Reymond, A., et al., The tripartite motif family identifies cell compartments. EMBO J, 2001. **20**(9): p. 2140-51.
18. Huang, N., et al., TRIM family contribute to tumorigenesis, cancer development, and drug resistance. Exp Hematol Oncol, 2022. **11**(1): p. 75.
19. Lionnard, L., et al., TRIM17 and TRIM28 antagonistically regulate the ubiquitination and anti-apoptotic activity of BCL2A1. Cell Death Differ, 2019. **26**(5): p. 902-917.
20. Basu-Shrivastava, M., et al., Trim39 regulates neuronal apoptosis by acting as a SUMO-targeted E3 ubiquitin-ligase for the transcription factor NFATc3. Cell Death Differ, 2022. **29**(11): p. 2107-2122.
21. Mandell, M.A., et al., TRIM proteins regulate autophagy and can target autophagic substrates by direct recognition. Dev Cell, 2014. **30**(4): p. 394-409.
22. Endo, H., et al., Terf/TRIM17 stimulates degradation of kinetochore protein ZWINT and regulates cell proliferation. J Biochem, 2012. **151**(2): p. 139-44.
23. Farlow, J.L., et al., *Whole-Exome Sequencing in Familial Parkinson Disease.* JAMA Neurol, 2016. **73**(1): p. 68-75.

24. Satterstrom, F.K., et al., Large-Scale Exome Sequencing Study Implicates Both Developmental and Functional Changes in the Neurobiology of Autism. Cell, 2020. **180**(3): p. 568-584 e23.
25. Najmabadi, H., et al., Deep sequencing reveals 50 novel genes for recessive cognitive disorders. Nature, 2011. **478**(7367): p. 57-63.