Original Article

A pancancer analysis of histone deacetylase 3 in human tumors

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Background: Histone deacetylase 3 (*HDAC3*) is known to be an important role in various kinds of cancer, but its effect has not been examined on the pancancer level. Thus, a systematic pancancer analysis was conducted to explore its potential role in pancancer diagnosis, prognosis, and immune correlation research.

Methods: We used a series of databases including The Cancer Genome Atlas (TCGA), Genotype-Tissue Expression (GTEx) Project, The University of Alabama at Birmingham Cancer data analysis portal (UALCAN), Tumor Immune Estimation Resource (TIMER), and Search Tool for the Retrieval of Interacting Genes/Proteins (STRING), among others, to analyze the relationship between the expression of *HDAC3* and the diagnosis and prognosis of cancer, the tumor microenvironment (TME), immune infiltration, tumor mutational burden (TMB), microsatellite instability (MSI), mismatch repair (MMR) system using various bioinformatics methods. Downstream pathways of *HDAC3* were identified by gene set enrichment analysis (GSEA). Furthermore, the protein expression of HDAC3 in tumor tissues and normal tissues of 17 patients with gliomas was analyzed via western blotting.

Results: The expression of *HDAC3* changed in most types of tumors, which was closely related to most tumor diagnoses and negatively related to some patients' overall survival (OS) and recurrence-free survival (RFS). The pan-cancer analysis demonstrated that it was tightly correlated to DNA methylation and RNA methylation modifications and associated with TMB and MSI. The expression level of *HDAC3* was positively correlated with many immune checkpoint molecules and regulators and positively associated with the infiltration levels of immune cells in the TME in most tumor types. Furthermore, enrichment analysis revealed that transcriptional misregulation in cancer and RNA splicing functions were involved in the functional mechanism of *HDAC3*-related genes. Experimental research showed that the protein expression of HDAC3 was elevated in tumor tissues of patients with glioma.

Conclusions: Through our comprehensive bioinformatics analysis, we evaluated the role of *HDAC3* in pancancer, and our findings suggest that it may be an indicator for some cancer diagnoses and influence immune balance.

Keywords: Histone deacetylase 3 (*HDAC3*); pancancer; DNA methylation; diagnosis

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Introduction

Cancer has been one of the leading causes of death in the 21st century (1), with its incidence and mortality rapidly growing worldwide (2). Scientists are exploring new treatment methods that involve biomarkers and novel immunotherapeutic targets.

Epigenetic alterations result in tumor initiation and development by affecting normal gene expression (3). Histone deacetylase 3 (*HDAC3*) is an important zinc-dependent metalloenzyme that can arise from various types of disease in humans through epigenetic modulations (4). The expression of *HDAC3* is correlated with several cancers, including lung cancer, breast cancer, liver cancer, lower-grade glioma, colorectal carcinoma, and prostate cancer (5-10). HDAC inhibitors are small-molecule drugs and have been approved by the US Food and Drug Administration (FDA) as anticancer drugs due to their remarkable effectiveness (11). However, the research into *HDAC3* has been limited to a few tumor types, and the function of *HDAC3* in pancancer has not been investigated.

We therefore conducted a bioinformatics analysis to comprehensively characterize the expression of *HDAC3* in pancancer in terms of differential gene expression; DNA methylation; diagnosis and prognosis; association with tumor mutational burden (TMB), microsatellite instability (MSI), mismatch repair (MMR) system, tumor infiltration, and immune-related gene research; and the pathways of different tumor types. The results indicated that *HDAC3* is altered in many types of cancers, with an overexpression of messenger RNA (mRNA) and protein in glioblastoma multiforme (GBM). We further examined the protein levels of HDAC3 in patients with glioma. High expression of *HDAC3* was often associated with poor prognosis and thus may be a valuable diagnostic indicator in a variety of cancers, including GBM and lung squamous cell carcinoma (LUSC). The methylation levels of *HDAC3* were elevated in several cancers and there were significant correlations of *HDAC3* with TMB, MSI, and MMRs in some tumor types. Moreover, *HDAC3* was closely associated with immune-related pathway enrichment and the expression of immune-related genes, while changes in *HDAC3* were accompanied by altered tumor lymphocyte infiltration. Overall, the role of *HDAC3* in various tumors should be considered in guiding future clinical diagnosis and treatment. We present this article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1228/rc).

Highlight box

Key findings

- There was a strong correlation between the level of histone deacetylase 3 (*HDAC3*) expression and the level of immune infiltration in the tumor tissue of patients.

What is known and what is new?

- *HDAC3* has been used as a target for the treatment of tumors, and specific inhibitors have been used to treat hematological tumors.
- The expression of *HDAC3* in various tumor types was altered depending on tumor immune infiltration, immune checkpoints, and immune chemokines. *HDAC3* demonstrated diagnostic and prognostic value across various tumor types.

What is the implication, and what should change now?

- The expression of *HDAC3* could be used as a diagnostic and therapeutic indicator for some tumors.

Methods

HDAC3 expression in pancancer

RNA sequencing and clinical data were downloaded from the UCSC Xena website (https://xenabrowser.net/datapages/), which included The Cancer Genome Atlas (TCGA), and Genotype–Tissue Expression (GTEx) Project databases. Using the "Proteomics" module from the University of Alabama At Birmingham Cancer data analysis portal (UALCAN) (12) (http://ualcan.path.uab.edu/index.html), we assessed the HDAC3 protein expression levels in normal tissues and tumors.

Prognosis and diagnostic research

The Kaplan-Meier plotter (13) (http://kmplot.com/analysis/) was used to determine the association between *HDAC3* expression and overall survival (OS) and recurrence-free survival (RFS) across diverse tumor types, and the prognostic value of *HDAC3* was determined according to the receiver operating characteristic (ROC). The calculated area under the curve (AUC) ranges from 0.5 to 0.1 corresponding to an identification potential of 50% to 100%. The data in this analysis were respectively analyzed and visualized with the "pROC" and "ggplot2" packages in R software version 3.6.3 (The R Foundation for Statistical Computing).

DNA methylation study

Data methylation levels of *HDAC3* in tumors and corresponding normal tissues were obtained from the UALCAN database. "*HDAC3*" was entered into the "TCGA Gene" module and "Methylation" was selected in the "Select links for analysis" to obtain these results. The beta value indicated a level of DNA methylation ranging from 0 (unmethylated) to 1 (fully methylated).

RNA modification, tumor infiltration, and immune-related gene analysis

Tumor Immune Estimation Resource (TIMER) (https://cistrome.shinyapps.io/timer/) and XCELL tools (https://xcell.ucsf.edu/) were used to evaluate the immunological roles of *HDAC3*. Pearson correlation analysis via Sangerbox (14) (http://vip.sangerbox.com/) was used to assess the correlation of *HDAC3* mRNA expression with RNA modification of 1-methyladenosine (m1A), 5-methylcytosine (m5C), N6-methyladenosine (m6A); five immune functions [chemokine, receptor, major histocompatibility complex (MHC), immune inhibitor, immune stimulator], and immune checkpoint pathway–related genes (inhibitory and stimulatory) in samples from TCGA database.

TMB, MSI, and MMRs analysis

TMB and MSI scores were accessed from TCGA database. Spearman correlation coefficient was used to determine the correlation between *HDAC3* expression and TMB and MSI. The TIMER2.0 database (http://timer.comp-genomics.org/) was used to determine the correlation between *HDAC3* and the expression of four methyltransferases.

Enrichment analysis of HDAC3-related genes

The terms "*HDAC3*" and "Homo sapiens" were searched on the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database (https://cn.string-db.org). The following settings were used obtain the HDAC3-associated protein–protein interaction (PPI) network: parameter minimum required interaction score set to "Low confidence" (0.150), a meaning of network edges set to "evidence", and the max number of interactors set to "no more than 50 interactors. Next, we used the Gene Expression Profiling Interactive Analysis 2 (GEPIA2; http://gepia2.cancer-pku.cn/#index) "Similar gene detection" module in TCGA datasets to acquire the top 200 genes related to *HDAC3*. The association heatmap of *HDAC3* and its related genes in different tumors was generated via TIMER2.0. The *HDAC3*-related genes were subjected to Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis and visualization via R software packages "ClusterProfiler" (15) and "ggplot2", respectively.

Gene set enrichment analysis (GSEA) of HDAC3

The R software package "ClusterProfiler" was used to conduct enrichment analysis of the ontology gene sets (C5) from the Molecular Signatures Database (MSigDB; https://www.gsea-msigdb.org/gsea/msigdb/index.jsp). Gene sets with a |normalized enrichment score (NES)| >1, adjusted P value <0.05, and false-discovery rate (FDR) <0.2 were considered to be significantly enriched.

Western blot experiments of in patients with glioma

Seventeen patients with glioma who underwent surgery in Tangshan Workers' Hospital were selected, and tumor tissues and normal tissues were obtained for Western blot experiments. The inclusion criteria were patients diagnosed with primary glioma and complete medical records. Meanwhile, the exclusion criterion was combination with other malignant tumors, autoimmune diseases, or other diseases. GraphPad Prism 8 (GraphPad Software) and ImageJ (US National Institutes of Health) were used to evaluate the experimental results.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Tangshan Workers' Hospital (No. GRYY-LL-KJ2022-K27). Informed consent was obtained from all the patients.

Reagents

Antibodies included in the experiment were those for *HDAC3* (cat. no. 3949; Cell Signaling Technology), GAPDH (cat. no. ET1601-4; HUABIO), anti-mouse immunoglobin (Ig) G (cat. no. B900620; Proteintech), and anti–rabbit IgG (cat. no. 30000-0-AP; Proteintech).

Statistical analysis

Data were visualized with the above-mentioned packages in R version 3.6.3. Analysis of variance was used to examine the Western blot results. Values of P<0.05 were regarded as

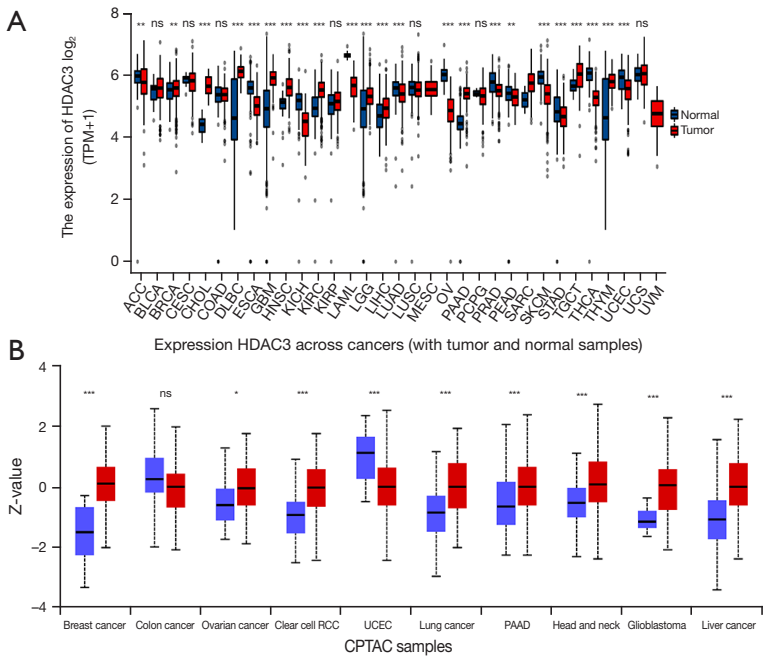

Figure 1 The analysis of *HDAC3* expression. (A) The differences in *HDAC3* mRNA expression between normal tissues in the GTEx database and tumor tissue in TCGA database. (B) The differences in HDAC3 protein expression were based on the UALCAN database and CPTAC data. ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CPTAC, Clinical Proteomic Tumor Analysis Consortium; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DLBC, lymphoid neoplasm diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; GTEx, Genotype-Tissue Expression; HDAC3, histone deacetylase 3; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, lower-grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; mRNA, messenger RNA; 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; TCGA, The Cancer Genome Atlas; TGCT, testicular germ cell tumors; THCA, thyroid carcinoma; THYM, thymoma; TPM, transcripts per million; UALCAN, The University of Alabama at Birmingham cancer data analysis portal; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma. *, P<0.05; **, P<0.01; ***, P<0.001; ns, no significance.

statistically significant difference.

Results

HDAC3 expression in pancancer

Due to the lack of normal tissue samples in the TCGA database, data of normal tissue from the GTEx database were combined with those of tumor tissue data from TCGA database to examine the differences of *HDAC3* expression in 33 cancers. The results showed that *HDAC3* expression was higher in 11 cancer types: (BRCA), cholangiocarcinoma (CHOL), lymphoid neoplasm diffuse large B-cell lymphoma (DLBC), GBM, head and neck squamous cell carcinoma (HNSC), kidney renal clear-cell carcinoma (KIRC), lower-grade glioma (LGG), liver hepatocellular carcinoma (LIHC), pancreatic adenocarcinoma (PAAD), testicular germ cell tumor (TGCT), and thymoma (THYM); meanwhile, *HDAC3* expression was lower in 12 cancer types: adrenocortical carcinoma (ACC), esophageal carcinoma (ESCA), kidney chromophobe (KICH), acute myeloid leukemia (LAML), lung adenocarcinoma (LUAD), ovarian serous cystadenocarcinoma (OV), prostate adenocarcinoma (PRAD), rectum adenocarcinoma (READ), skin cutaneous melanoma (SKCM), stomach adenocarcinoma (STAD), thyroid carcinoma (THCA), and uterine corpus endometrial carcinoma (UCEC) (all P values <0.05) (*Figure 1A*). Additionally, Clinical

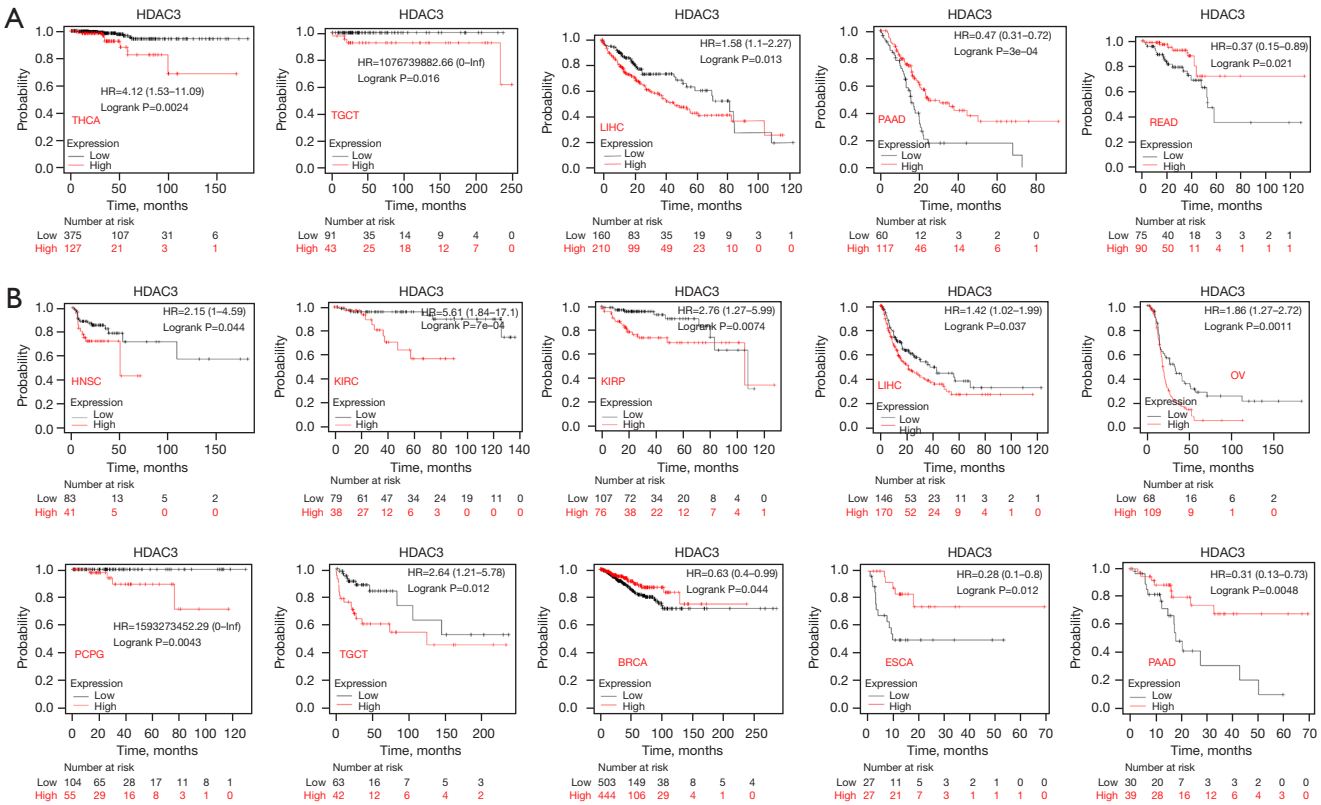

Figure 2 The relationship between prognosis and *HDAC3* expression. The patients' OS (A) and RFS (B) according to a high or low *HDAC3* expression level across tumor types as demonstrated by the Kaplan-Meier plotter. BRCA, breast invasive carcinoma; ESCA, esophageal carcinoma; HDAC3, histone deacetylase 3; HNSC, head and neck squamous cell carcinoma; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LIHC, liver hepatocellular carcinoma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; READ, rectum adenocarcinoma; THCA, thyroid carcinoma; TGCT, testicular germ cell tumor; OS, overall survival; RFS, recurrence-free survival.

Proteomic Tumor Analysis Consortium (CPTAC) data obtained from the UALCAN database were applied to assess HDAC3 protein expression in human cancers. HDAC3 was significantly elevated in breast cancer, ovarian cancer, clear-cell renal cell carcinoma (RCC), lung cancer, PAAD, head and neck cancer, glioblastoma, and liver cancer but decreased in UCEC (all P values <0.05) (*Figure 1B*). Our findings indicated that *HDAC3* may have opposing roles depending on the cancer type, acting as either a tumor-suppressing or a tumor-promoting molecule.

Relationship between prognosis and HDAC3 expression

To evaluate patients' OS and RFS, we used the Kaplan-Meier analysis method. The results showed that a high *HDAC3* level was negatively correlated with the OS of patient with THCA (P<0.001), TGCT (P=0.016), or LIHC (P=0.013) but positively correlated with the OS of patients with READ (P=0.021) or PAAD (P<0.001) (*Figure 2A*). Moreover, in patients with HNSC (P=0.044), KIRC (P<0.001), kidney renal papillary cell carcinoma (KIRP) (P=0.007), LIHC (P=0.037), OV (P=0.001), pheochromocytoma and paraganglioma (PCPG) (P=0.004), or TGCT (P=0.012), a high level of *HDAC3* was significantly associated with worse RFS; in contrast, it was associated with better RFS in patients with BRCA (P=0.044), ESCA (P=0.012), or PAAD (P=0.005) (*Figure 2B*). These results suggest that *HDAC3* may play a critical role in the survival of these patients.

A clinical diagnostic value assessment of HDAC3

The ROC curve was used to assess the diagnostic value of *HDAC3* in various cancers, which revealed the high

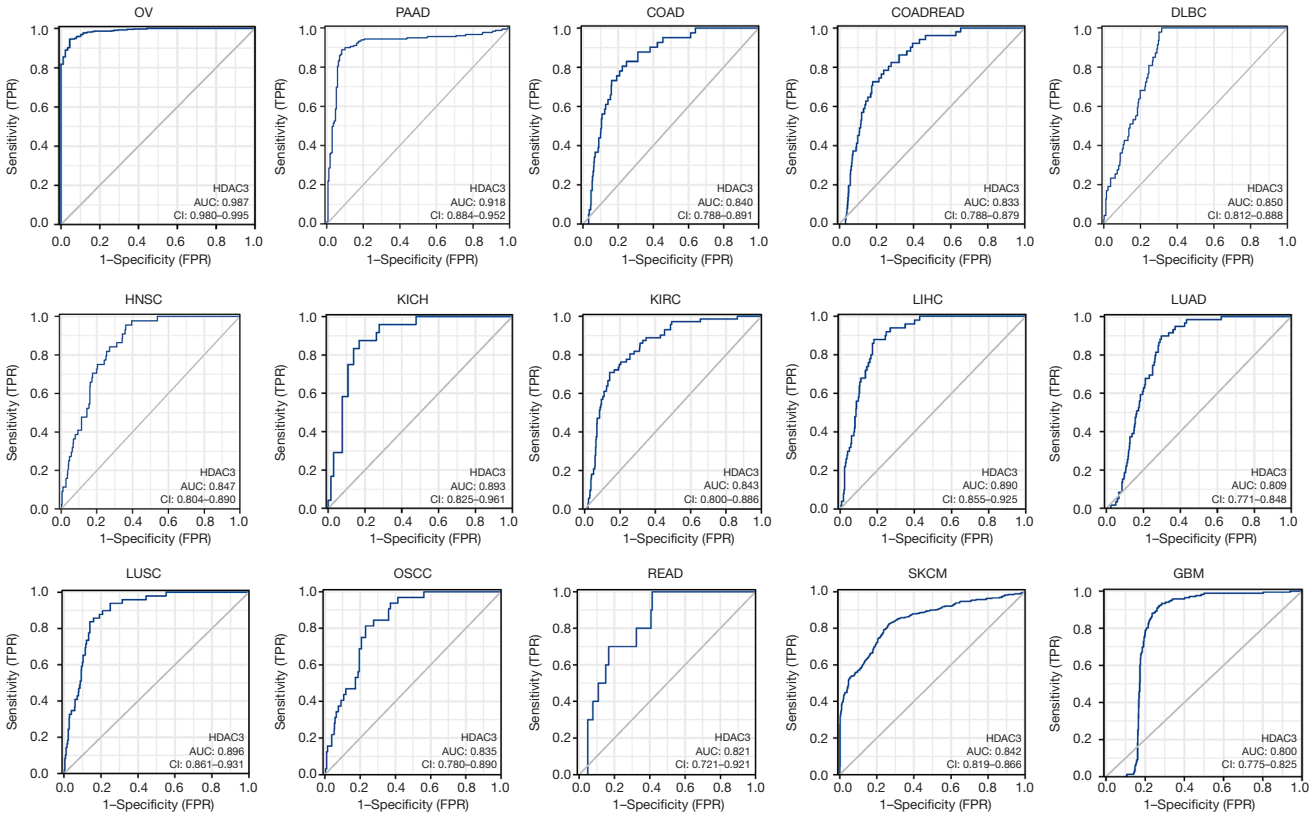

Figure 3 ROC curve of the diagnostic value of *HDAC3*. The association between *HDAC3* expression and prognostic value was evaluated using the "pROC" package in R. OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; COAD, colon adenocarcinoma; COADREAD, colon and rectal cancer; DLBC, diffuse large B-cell lymphoma; TPR, true-positive rate; HDAC3, histone deacetylase 3; AUC, area under the curve; FPR, false-positive rate; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; OSCC, oral squamous cell carcinoma; READ, rectum adenocarcinoma; SKCM, skin cutaneous melanoma; GBM, glioblastoma multiforme; ROC, receiver operating characteristic.

diagnostic value of *HDAC3* in OV and PAAD (AUC >0.9). Moreover, *HDAC3* demonstrated definitive value for diagnosing colon adenocarcinoma (COAD), colon and rectal cancer (COADREAD), DLBC, HNSC, KICH, KIRC, LIHC, LUAD, LUSC, oral squamous cell carcinoma (OSCC), READ, GBM, and SKCM (0.8≤ AUC <0.9) (*Figure 3*) and thus may be a diagnostic indicator in patients with these cancers.

Association of HDAC3 expression with DNA methylation and RNA methylation modifications

Methylation of tumor-suppressor genes is a common occurrence in various types of cancer, and the presence of methylated DNA has emerged as a promising biomarker for the early detection of cancer (16). Assessment of the methylation levels of the *HDAC3* in tumors and normal tissues in the UALCAN dataset showed that the methylation levels of the *HDAC3* was elevated in 11 tumor types, including BRCA (P<0.001), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC) (P<0.001), COAD (P<0.001), ESCA (P<0.001), HNSC (P<0.001), KIRC (P<0.001), KIRP (P<0.001), LUAD (P<0.001), LUSC (*P*<0.001), PRAD (P<0.001), and sarcoma (SARC) (P=0.012). Furthermore, the methylation levels in CHOL (P<0.001), TGCT (P<0.001), and bladder urothelial carcinoma (BLCA) (P<0.001) were significantly lower than those in normal tissues (*Figure 4A*). Therefore, DNA methylation level of *HDAC3* may serve as an early diagnostic indicator for patients with cancer.

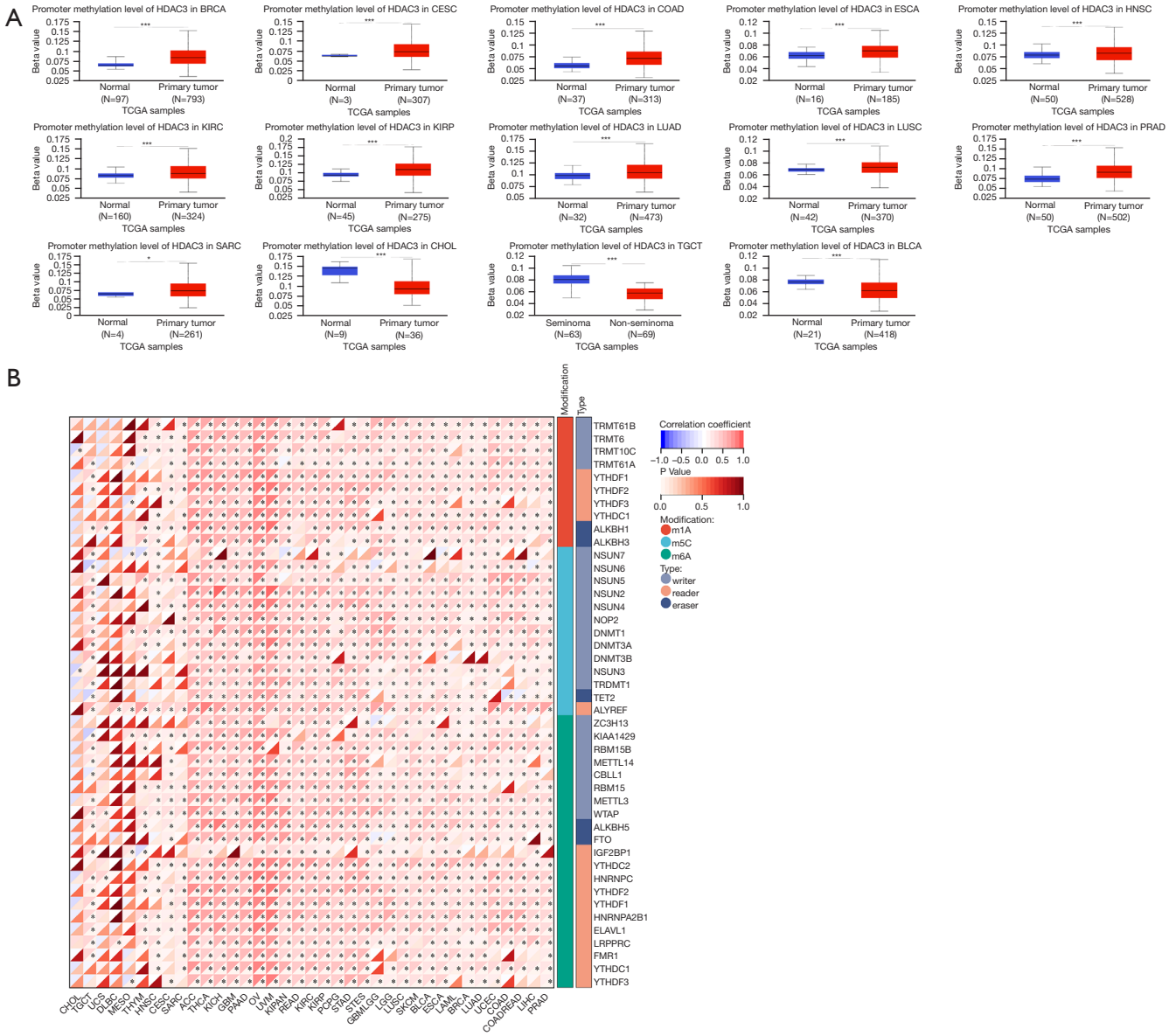

Figure 4 The association of *HDAC3* expression with DNA methylation and RNA methylation modifications. (A) The promoter methylation levels of *HDAC3* in tumors and normal tissue in the UALCAN dataset. (B) The correlation between mRNA expression of *HDAC3* and RNA modification (m1A, m5C, m6A) according to Sangerbox. ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; COADREAD, colon and rectal cancer; DLBC, diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; GBMLGG, lower-grade glioma and glioblastoma; HDAC3, histone deacetylase 3; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, lower-grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; m1A, N1-methyladenosine; m5C, 5-methylcytosine; m6A, N6-methyladenosine; 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; TCGA, The Cancer Genome Atlas; TGCT, testicular germ cell tumor; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma; UALCAN, The University of Alabama at Birmingham cancer data analysis portal; KIPAN, pankidney cohort; STES, stomach and esophageal carcinoma. *, P<0.05; ***, P<0.001.

Methylation modifications of mRNA can regulate mRNA translation and are a critical component of mRNA metabolism. There are several types of RNA methylation modifications, with the most widely recognized ones being m6A RNA methylation, m5C RNA methylation, and m1A RNA methylation (17). Three classes of essential proteins, writer, eraser, and reader, are critical to the process of RNA methylation. Writer proteins are responsible for catalyzing the methylation process, whereas eraser proteins catalyze the demethylation process. After the formation of RNA methylation, readers directly recognize and bind the methylation site to regulate mRNA translation (18). We examined the relationship between *HDAC3* and mRNA methylation modification, including writer, eraser, and reader proteins, in m6A RNA methylation, m5C RNA methylation, and m1A RNA methylation. The results demonstrated that *HDAC3* was positively correlated to the majority of writer, eraser, and reader proteins of m6A RNA methylation, m5C RNA methylation, and m1A RNA methylation in pancancer (all P values <0.05) (*Figure 4B*).

The relationship between HDAC3 expression and TMB, MSI, and MMRs

A positive association was observed between *HDAC3* and TMB in LGG (P<0.001), KICH (P=0.02), STAD (P<0.001), GBM (P=0.006), LIHC (P=0.01), and SKCM (P=0.008), but a negative one was observed for BRCA (P<0.001), LUAD (P<0.001), THCA (P<0.001), THYM (P<0.001), and UVM (P=0.004) (*Figure 5A*). *HDAC3* was positively correlated with MSI in UCEC (P=0.008) but negatively correlated with MSI in HNSC (P=0.04), THCA (P=0.03), and LUAD (P<0.001) (*Figure 5B*). The findings indicate that *HDAC3* significantly impacts TMB and MSI. MMRs is a major pathway that functions to maintain genomic integrity. It is involved in mitotic and meiotic recombination, apoptosis, immunoglobulin gene rearrangement, and other processes (19). Notably, we found that *HDAC3* was highly correlated with MMRs genes (all P values <0.05) (*Figure 5C*).

Relationship between HDAC3 expression and tumor-infiltrating immune cells, immune regulators, and immune checkpoints in pancancer

As immune-infiltrating cells play an important role in tumor emergence and development, we sought to determine the correlation between *HDAC3* expression and the infiltration degree of immune cells in 32 types of cancers using the TIMER database. We found that *HDAC3* was associated with the infiltration level of B cells in 13 types of cancer, $CD4^+$ T cells in 12 types of cancers, $CD8^+$ T cells in 13 types of cancer, macrophages in 12 types of cancers, neutrophils in 18 types of cancer, and myeloid dendritic cells in 14 types of cancer (*Figure 6A*). Additionally, *HDAC3* was positive associated with twelve kinds of immune cells in BLCA, BRCA, KICH, KIRC, KIRP, LGG, LIHC, PAAD, PCPG, PRAD, STAD, and THYM but negatively correlated with these immune cells in LUSC and TGCT (all P values <0.05) (*Figure 6A*). To ensure the accuracy of our results, we used the xCell database to further confirm the relationship between *HDAC3* levels and infiltration of 38 immune cell subtypes. The results indicated that *HDAC3* was negatively correlated with the infiltration levels of most immune cells in LUSC, GBM, SARC, SKCM, TGCT, and UCEC but positively correlated with these immune cells in LGG and STAD (all P values <0.05) (*Figure 6B*). Overall, cancer types characterized by elevated *HDAC3* expression, a reduced level of immune cell infiltration into the tumor was commonly observed.

Furthermore, we examined the relationship between *HDAC3* and immune regulators, including chemokines, chemokine receptors, MHC, immune inhibitors, and immune stimulators (*Figure 6C*) and that between *HDAC3* and immune checkpoint molecules, including immunosuppressive checkpoints and immunostimulatory checkpoints (*Figure 6D*). The findings indicated that the expression of *HDAC3* was positively associated with most of immune-associated genes (all P values <0.05) and may thus potentially the influence the tumor by modulating immune expression levels.

HDAC3 GSEA

Human tumor samples from the GSEA database were divided into high and low *HDAC3* expression groups and examined in terms of enrichment status via GO pathway analysis. The top five most-enriched signaling pathways were found in ACC, GBM, lower-grade glioma and glioblastoma (GBMLGG), KIRP, LGG, LIHC, PCPG, PRAD, SARC, SKCM, and THCA (*Figure 7*). Furthermore, the GSEA outcomes demonstrated that *HDAC3* was positively associated with several immune-related pathways, such as the immune response regulation signaling pathway, B-cell activation, T-cell activation, and regulation of the immune effector process in GBMLGG, LGG, and LIHC. The expression of *HDAC3* in ACC, GBM, SARC, SKCM,

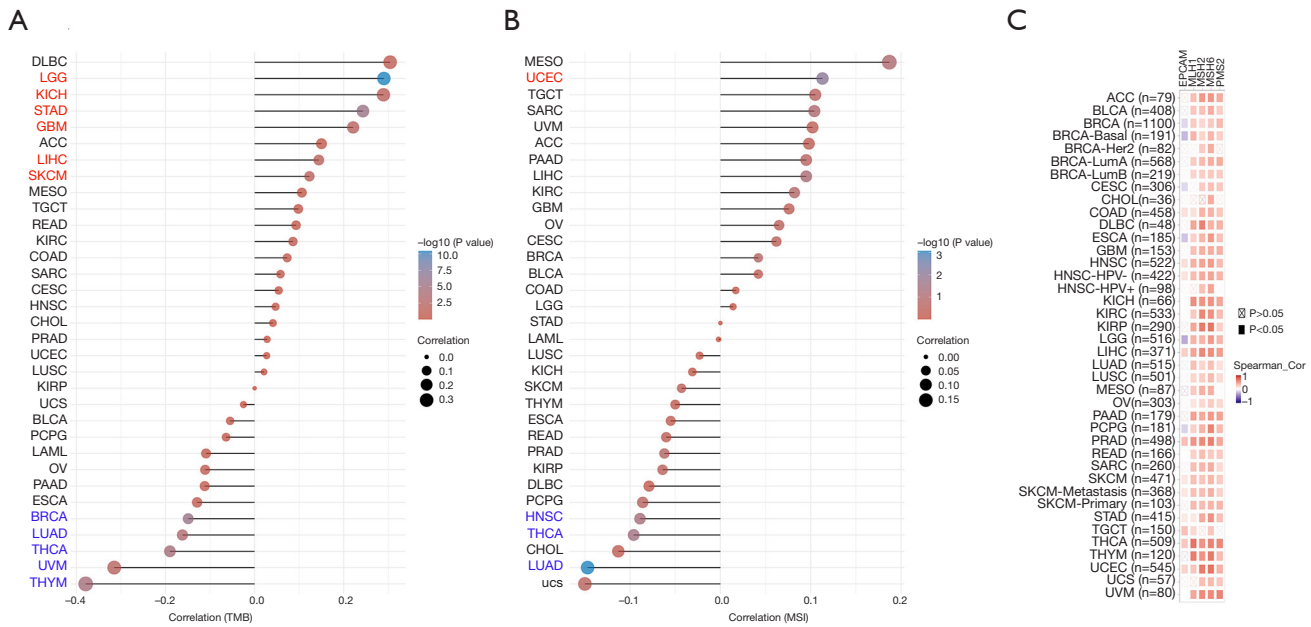

Figure 5 The relationship between *HDAC3* expression and TMB, MSI, and MMRs. The correlation between *HDAC3* expression and TMB (A) and MSI (B) according to TCGA database. The expression of the four methyltransferases, including DNMT1, DNMT2, DNMT3A, and DNMT3B according to the TIMER 2.0 database (C). ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; COADREAD, colon and rectal cancer; DLBC, diffuse large B-cell lymphoma; EPCAM, epithelial cell adhesion molecule; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; GBMLGG, lower-grade glioma and glioblastoma; HDAC3, histone deacetylase 3; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, brain lower-grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; m1A, N1-methyladenosine; MESO, mesothelioma; MLH1, mutL homolog 1; MSH2, mutS homolog 2; MSH6, mutS homolog 6; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PMS2, mismatch repair protein 2; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; TCGA, The Cancer Genome Atlas; TGCT, testicular germ cell tumor; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma; TIMER, Tumor Immune Estimation Resource; TMB, tumor mutational burden; MSI, microsatellite instability; MMRs, mismatch repair system.

and THCA was negatively associated with the external side of the plasma membrane, positive regulation of cell activation, phagocytosis, and sensory perception of a smell. This suggests that *HDAC3* is extensively implicated in the positive regulation of cellular biological functions in pancancer.

Functional enrichment analysis of HDAC3

To clarify the possible mechanism of *HDAC3* in tumorigenesis and cancer progression, we built a PPI network of 50 HDAC3–binding protein interactions supported by experimental evidence from the STRING online database (*Figure 8A*). We then selected the 200 genes (table available at https://cdn.amegroups.cn/static/public/tcr-23-1228-1.xlsx) most strongly correlated with *HDAC3* expression in TCGA using the GEPIA2 database. The corresponding heatmap showed a positive correlation expression between *HDAC3* and the top five correlated genes including histidyl-tRNA synthetase (*HARS*) (R=0.51), histidyl-tRNA synthetase 2 (*HARS2*) (R=0.52), IK cytokine (*IK*) (R=0.53), ubiquitin conjugating enzyme E2D2 (*UBE2D2*) (R=0.53), and ubiquitin interaction motif containing 1 (*UIMC1*) (R=0.52) (*Figure 8B*). In addition, we performed KEGG and GO pathway enrichment analysis with a combined dataset of the binding and

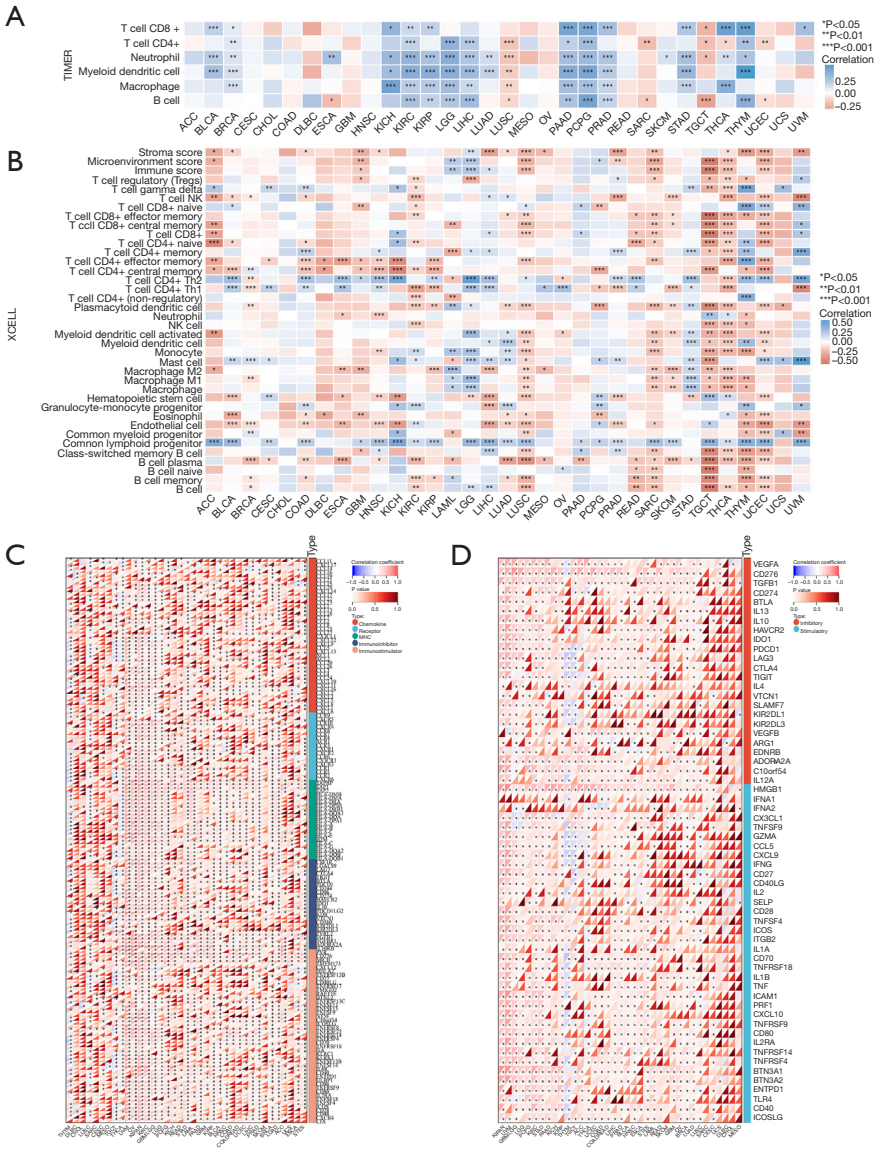

Figure 6 The relationship between *HDAC3* expression and tumor-infiltrating immune cells, immune regulators, and immune checkpoints in pancancer. The correlation between *HDAC3* expression and the infiltration degree of immune cells (A) and immune cell types (B) according to the TIMER database and xCell database. The correlation of *HDAC3* with immune regulators genes (C), and immune checkpoint molecules (D) according to Sangerbox. *, P<0.05; **, P<0.01; ***, P<0.001. ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; COADREAD, colon and rectal cancer; DLBC, diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; GBMLGG, lower-grade glioma and glioblastoma; HDAC3, histone deacetylase 3; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIPAN, pankidney cohort; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, 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 tumor; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma; TIMER, Tumor Immune Estimation Resource; NK, natural killer cell; MHC, major histocompatibility complex.

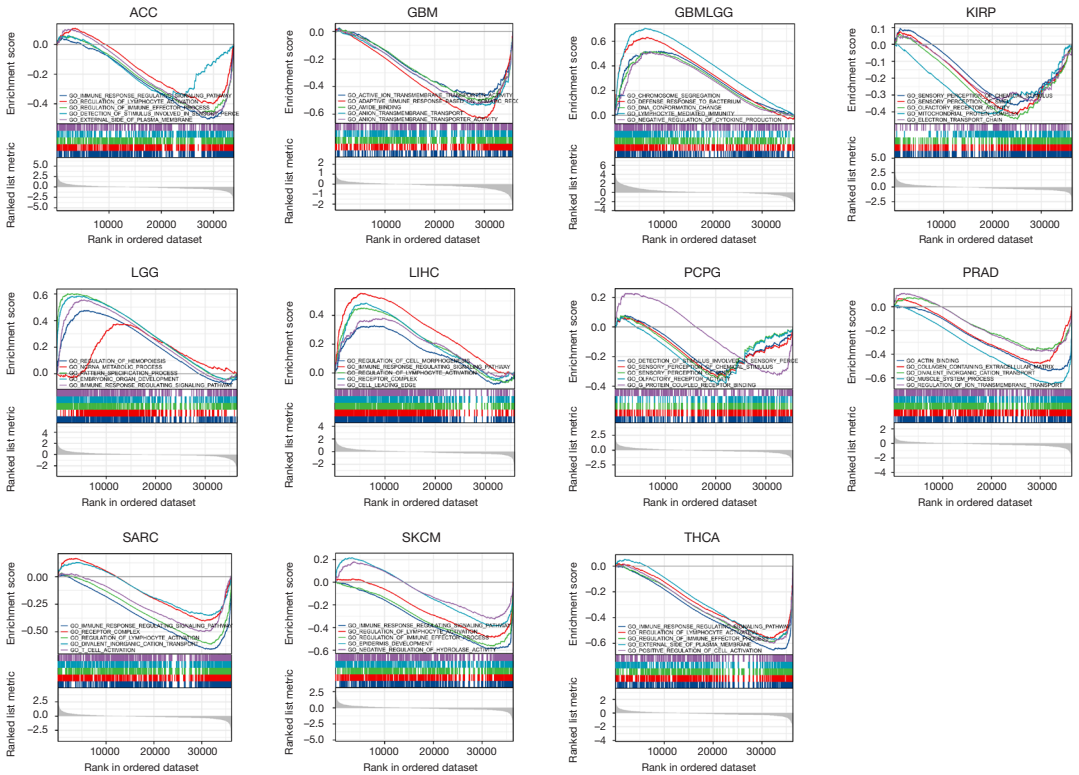

Figure 7 GSEA analysis of *HDAC3*. The *HDAC3* enrichment status in the GO pathway set of the GSEA database according to analysis conducted with the "ClusterProfiler" package in R. ACC, adrenocortical carcinoma; GBM, glioblastoma multiforme; GBMLGG, lower-grade glioma and glioblastoma; KIRP, kidney renal papillary cell carcinoma; LGG, brain lower-grade glioma; LIHC, liver hepatocellular carcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; THCA, thyroid carcinoma; GSEA, gene set enrichment analysis; HDAC3, histone deacetylase 3; GO, Gene Ontology.

correlated genes of *HDAC3* (*Figure 8C*). The KEGG data revealed that spliceosome, transcriptional misregulation in cancer, Epstein-Barr virus infection, viral carcinogenesis, and acute myeloid leukemia may be involved in the tumorigenic effects of *HDAC3*. According to the results of the GO database, the majority of genes related to *HDAC3* expression are engaged in RNA splicing in the biological process (BP) category, nuclear chromatin in the cell component (CC) category, and HDAC binding in the molecular function (MF) category.

Expression of HDAC3 in patients with glioma

Previous research demonstrated an elevated HDAC3 protein level in patients with glioma, indicating its potential role in glioma diagnosis and treatment (20). HDAC1, 4, 5, 8, 9, and 10 proteins have also been shown to be elevated in glioma (21-23). Furthermore, the combination of RGFP109, an inhibitor of HDAC3, and temozolomide (TMZ) was reported to be a promising therapeutic option for patients with TMZ-resistant GBM (24). In our study, we determined the protein expression of HDAC3 in glioma tumor tissues and normal tissues using Western blotting (*Figure 9A,9B*). The results revealed a significant increase in HDAC3 in tumor tissues compared to normal tissues, which corroborated our bioinformatics results.

Discussion

HDACs had been linked to cancer development, cell proliferation, apoptosis, and cell cycle regulation (25). Among the HDACs, *HDAC3* is an epigenetic drug target, and *HDAC3* inhibitors have been used to treat not only neurodegenerative diseases, heart diseases, HIV, inflammatory diseases, and rheumatoid arthritis, but also various tumors (26). *HDAC3* mRNA is expressed at higher

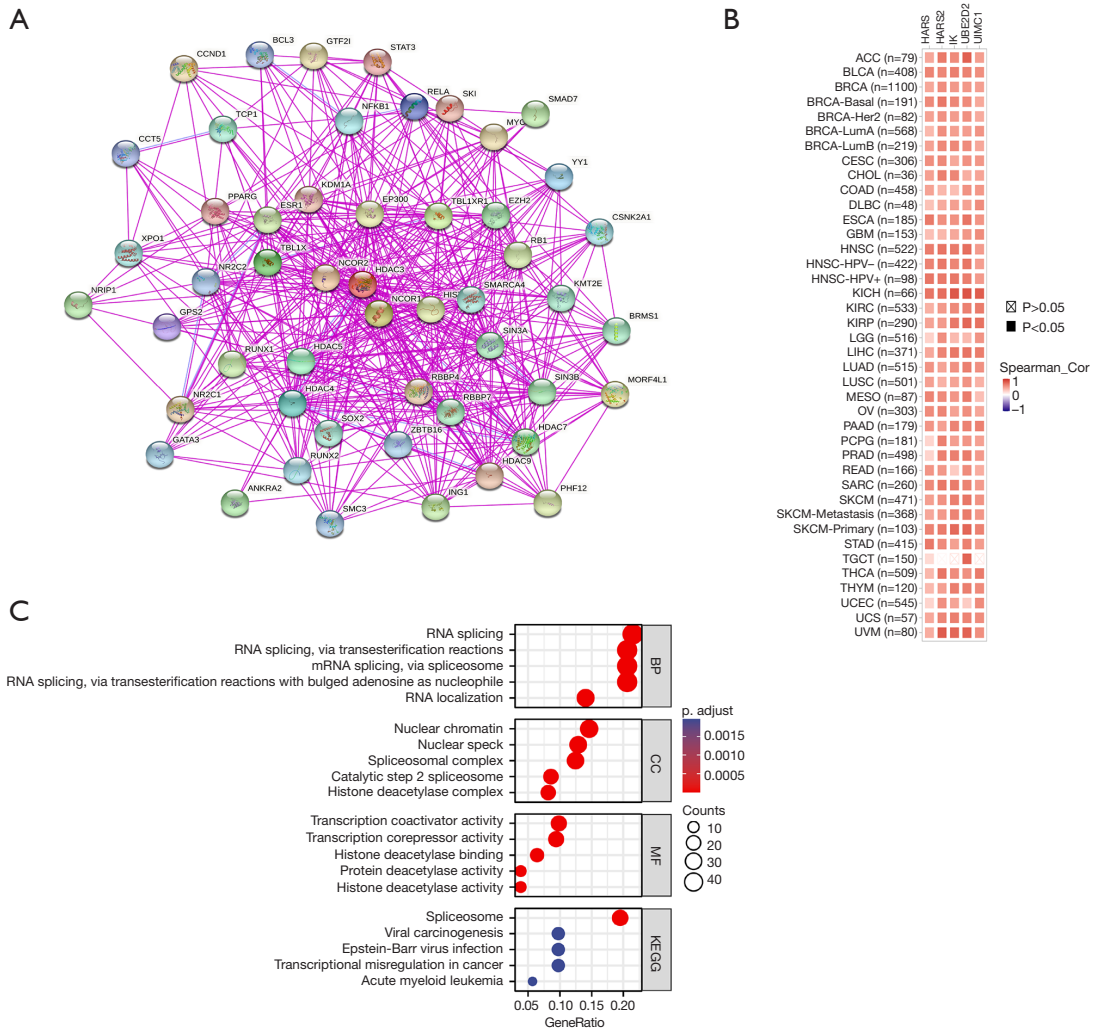

Figure 8 Functional enrichment analysis of HDAC3. (A) The HDAC3-associated protein–protein interaction networks were obtained from the STRING online database. (B) The top 200 genes with the strongest association with *HDAC3* expression were sorted in the GEPIA2 database. The top five correlated genes were visualized in a heatmap using the TIMER2.0 database. (C) The GO and KEGG enrichment analysis of *HDAC3*-related genes according to the "clusterProfiler" package in R software. ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; COADREAD, colon and rectal cancer; DLBC, diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; GBMLGG, lower-grade glioma and glioblastoma; HARS, histidyl-tRNA synthetase; HDAC3, HISTONE DEACETYLASE 3; HPV, human papillomavirus; HNSC, head and neck squamous cell carcinoma; IK, IK cytokine; KICH, kidney chromophobe; KIPAN, pankidney cohort; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, 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 tumor; THCA, thyroid carcinoma; THYM, thymoma; UBE2D2, ubiquitin conjugating enzyme E2D2; UCEC, uterine corpus endometrial carcinoma; UIMC1, ubiquitin interaction motif containing 1; UCS, uterine carcinosarcoma; UVM, uveal melanoma; BP, biological process; CC, cell component; MF, molecular function; GEPIA, Gene Expression Profiling Interactive Analysis; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; STRING, Search Tool for the Retrieval of Interacting Genes/Proteins; melanoma; TIMER, Tumor Immune Estimation Resource.

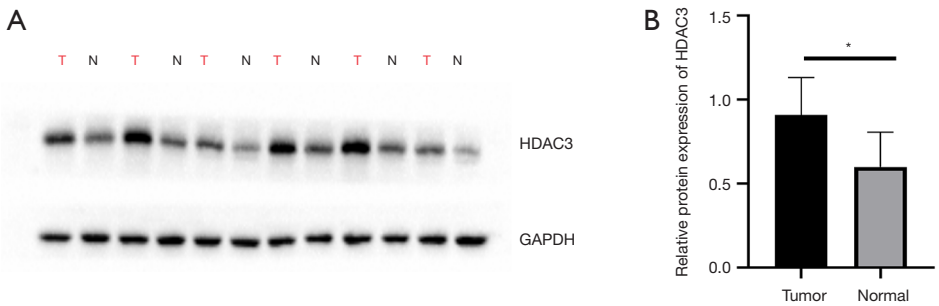

Figure 9 Expression of HDAC3 in patients with glioma. (A) Western blot image of HDAC3 expression in glioma tumor tissues and paraneoplastic tissues; "T" indicates tumor, and "N" indicates normal. (B) Western blot analysis of HDAC3 expression according analysis of variance. GraphPad Prism 8 and ImageJ were used to evaluate the experimental results. *, P<0.05. GAPDH, glyceraldehyde 3-phosphate dehydrogenase; HDAC3, histone deacetylase 3.

levels in gliomas than in normal glial cell lines, low *HDAC3* mRNA expression levels can predict better OS, and *HDAC3* expression may be a biomarker for differentiating glioma grade (27). In addition, the HDAC3–KDELR2 axis was shown to promote breast cancer cell proliferation and tumorigenesis *in vitro* and *in vivo* (28), and *HDAC3* has also been shown to maintain fat mass and obesity associated gene (FTO)–m6A–myelocytomatosis viral oncogene homolog (MYC) signaling and regulate gastric cancer progression, as supported by the data from an *in vivo* animal study (29). Given the prominent role of *HDAC3* in multiple tumor types, we used advanced bioinformatics tools to perform a systematic analysis of *HDAC3* at the pancancer level, with the specific aim of examining *HDAC3* expression patterns, the prognostic and diagnostic value of *HDAC3*, and *HDAC3*-related tumor tissue immune infiltration and gene enrichment.

Analysis using the TCGA, GTEx, and UALCAN databases demonstrated that *HDAC3* expression is elevated in BLCA, COAD, and LUAD cancers, which is in line with previous research (30-32). Our comprehensive Kaplan-Meier plot survival analysis revealed a negative association between *HDAC3* expression and RFS in patients with BRCA, HNSC, PAAD, ESCA, or KIRC. Previous clinical results demonstrated that *HDAC3* is an appropriate prognostic indicator for patients with invasive ductal breast cancer (33), and other research has reported an elevated expression of HDAC3 in patients with glioma (20). Consistent with this literature, our Western blot test revealed that HDAC3 expression was significantly higher in tumor tissues compared to normal tissues. Therefore, the abnormal expression of *HDAC3* could be used as a prognostic indicator in some tumor types.

DNA methylation can regulate eukaryotic cell proliferation, apoptosis, and cell cycle through epigenetic mechanisms, and DNA methylation levels can be used as early diagnostic and prognostic markers for cancer (34). In one study, knockdown of *HDAC3* downregulated the DNA methyltransferase 1 (DNMT1)-mediated expression of multiple myeloma cell proliferation (35). In our UALCAN database analysis, we found significant differences in *HDAC3* methylation levels between tissues of multiple tumor types and normal tissues. This suggests that the DNA methylation level of *HDAC3* may be an early diagnostic indicator of cancer. RNA methylation has recently been discovered to be a crucial regulator of transcript expression, with a growing body of evidence linking it to cancer cell proliferation, cell stress, metastasis, and immune response (36,37). RNA methylation-related proteins have emerged as promising targets for cancer therapy (38,39). In our study, *HDAC3* showed a positive correlation with the majority of mRNA methylation types in pancancer. These findings highlight the potential of targeting mRNA methylation of *HDAC3* as a novel approach to cancer therapy.

TMB is a useful biomarker for immune checkpoint blockade (ICB) selection in some cancer types (40). A recent clinical study found that programmed cell death protein 1 (PD-1)–based immunotherapy significantly improves clinical outcomes in patients with MSI high- or MMR-deficient tumors (41). Our bioinformatics analysis revealed a positive correlation between *HDAC3* expression and TMB in patients with LGG, KICH, STAD, or GBM, thus providing a new direction for tumor immunotherapy research.

Novel immunotherapy approaches, including those using antiangiogenic drugs (42), ICB (43), chimeric antigen

receptor T cells (44), and nanoimmunotherapy (45), are being increasingly used in clinical settings. A tumor microenvironment (TME) consisting of tumor immune cells and fibroblasts influences ICB (46) and thus tumor immunotherapy. In this study, we showed that *HDAC3* expression in tumors is correlated with the infiltration of various immune cells in the TME, including $CD4^+$ T cells, $CD8^+$ T cells, and natural killer T cells (NKTs). Moreover, our enrichment analysis showed that *HDAC3*-related genes are positively correlated with several immune-related pathways, including immune response regulatory signaling pathways, B-cell activation, T-cell activation, and immune effector process regulation. In a recent study, the positive prognostic significance of $CD8^+$ T cells was established in nearly 200,000 patients and across 17 different types of solid cancers (47). Similar results were reported regarding $CD4^+$ T cells (48), and it has been shown that *HDAC3* is essential for the development and maturation of $CD4^+$ T cells, $CD8^+$ T cells (49), and NKTs (50). Furthermore, treatment of cancer cells with small interfering RNA against *HDAC3* (siHDAC3) can enhance tumor-infiltrating immune cells and suppress tumor growth (10,51). Therefore, *HDAC3* can be considered an important molecule for tumor immunotherapy.

Conclusions

Our study examined the *HDAC3* expression at the pancancer level. We found that the protein expression of HDAC3 is elevated in patients with glioma. ROC analysis revealed that *HDAC3* could serve as a promising diagnostic indicator for tumors. Furthermore, the level of DNA methylation in *HDAC3* could serve as a diagnostic marker, while the grade of mRNA methylation in *HDAC3* showed promise as a target for cancer therapy. The close correlation of *HDAC3* with immune-related pathway expression, tumor immune infiltration level, and immune-related gene expression highlights its role in regulating tumors at the immune level. Overall, although clinical trials are needed to confirm these findings, our study provides novel insights into the role of *HDAC3* in tumors and points to potentially valuable targets for cancer diagnosis and therapy.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1228/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1228/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1228/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) and was approved by the Ethics Committee of Tangshan Workers' Hospital (No. GRYY-LL-KJ2022-K27). Informed consent was obtained from all the patients.

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