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Research article

TRPV1 is a potential biomarker for the prediction and treatment of multiple cancers based on a pan-cancer analysis

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Abstract: *Background*: Transient receptor potential cation channel subfamily V member 1 (*TRPV1*) was considered to play pivotal roles in multiple cancers; however, the expression and clinical significance of the *TRPV1* remain unclear, which were explored in this study. *Results*: The pan-cancer analysis was performed based on 10,236 samples in 32 cancers. Differential *TRPV1* expression levels were detected in 12 cancers ($p < 0.05$). *TRPV1* demonstrated its conspicuous prognosis significance and prediction effects for some cancers (e.g., lung adenocarcinoma), indicating its potential as a valuable and novel biomarker in treating and predicting cancers. *TRPV1* expression was relevant to DNA methyltransferases, mismatch repair genes, tumor mutational burden, and microsatellite instability. *TRPV1* expression was associated with the immune microenvironment of some cancers, and its roles in different cancers may be mediated by affecting various immune cells. Gene set enrichment analysis discloses the significant relevance of *TRPV1* expression with a series of metabolic and immunoregulatory-related pathways. *Conclusions*: This study provided a comprehensive workflow of the expression, clinical significance, and underlying mechanisms of *TRPV1* in pan-cancer. *TRPV1* may be an underlying biomarker for predicting and treating multiple cancer.

Keywords: cancer biology; cancer genetics; prognosis; immunology; biomarkers

1. Introduction

Cancer and cardiovascular disease are the two most common causes of death worldwide. The incidence and mortality of cardiovascular disease decreased significantly, while the incidence and

mortality of cancer increased [1]. As predicted, 19.3 million cancer patients would be diagnosed, and nearly 10.0 million individuals would die of various cancers globally in 2020 [2]. Compared to traditional clinical management methods of cancers, such as surgical treatment, chemotherapy, and radiotherapy, targeted therapy shows increasingly prominent potential [3]. The significant progress of targeted therapy can be seen in some cancers (e.g., melanoma); however, quite a few patients with certain cancers (e.g., non-small-cell lung carcinoma) fail to benefit significantly from targeted therapy and have unfavorable prognoses [4,5]. Thus, more research on valuable biomarkers for cancer treatment and prediction is necessary.

Transient receptor potential cation channel subfamily V member 1 (TRPV1) protein is encoded by the gene located on chromosome 17p13 – *TRPV1*. TRPV1 is a transmembrane protein (a nonselective cation channel) associated with pain conduction, which stimulates various physical and chemical factors, thus promoting the cellular influx of calcium and sodium ions and resulting in cell death [6]. Increasing studies identified the pivotal roles of *TRPV1* in multiple cancers [7]. For example, upregulated *TRPV1* expression was detected in brain tumors and was relevant to tumor grading [8]. High-*TRPV1* expression was discovered in breast cancer and suppressed the growth of certain types of breast cancer cells [9]. Indeed, *TRPV1* demonstrated essential and complex factors in several biological processes, including proliferation, metastasis, and death of cancer cells [6]. Little is understood about the clinical value and mechanisms of *TRPV1* in pan-cancer, and more efforts should focus on this vacancy.

The current study investigated the expression, clinical value, and underlying mechanisms of *TRPV1* in pan-cancer. By using 10,236 samples from Cancer Cell Line Encyclopedia (CCLE) and The Cancer Genome Atlas (TCGA), the research provided an overview of *TRPV1* expression in 32 cancers. Clinical relevance, clinical significance, and immune relevance of *TRPV1* in multiple cancers were also evaluated, determining *TRPV1* as a potential biomarker for cancers. Enrichment analyses were performed to explore the underlying molecular mechanisms of *TRPV1* in pan-cancer, contributing to the understanding of the pathogenesis of some cancers.

2. Materials and methods

2.1. Expression data acquisition and selection

Data on *TRPV1* mRNA expression in various cancer cell lines of CCLE [10] was downloaded from Depmap Portal on November 16, 2021. Whole-genome RNA expression data of TCGA were obtained from the Xena database on November 17, 2021. For TCGA data, three types of samples—primary tumor, solid tissue normal, and primary blood-derived cancer peripheral blood—were considered for analyses in the present study. Cancers selected in the study and their sample numbers are shown in Supplementary Appendixes 1 and 2. Cancer with less than six samples (three cancer samples and three normal samples) was excluded in analyses of the expression and prediction value of *TRPV1*.

Tumor Immune Single-cell Hub (http://tisch.comp-genomics.org/home/) provides the single-cell RNA-seq data on 1,944,551 cells of 28 cancer types. Data in this database had been performed with quality control, clustering, and cell-type annotation, which were used to examine cell types of highly expressed *TRPV1*.

2.2. Clinical relevance and clinical significance

Three clinical parameters (age, gender, and American Joint Committee on Cancer stages) and four types of prognosis data—overall survival (OS), disease-specific survival (DSS), disease-free interval (DFI), and progression-free interval (PFI)—of TCGA were collected from the Xena database on November 17, 2021.

For evaluating the prognosis effects of *TRPV1* in 32 cancers, univariate Cox regression analysis and Kaplan-Meier curves were applied to investigate the correlation of *TRPV1* expression with OS, DSS, DFI, and PFI. Receiver operator characteristic curves were generated to determine whether *TRPV1* can be identified as a potential marker for predicting cancers or not, which was judged by the value of the area under the curve (AUC). The greater the AUC value (the maximum value is 1), the more precisely *TRPV1* expression predicted cancer.

2.3. Genome heterogeneity

A series of datasets of simple nucleotide variation (SNV) from TCGA, which had been processed by MuTect2 software [11], was downloaded from the GDC portal and visualized in Sanger Box (v3.0). DNA methyltransferases and mismatch repair (MMR) genes data were extracted from the TCGA cohort. Tumor mutational burden (TMB) and microsatellite instability (MSI) data of previous studies [12,13] were downloaded from Sanger Box (v3.0).

2.4. Immune relevance

TIMER [14,15,16,17] and ESTIMATE [13,18,19,20] were two algorithms feasible to predict the immune microenvironment. TIMER was used to calculate the abundance of six types of immune cells, containing B cells, CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and dendritic cells. Three ESTIMATE scores—stromal score, immune score, and estimated score—were generated to evaluate stromal cell infiltration levels, immune cell infiltration levels, and tumor purity. Relationships of *TRPV1* expression with the immune microenvironment and a series of immune checkpoint genes (extracted from the TCGA cohort) expression were investigated in the study.

2.5. Gene set enrichment analysis

For studying potential mechanisms of *TRPV1* in pan-cancer, *TRPV1*-related KEGG (Kyoto Encyclopedia of Genes and Genomes) signaling pathways were explored based on gene set enrichment analysis (GSEA) with the *clusterProfile*r package [21]. In the process, samples from the TCGA dataset were divided into the high-*TRPV1* expression group and the low-*TRPV1* expression group based on the median level of *TRPV1* expression. Signaling pathways with a p-value less than 0.05 were selected in the study.

2.6. Weighted gene co-expression network analysis

To further explore the mechanisms of *TRPV1* in certain cancers, hub genes associated with *TRPV1* expression were selected based on the weighted gene co-expression network analysis (WGCNA) by using the *WGCNA* package [22]. In this analysis: 1) all genes in the dataset (extracted from the TCGA

dataset) for single cancer with a median absolute deviation of more than one were conserved for WGCNA; 2) the top 5000 genes ranked by the median absolute deviation values were classified into multiple modules associated with *TRPV1* expression; 3) a scale-free network was determined with the minimum quantified soft threshold; 4) genes of the most significant module were prepared for identifying hub genes. Then, using the "degree" algorithm, hub genes of certain cancers were chosen in Cytoscape (v3.9.0).

2.7. Drug sensitivity analysis

CellMiner [23] collects a large of drugs and gene expression data. Using IC50 (half maximal inhibitory concentration) data from this database, drugs sensitive to cells with *TRPV1* overexpression were selected with a *p*-value less than 0.01.

2.8. Statistical analysis

All data on *TRPV1* gene expression levels were normalized with $\log_2$ (transcripts per million + 1) conversion. Wilcoxon rank-sum tests and Kruskal-Wallis tests were applied to identify the different expression levels of *TRPV1*. All correlation analyses in the study were performed based on Spearman's rank correlation coefficient. Processes of statistical analyses were performed in R (v4.1.0). If there was no particular explanation, a *p*-value less than 0.05 represented statistical significance in this study. Figure 1 shows an overview of the study.

3. Results

3.1. The expression of TRPV1 in pan-cancer and its correlation with clinical features

Through CCLE data, *TRPV1* expression was significantly different in 13 cancer cell lines ($p < 0.05$) (Figure 2A). Furthermore, based on TCGA data, the expression levels of *TRPV1* in distinct cancer tissues were notably various from their normal tissues. In 20 cancers, *TRPV1* was highly expressed in eight cancers – BLCA, HNSCC, KIRC, KIRP, LIHC, LUAD, LUSC, and STAD. On the contrary, *TRPV1* was lowly expressed in four types of cancer – BRCA, COAD, GBM, and KICH (Figure 2B).

Single-cell RNA-Seq data from Tumor Immune Single-cell Hub were utilized to investigate *TRPV1* expression in cell types of the five eights cancers (no *TRPV1* expression data can be found for BLCA, KIRP, and STAD) with upregulated *TRPV1* expression. As a result, conspicuously elevated expression of *TRPV1* can be detected in various cell types for different cancers (CD4 T cells for HNSCC, plasma for KIRC, proliferating T cells for LIHC, and monocytes or macrophages for non-small-cell lung carcinoma [for LUAD and LUSC]) (Supplementary Appendix 3).

Upregulated *TRPV1* expression was determined at advanced stages in ACC, while it was found at lower stages in BLCA, KIRP, LIHC, LUAD, and STAD (Figure 2C). Compared to the young, the elderly (≥ 65 years old) patients with LUAD tend to have reduced *TRPV1* expression levels (Figure 2C). For BLCA and KIRC, the differential expression levels of *TRPV1* were detected in various gender groups (Figure 2C).

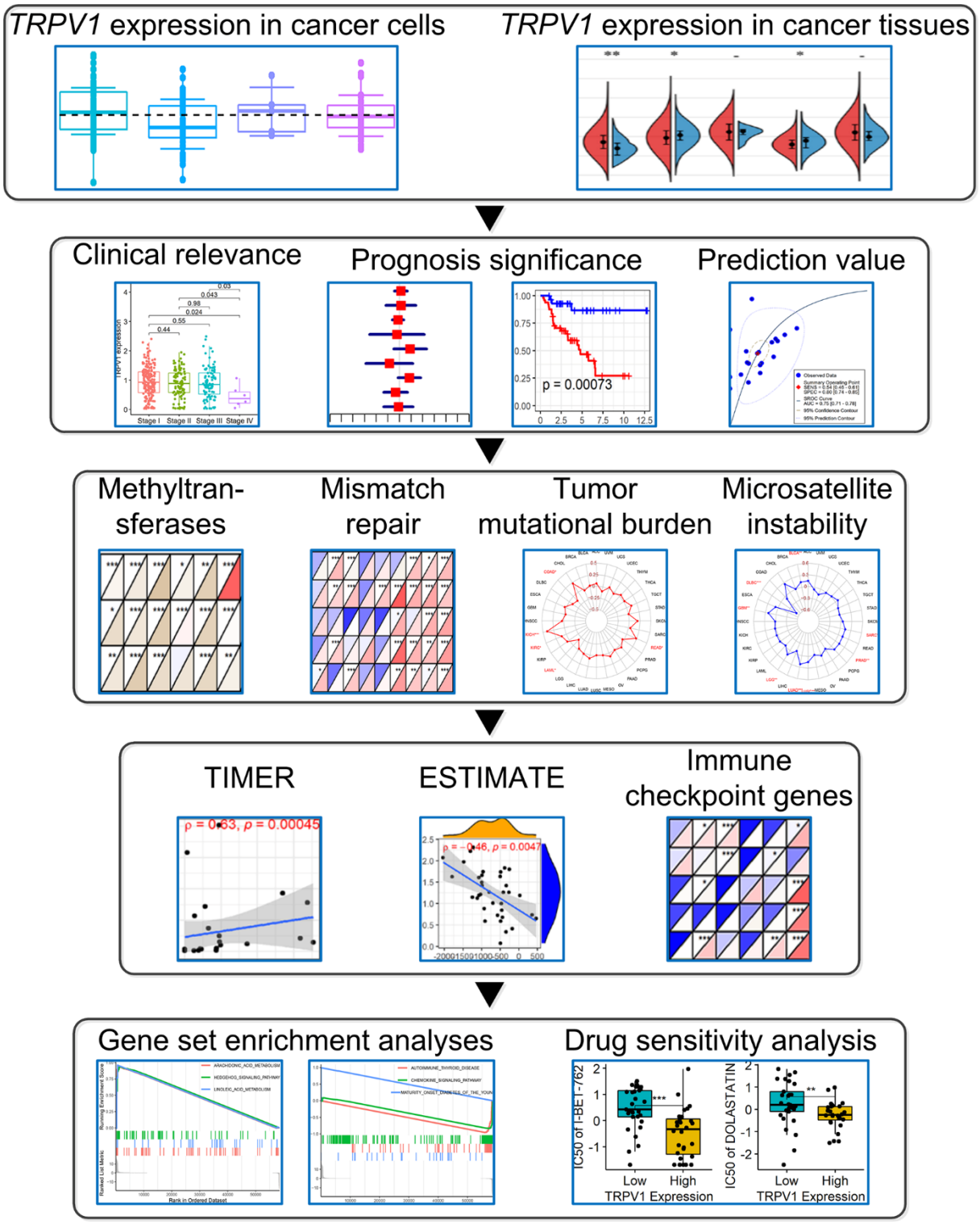

Figure 1. An overview of the study.

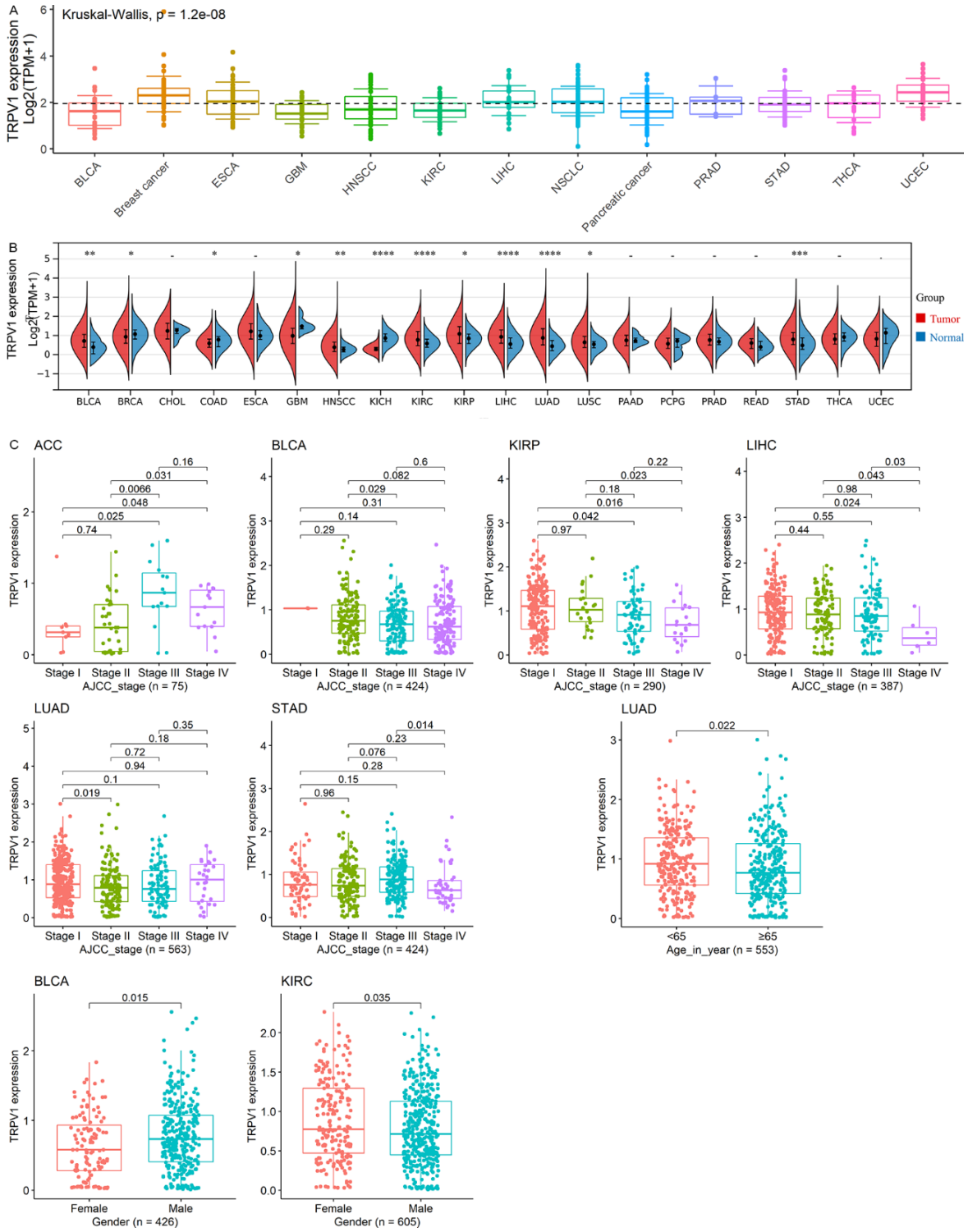

Figure 2. The *TRPV1* mRNA expression and its correlation with clinical features in pan-cancer. Panel A: *TRPV1* mRNA expression in cancer cell lines; NSCLC, non-small-cell lung carcinoma. Panel B: *TRPV1* mRNA expression between cancer and normal tissues; *p-value of Kruskal-Wallis tests < 0.05. Panel C: Correlation between *TRPV1* mRNA expression and clinical features; numbers on the top of boxes are p values of Wilcoxon rank-sum tests or Kruskal-Wallis tests.

3.2. *Prognosis significance of TRPV1 in pan-cancer*

TRPV1 expression has different prognostic values in various cancers. In OS, high *TRPV1* expression predicted poor overall survival for patients with ACC and PRAD, while it was associated with a favorable prognosis for patients with BLCA, HNSCC, PAAD, and READ (Figure 3A). The same situation can be observed in DSS, and *TRPV1* also played a protective role for KIRP patients and a risk role for patients with MESO and THCA (Figure 3C). Analyses of the Kaplan-Meier curves consistently supported the results in univariate Cox analysis (Figures 3B and D). In several cancers, upregulated *TRPV1* expression also demonstrated its correlations with unfavorable DFI (LUAD and PRAD) (Figures 4A and C) and PFI (ACC, PCPG, and PRAD) (Figures 4B and D), and both favorable DFI and PFI for patients with PAAD (Figure 4).

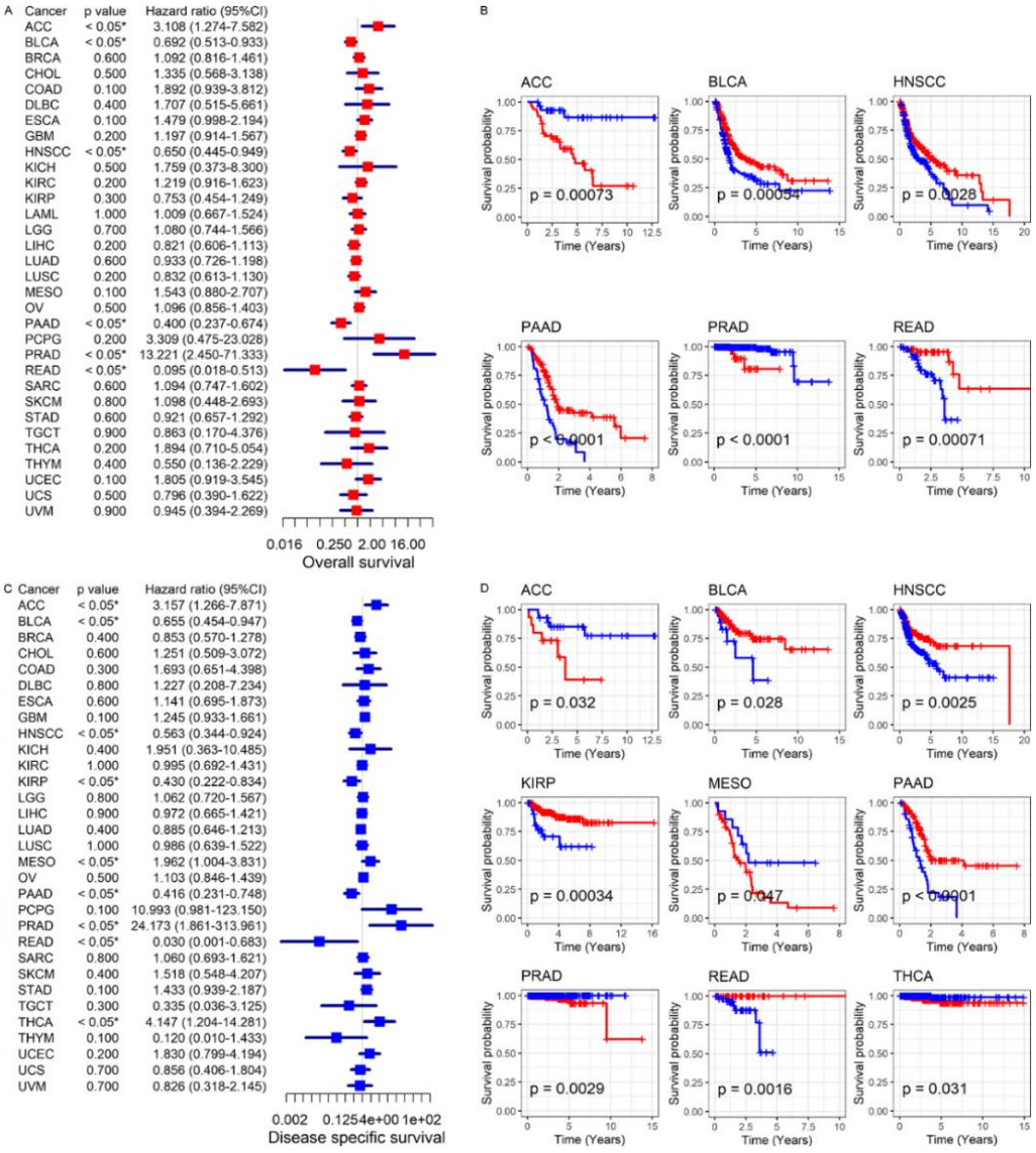

Figure 3. Correlations of *TRPV1* expression with overall survival and disease-specific survival in pan-cancer. Panels A and C: Univariate Cox regression analysis. Panels B and D: Kaplan-Meier curves.

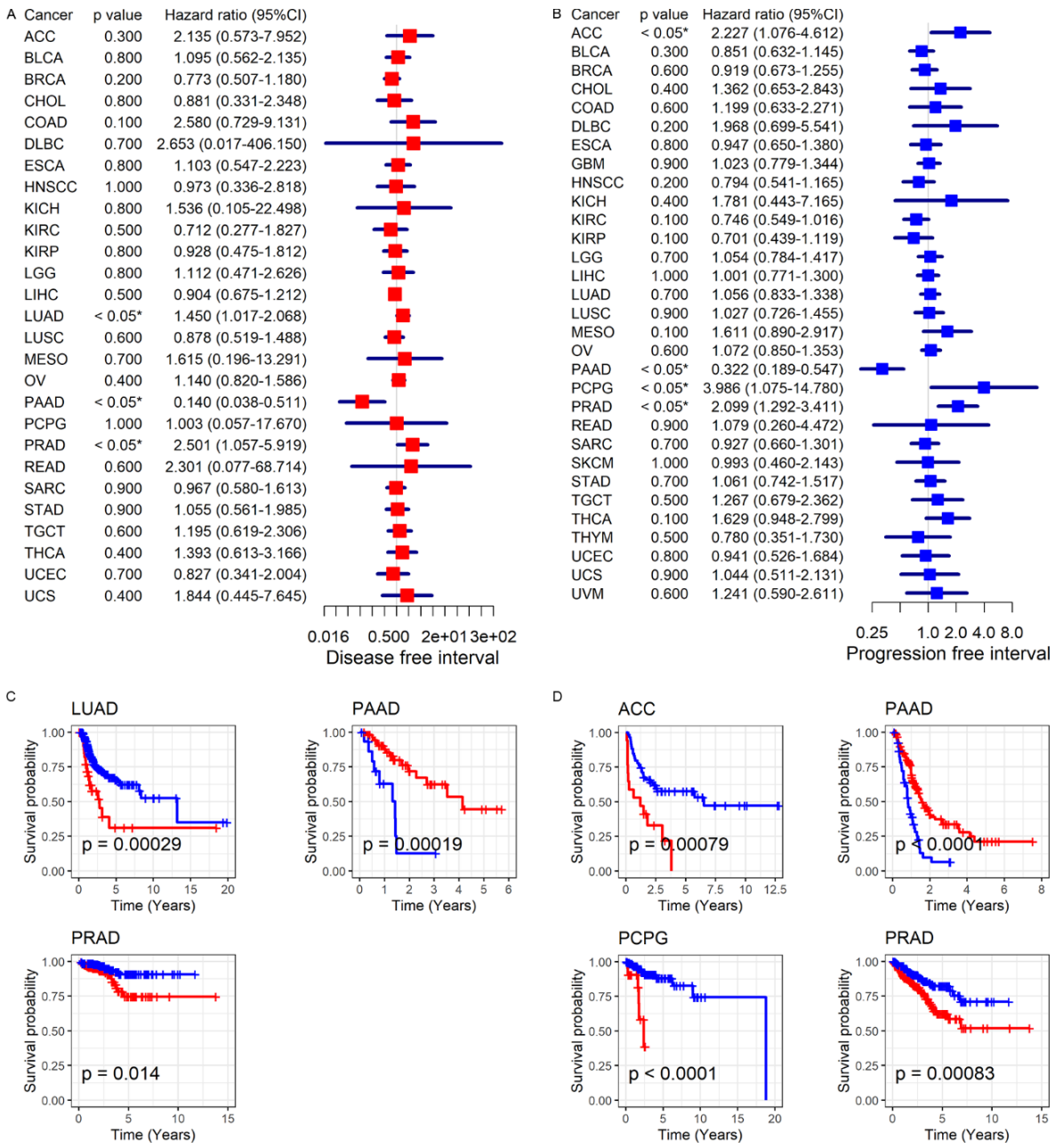

Figure 4. Correlations of *TRPV1* expression with disease-free interval and progression-free interval in pan-cancer. Panels A–B: Univariate Cox regression analysis. Panels C–D: Kaplan-Meier curves.

3.3. The prediction value on cancers of TRPV1

TRPV1 expression showed different predictive abilities in various cancers. In KICH, the effect of *TRPV1* expression on identifying cancer tissues and non-cancer tissues was significant (AUC = 0.941). In BLCA, GBM, and LUAD, *TRPV1* expression made it feasible to identify these cancer tissues (AUC > 0.7), while such an effect for the rest 16 cancers was not conscious (AUC < 0.7) (Figure 5A). In an overview of the 20 types of cancers, AUC for *TRPV1* expression was equal to 0.75 (95 % CI: 0.71–0.78) (Figure 5B). Therefore, *TRPV1* expression had prediction significance for cancers, suggesting its potential for screening some cancers, especially KICH, BLCA, GBM, and LUAD.

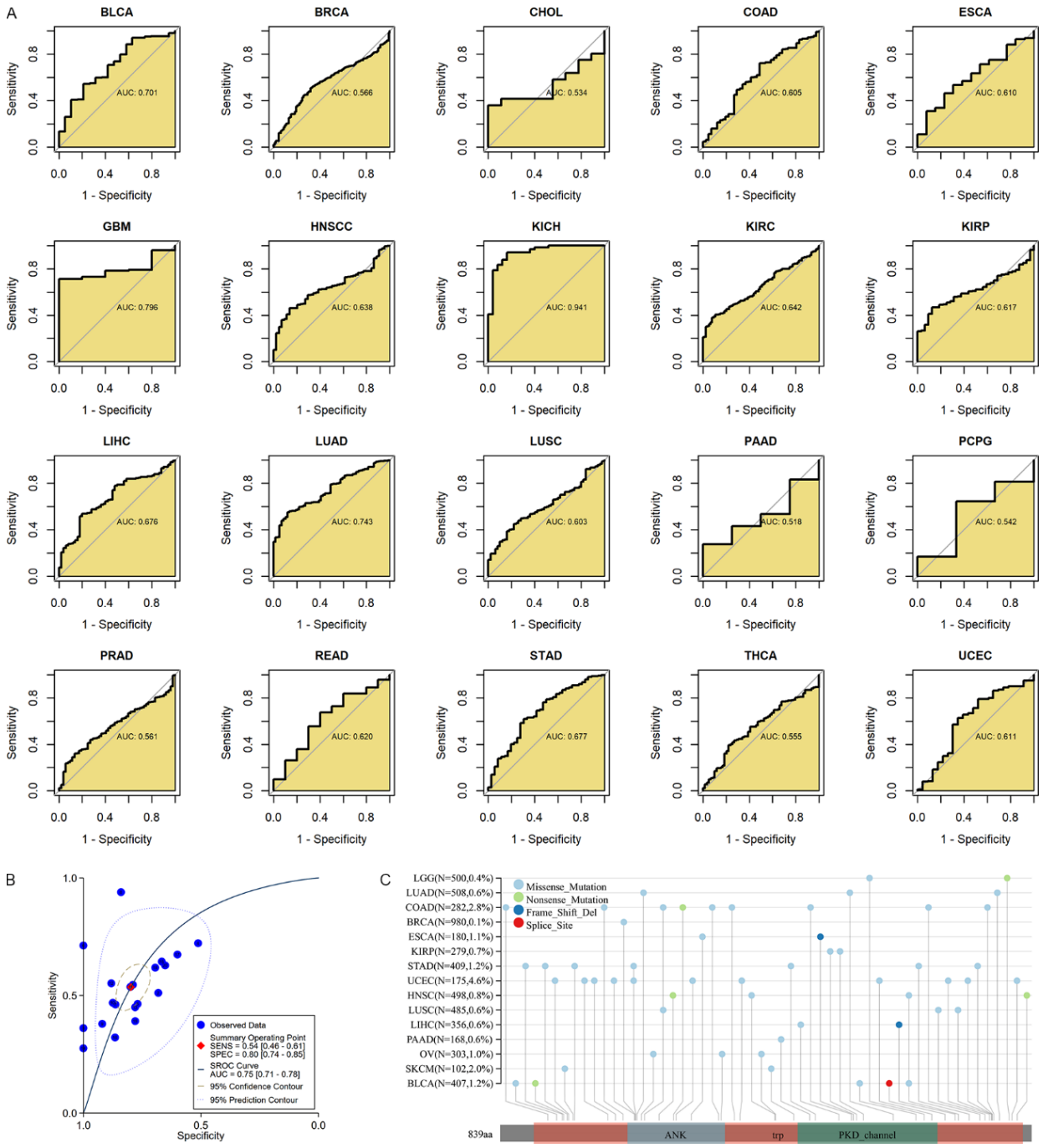

Figure 5. Distinguish effects of *TRPV1* expression for cancers and its simple nucleotide variation in pan-cancer. Panel A: receiver operator characteristic curves. Panel B: a summary receiver characteristic curve; SENS, sensitivity; SPEC, specificity; AUC, area under the curve. Panel C: simple nucleotide variation of *TRPV1*.

3.4. SNVs of TRPV1 in pan-cancer, and correlation of TRPV1 expression with methyltransferases, MMR, TMB, and MSI

Among the four types of mutations detected, the missense mutation was the most common, and the splice site was the rarest form of *TRPV1*'s SNVs. Moreover, UCEC had the highest frequency of *TRPV1*'s SNV (4.6 %) (Figure 5C).

In almost all 32 cancers, *TRPV1* was conspicuously related to three DNA methyltransferases. The positive expression correlation between *TRPV1* and DNMT3B was the most significant in DLBC (Spearman's ρ = 0.806, $p < 0.001$). A conspicuous positive relevance between *TRPV1* and some methyltransferases was also observed in LAML (DNMT3A) and UVM (all of DNMT1, DNMT3A, and DNMT3B) (Figure 6A). In addition to CHOL, PAAD, and READ, expression associations (mainly positive) of *TRPV1* with at least one MMR gene were detected in 29 cancers (Figure 6B).

As shown in Figure 6C, in MESO and THYM, *TRPV1* expression was positively correlated with TMB; in BRCA and PAAD, *TRPV1* expression was negatively relevant to TMB (Figure 6C). A significantly negative relationship between *TRPV1* expression and MSI was observed in DLBC and LIHC. In contrast, weak correlations between *TRPV1* expression and MSI can be detected in BLCA, GBM, LGG, LUAD, LUSC, PRAD, SARC, STAD, and THCA (Figure 6D).

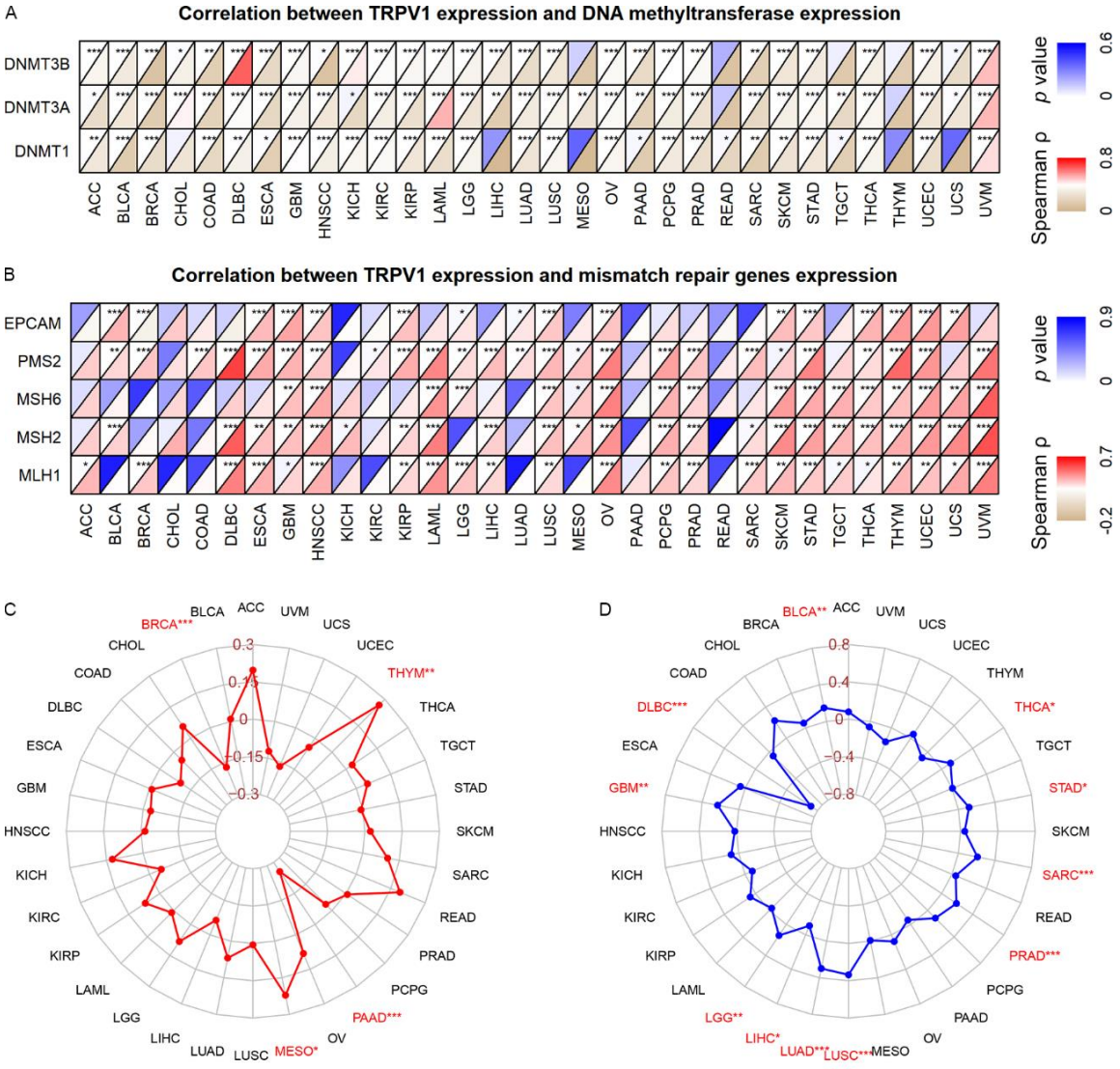

Figure 6. Correlation of *TRPV1* expression with DNA methyltransferases, mismatch repair, tumor mutational burden, and microsatellite instability. Panel C: tumor mutational burden. Panel D: microsatellite instability. *p* values of the figure are based on Spearman correlation analysis; $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

3.5. Immune relevance of TRPV1 expression in pan-cancer

According to the TIMER algorithm, *TRPV1* was significantly associated with infiltration levels of six immune cells in DLBC, CHOL, and SKCM (Figure 7A). *TRPV1* expression was positively related to B cell infiltration levels in DLBC (Spearman's $\rho = 0.63$, $p < 0.05$), and negatively correlated with dendritic cell infiltration levels in CHOL (Spearman's $\rho = -0.39$, $p = 0.018$). A positive correlation between *TRPV1* expression and the infiltration levels of neutrophils and macrophages could be detected in SKCM (Spearman's $\rho > 0.30$, $p < 0.05$) (Figure 7A). Based on the ESTIMATE algorithm, the three cancers with the most significant negative correlations between *TRPV1* and the three ESTIMATE scores were CHOL, LAML, and LGG (Figure 7B). Thus, *TRPV1* expression was associated with the immune microenvironment of some cancers, although its roles in different cancers may be mediated by affecting various immune cells.

In seven cancers – DLBC, LAML, OV, READ, SKCM, THYM, and UVM, *TRPV1* expression was found to be positively associated with almost a third (15/46) of the immune checkpoint genes included in the study (Spearman's $\rho > 0.2$, $p < 0.05$, Figure 7C).

3.6. Potential mechanisms of TRPV1 in pan-cancer

Association of *TRPV1* with at least three KEGG signaling pathways were detected in four cancers —ACC, BLCA, GBM, and OV. It can be seen from Figure 8A that *TRPV1* was significantly relevant to a series of metabolic-related pathways (e.g., "ARACHIDONIC ACID METABOLISM" and "MATURITY ONSET DIABETES OF THE YOUNG") and immunoregulatory-related pathways (e.g., "AUTOIMMUNE THYROID DISEASE" and "CHEMOKINE SIGNALING PATHWAY") (Figure 8A). Furthermore, a notable tumor-related pathway ("HEDGEHOG SIGNALING PATHWAY") was also detected in ACC (Figure 8A).

Gene regulatory network analysis was common for further identifying hub genes in specific classification (e.g., clinical features and gene expression) [24,25]. To explore the hub genes significantly associated with *TRPV1* in ACC, BLCA, GBM, and OV, WGCNA was performed. For ACC, six outlying specimens were removed, and the remaining were used to carry out WGCNA (Supplementary Appendix 4A). A scale-free network was established with the soft threshold equaling 4 (Supplementary Appendix 4B). The hierarchical clustering identified eight modules (Supplementary Appendix 4C). The module strongly correlated with *TRPV1* expression was the "brown" module (Supplementary Appendix 4D). In the brown" module, genes with high module membership generally had elevated gene significance (Supplementary Appendix 4E). Ultimately, *CDCA8* was identified as the hub gene via the WGCNA weight score and "degree" algorithm (Supplementary Appendix 4F). Similarly, hub genes were determined for BLCA, GBM, and OV; in detail, *HID1* for BLCA (Supplementary Appendixes 5A–F), *LY6G5B* for GBM (Supplementary Appendixes 6A–F), and three genes (*EFR3B*, *TMSB15B*, and *EFS*) for OV (Supplementary Appendixes 7A–F).

3.7. Drug sensitivity analysis

This study selected drugs sensitive to highly expressed *TRPV1* cells from 574 drugs validated by clinical trials and 218 drugs approved by the American Food and Drug Administration. As a result, IC50 values of 34 drugs were associated with *TRPV1* expression ($p < 0.01$; Supplementary Appendix 8). Among these drugs, three (I-BET-762, DOLASTATIN 10, and ABBV-075) were sensitive to

TRPV1, as they had lower IC50 values for high-*TRPV1* expression cells ($p < 0.01$; Figure 8B).

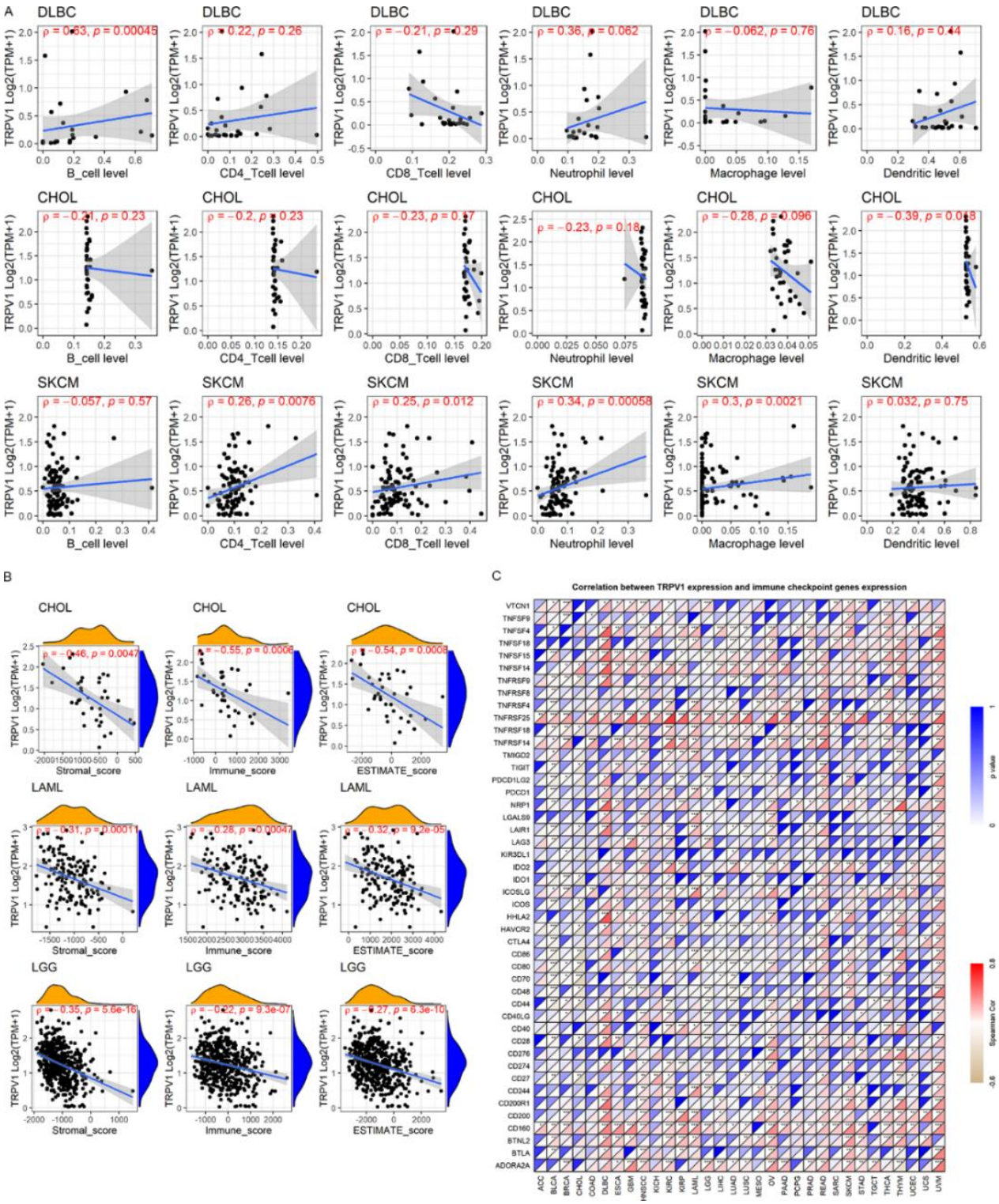

Figure 7. Relationship of *TRPV1* expression with the immune environment. Panel A: correlation of *TRPV1* expression and TIMER scores. Panel B: correlation of *TRPV1* expression and ESTIMATE scores. Panel C: correlation of *TRPV1* expression and immune checkpoint genes expression; $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

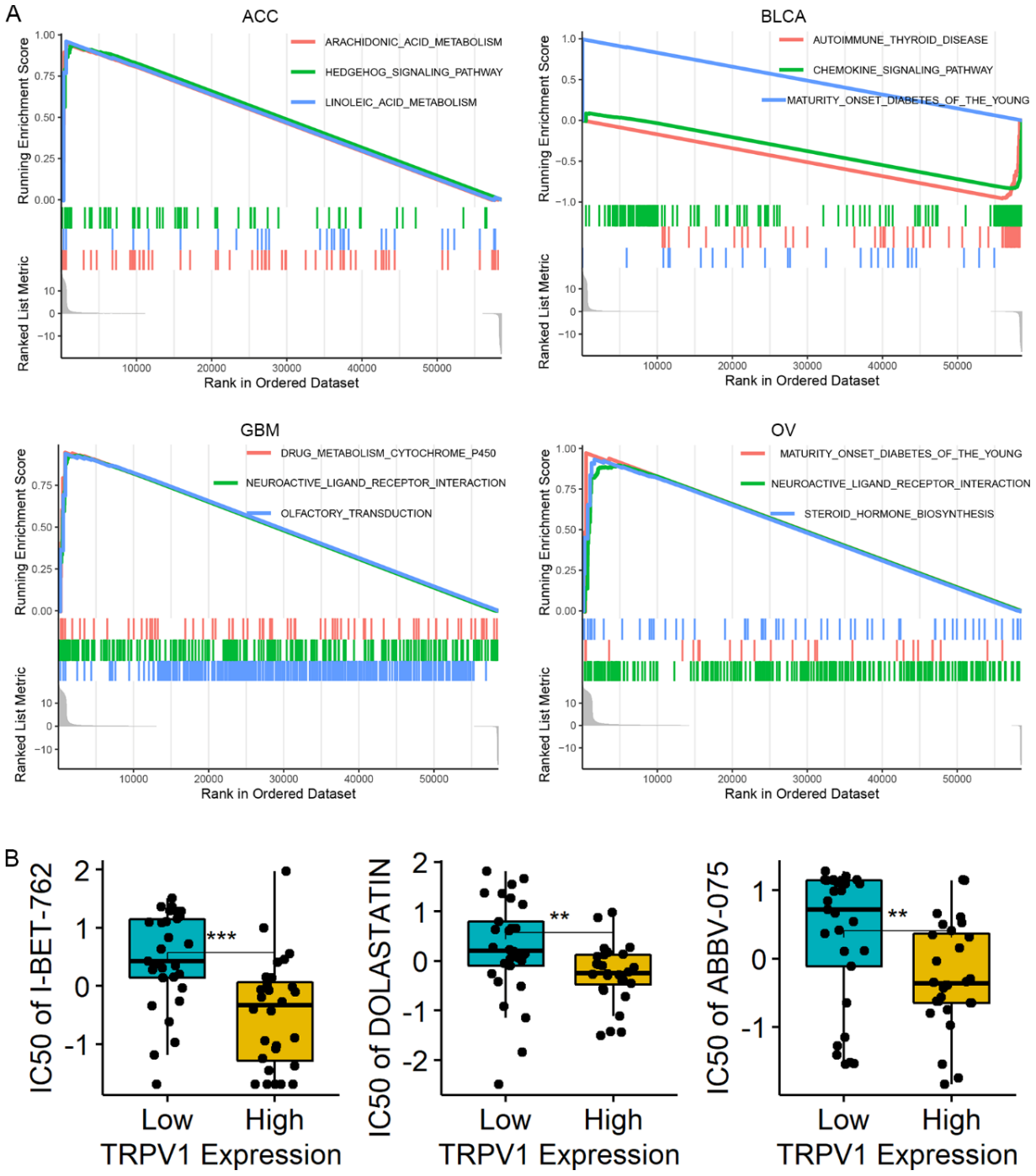

Figure 8. Gene set enrichment analyses (panel A) and drug sensitivity analysis (panel B) of *TRPV1* in pan-cancer. For panel B: *p*-value is calculated by Wilcoxon rank-sum test; $^{**}p < 0.01$; $^{***}p < 0.001$.

4. Discussion

The current study provided a comprehensive workflow of the expression, clinical significance, and underlying mechanisms of *TRPV1* in pan-cancer. Using 10,236 samples, differential *TRPV1* expression levels were detected in multiple cancers. *TRPV1* demonstrated its conspicuous prognosis significance and prediction effects for some cancers, indicating its potential as a valuable and potential

biomarker in treating and predicting cancers. *TRPV1* expression was relevant to DNA methyltransferases, MMR, TMB, and MSI. *TRPV1* expression was associated with the immune microenvironment of some cancers, and its roles in different cancers may be mediated by affecting various immune cells. GSEA discloses the significant relevance of *TRPV1* expression with a series of metabolic and immunoregulatory-related pathways.

TRPV1 demonstrated different expression levels and prognosis significance in various cancers. Previously, Han et al. [26,27] identified overexpression of *TRPV1* and its risk factor for prognosis in both cervical cancer and epithelial ovarian cancer. On the contrary, Gao et al. [28] discovered decreased *TRPV1* expression in gastric cancer and the association of high-*TRPV1* expression with a favorable prognosis. Different *TRPV1* expression levels were detected in 13 cancer cell lines in my study. The expression levels of *TRPV1* in distinct cancer tissues varied from their normal tissues: upregulated in BLCA, HNSCC, KIRC, KIRP, LIHC, LUAD, LUSC, and STAD, while downregulated in BRCA, COAD, GBM, and KICH. For certain cancers with elevated *TRPV1* expression, high gene expression of *TRPV1* was mainly found in immune cells, including CD4 T cells, plasma, proliferating T cells, and monocytes or macrophages. Furthermore, *TRPV1* expression had conspicuous prognosis values in numerous cancers. Both univariate Cox regression and Kaplan-Meier curves revealed that: (1) *TRPV1* expression was related to the inferior OS of patients with ACC and PRAD and good OS of patients with BLCA, HNSCC, PAAD, and READ. (2) For DSS, *TRPV1* expression was associated with unfavorable prognosis of patients with ACC, MESO, PRAD, and THCA, and favorable prognosis of patients with BLCA, HNSCC, KIRP, PAAD, and READ. (3) The gene represented a risk factor for DFI of LUAD and PRAD and a protective role for DFI of PAAD. (4) In PFI, *TRPV1* expression also acted as a negative factor for patients with ACC, PCPG, and PRAD and a positive role in PAAD patients' prognosis. Taken together, *TRPV1* expression was closely relevant to the prognosis of multiple cancers, and it played distinct roles in various cancers.

TRPV1 may be a potential predictor of tumor status. Through AUC values, the significant effects of *TRPV1* expression on identifying cancer tissues and their control tissues were detected in several cancers, including BLCA, GBM, KICH, and LUAD. Thus, *TRPV1* can be considered an underlying marker for predicting and screening these cancers. To my best knowledge, such a finding has not been previously revealed, and more research focusing on the novel discovery should be performed in the future.

Genome heterogeneity may be an important factor resulting in the different roles of *TRPV1* in various cancers. My study discussed the relationships of *TRPV1* expression with SNV, DNA methyltransferases, MMR, TMB, and MSI. Missense mutation enables a polypeptide chain encoded by the corresponding gene to lose its original function, and abnormal functions of quite a few proteins result from missense mutations. A typical example is that the wild-type p53 protein has an anti-cancer effect, whereas the missense mutant p53 plays a role in promoting cancer [29,30]. Bosson et al. [31] revealed that *TRPV1* missense mutation could alter the reactivity of *TRPV1* protein to its natural agonist, suggesting that *TRPV1* missense mutation may affect specific processes of cells. Based on my work, missense mutations in *TRPV1* are not rare in pan-cancer, indicating that SNVs deserve further study. Similarly, different roles of *TRPV1* in various tumors may also be attributed to different statuses of DNA methyltransferases, MMR, TMB, and MSI [32,33,34], with the fact that significant associations of *TRPV1* expression with DNA methyltransferases expression and MMR genes expression were demonstrated in my study.

Similar to genome heterogeneity, the immune microenvironment may also affect the roles of *TRPV1* in cancers. Increasing evidence supported that *TRPV1* participated in pivotal immune cell functions [6]. *TRPV1* expression was detected in several immune cells, including T cells, macrophages, dendritic cells, and natural killer cells [35]. Bertin et al. [36] identified the expression of two critical molecules of CD4+ T cells activation — NFAT and NFκB, was downregulated in *TRPV1* knockout mice, demonstrating the essential role of *TRPV1* in T-cells activating. In my study focusing on pan-cancer, *TRPV1* expression was positively related to B cell infiltration levels in DLBC and negatively correlated with dendritic cell infiltration levels in CHOL. A positive correlation between *TRPV1* expression and the infiltration levels of neutrophils and macrophages could be detected in SKCM. Negative correlations of *TRPV1* expression with three ESTIMATE scores were also discovered in certain cancers including CHOL, LAML, and LGG. Furthermore, *TRPV1* expression was positively associated with the expression of quite a few immune checkpoint genes in several cancers – DLBC, LAML, OV, READ, SKCM, THYM, and UVM, suggesting its potential in treatment concerning immune checkpoint blockades.

The mechanisms of *TRPV1* in the tumorigenesis and development of cancers remained complex and needed to be further explored. *TRPV1* was considered a nonselective cation ion channel (another known function was identified as a nociceptive stimuli receptor [6,37]) and involved in cellular processes: activation of *TRPV1* promoted the flow of calcium and sodium ions into cells; subsequently, excessive calcium and sodium ions in the cells led to cell death [38,39]. Indeed, increasingly studies have shown that the mechanism of *TRPV1* in cancer is not only here but also involves many aspects of the tumor microenvironment (e.g., extracellular mechanism, angiogenesis, immune regulation) [6,36,40], indicating the complexity of the mechanism of *TRPV1* in cancer. Based on the GSEA in my study, *TRPV1* was relevant to several metabolic-related pathways (e.g., "AUTOIMMUNE THYROID DISEASE"), immunoregulatory-related pathways (e.g., "CHEMOKINE SIGNALING PATHWAY"), and tumor-related pathways (e.g., "HEDGEHOG SIGNALING PATHWAY"), to some extent implying the potential molecular mechanisms of *TRPV1* in pan-cancer. Furthermore, hub genes associated with *TRPV1* expression in ACC, BLCA, GBM, and OV were also explored based on WGCNA (i.e., *CDCA8* for ACC, *HID1* for BLCA, *LY6G5B* for GBM, and *EFR3B*, *TMSB15B*, and *EFS* for OV.). Previously, *CDCA8* has been reported to represent aggressive progression and poor prognosis of ACC [41], and *HID1* has been determined as a cancer marker for BLCA development [42]. However, the role of *LY6G5B* in GBM and the roles of *EFR3B*, *TMSB15B*, and *EFS* in OV have not been reported before; the mechanisms of these hub genes in ACC, BLCA, GBM, and OV also remain unclear, which still need more research to confirm.

Three drugs—I-BET-762, DOLASTATIN 10, and ABBV-075—may target *TRPV1*, as their IC50 values were negatively related to *TRPV1* expression, and low IC50 values of them can be detected in high-*TRPV1* expression cells. However, more pharmacological experiments should be performed to verify this finding.

Additionally, the current study provides some ideas for similar clinical investigation: 1) based on pan-cancer data, differentially expressed genes in a variety of tumors can be screened from thousands of genes; 2) using the existing clinical information, the clinical significance of differentially expressed genes can be explored, including prognostic correlation, prediction of tumor status analysis; 3) statistical analysis reveals whether a gene is associated with the immune microenvironment of several tumors and multiple immune checkpoints, to clarify whether the gene has the potential as a target for immunotherapy; 4) the potential molecular mechanism of a gene can be explored by methods such as

GSEA; 5) drugs that may target a specific gene can be selected by drug sensitivity analysis. Based on these ideas, a "virtual laboratory" may be helpful for further pharmacological and clinical studies can be constructed.

Some limitations in my study should be concerned. The current research is a retrospective study, and multicenter samples need to be collected for prospective studies to confirm further the expression and clinical significance of *TRPV1* in pan-cancer. There are deficiencies in the analysis of the potential mechanism of *TRPV1* in pan-cancer. First, the results of underlying mechanism analysis may be biased due to the lack of control of potential confounding factors in carrying out mechanism-related research. Second, due to the lack of data (e.g., ion channel activity state), this study failed to further clarify the potential mechanism of *TRPV1* in pan-cancer through machine learning based on big data (e.g., constructing deterministic models) and molecular biology experiments. Third, in addition to the current statistical analysis, future in vivo and in vitro experiments are necessary to clarify the molecular mechanism of *TRPV1* in various cancers.

5. Conclusions

Herein, the present study initially provided an overview of the expression, clinical value, and underlying mechanisms of *TRPV1* in numerous cancers. The study revealed *TRPV1*'s potential as a novel biomarker for predicting and treating multiple cancer.

Acknowledgments

The datasets for this study can be found in the Depmap Portal at https://depmap.org/portal/download/, Xena database (for TCGA data) at http://xena.ucsc.edu/, and Sanger Box 3.0 at http://vip.sangerbox.com/.

Conflict of interest

The author has no conflicts of interest to declare.

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