DOI: 10.53469/jcmp.2025.07(05).18

Gene DSCC1 is a Potential Biomarker in Pan-cancer

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Abstract: ***Background:*** *DNA replication and sister chromatid cohesion1 (DSCC1) is a component of the alternative replication factor C complex (RFC), which plays an important role in sister chromatid cohesion and regulates the cell cycle. DSCC1 is reported to have increased expression in tumor progression, but the underlying mechanisms of DSCC1 in tumor immunity remain obscure.* ***Methods:*** *Data were collected from The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) project to obtain DSCC1 expression and clinicopathologically relevant data. Differential expression of DSCC1 and its association with prognosis, tumor microenvironment, immune infiltration, immune regulation, and genomic stability in various cancers were analyzed using R software.* ***Results:*** *The results of pan-cancer analysis showed that DSCC1 expression was elevated in 22 tumors. In 15 tumors, high expression of DSCC1 was observed to correlate with dismal overall survival. Furthermore, a correlation between DSCC1 expression and immune checkpoints was determined. In addition, DSCC1 expression was correlated with tumor-infiltrating immune cells, especially in Thymoma (THYM). Finally, gene set enrichment analysis (GSEA) demonstrated that DSCC1 is critically involved in tumor proliferation, immunity, and metabolism.* ***Conclusions:*** *High DSCC1 expression is found in many common tumors and is associated with poor prognosis. The gene is an essential factor in sister chromatid cohesion and may contribute to tumor progression by affecting the tumor immune microenvironment and genomic stability. DSCC1 has the potential to be a prognostic marker, and therapies targeting it may benefit patients.*

Keywords: DNA replication and sister chromatid cohesion1 (DSCC1), Pan-cancer analysis, Immunity.

1. Introduction

Cancer is a serious public health problem and one of the leading causes of death worldwide [1]. Due to its widespread prevalence, there is an urgent need for more effective treatments. In recent years, despite the fact that patients have benefited greatly from surgical treatment, radiation therapy, chemotherapy, targeted therapy and especially immunotherapy, the prognosis for most patients is still poor [2, 3]. Therefore, there is an urgent need to develop new therapeutic modalities and to explore the underlying molecular mechanisms that drive cancer development.

DNA replication and sister chromatid cohesion1 (DSCC1, also known as DCC1), which locates in human chromosome 8q24 is a component of the alternative replication factor C complex (RFC) [4]. Consisting of five subunits (Rfc 1-5), replication factor C (RFC) functions by loading processivity factor Proliferating Cell Nuclear Antigen (PCNA) onto DNA and unloading PCNA [5, 6]. DNA replication and repair processes requires the primitive member (Rfc1-RFC) [7, 8]. The Ctf18-RFC complex is formed by the substitution of Rfc1 subunit in RFC by chromosome transmission fidelity protein 18 (Ctf18) [9]. Unlike other RFCs, the Ctf18-RFC complex includes the Ctf18-DSCC1-Ctf8 module, in which two non-RFC subunits DSCC1 and Ctf8 bind [10, 11]. As an essential factor in sister chromatid cohesion, Ctf18-RFC complex plays important roles in DNA replication, spindle checkpoints, DNA repair, and genome stabilization during the S-phase of the cell cycle [4, 12]. Additionally, DSCC1 expression is elevated in a variety of cancers, such as colon cancer [13], hepatocellular carcinoma [4], breast cancer [14], Lung Adenocarcinoma [15], Gastrointestinal Goblet cell adenocarcinoma [16] and neuroblastoma [17], and its elevated expression may lead to poor prognosis. However, the mechanism of DSCC1 in tumor development is not fully understood, and therefore, comprehensive pan-cancer analysis is needed to determine the possible immune, metabolic, and proliferation-related mechanisms involved in DSCC1 as a new target for tumor therapy.

In this study, we analyzed DSCC1 expression levels and their association with prognosis in a range of different cancers using data from the Genotype-Tissue Expression (GTEx) project, The Cancer Genome Atlas (TCGA), and The Clinical Proteomic Tumor Analysis Consortium (UPTAC). In addition, to understand the impact of DSCC1 on the immune microenvironment and tumor malignant progression, we examined the association of DSCC1 expression with immune regulation, tumor-infiltrating immune cells (TIICs), microsatellite instability (MSIs), tumor mutational load (TMB), stemness scores based on mRNA expression (RNAss), and stemness scores based on DNA methylation (DNAss) relationships. To investigate the role of DSCC1 in cancer in more detail, we also performed gene set enrichment analysis (GSEA).

2. Materials and Methods

2.1 Data Source

First, we collected data from RNA sequencing in normal and tumor tissues from the GTEx database (https://commonfund.nih.gov/GTEx/) and TCGA database (http://cancergenome.nih.gov/), respectively, and obtained relevant clinicopathological data from them. Moreover, DSCC1 protein expression data was obtained from The Clinical Proteomic Tumor Analysis Consortium (UPTAC) [18]. In addition, cancer immune infiltration scores were analyzed with data from the Tumor Immunity Estimation Resource (TIMER) dataset (http://timer.cistrome.org/) [19].

2.2 Expression Analysis of DSCC1

Differences in DSSC1 mRNA expression between cancerous and adjacent normal tissues were analyzed in the Gene_DE module of TIMER 2.0. For cancer types lacking sufficient normal adjacent samples, GTEx and TCGA data were used and analyzed by the box plot module in the expression DIY function of GEPIA 2.0 (http://gepia2.cancer-pku.cn/) [20]; the absolute log 2FC cutoff and p-value cutoff were set as 0.585 and 0.01, respectively. In addition, mRNA expression differences in cancer stage were also presented in the stage map module. The Clinical Proteomic Tumor Analysis Consortium (UPTAC) data obtained from UALCAN (http: //ualcan.path.uab.edu/) were used to compare the DSSC1 protein expression differences between cancer and normal tissues [18].

2.3 Survival Prognosis Analysis of DSCC1 in Pan-caner

Clinical phenotypes and survival information of TCGA cases were extracted. Univariate regression was used to assess the association of DSCC1 with the following four prognostic indicators in different tumors: overall survival (OS) rate, disease-specific survival (DSS), and disease-free interval (DFI), progression-free interval (PFI). Cases were categorized into high-expression or low-expression groups based on median DSSC1 levels. Survival analysis was performed using the Kaplan-Meier method and log-rank test. In addition, forest plots were obtained for each cancer.

2.4 Correlation Analysis of DSCC1 Expression Level and Immunity

Immune checkpoints and the tumor microenvironment (TME) were analyzed. First, Spearman's rank correlation coefficient was performed to analyze the association between DSCC1 expression and immune checkpoints, which include chemokine receptor proteins, chemokine, immune activation proteins, and immunosuppressive proteins.

Similar analyses but using Pearson correlation coefficients were also applied to evaluate the correlation of DSCC1 expression and tumor-infiltrating immune cells, including B cells, CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and dendritic cells (DC). Furthermore, immune core, stromal score, and ESTIMATE score were obtained with the Estimation of Stromal and Immune Cells in Malignant Tumors Using Expression data (ESTIMATE) algorithm [21].

2.5 Correlation Analysis of DSCC1 Expression Level with DNAss, RNAss, TMB, and MSI

Pearson correlation coefficient was employed to explore the association of DSCC1 expression with DNAss, RNAss, TMB, and MSI. Radar charts were obtained.

2.6 GSEA

The target gene was uploaded to a search tool that retrieves interacting genes/proteins to analyze its protein-protein interaction (PPI) network (https:// string- db. org/) [22]. GSEA enrichment analysis was applied to identify signaling pathways enriched with significant differences in the high and low expression DSCC1 groups. The Hallmark gene set and the Kyoto Encyclopedia of Genes and Genomes database (KEGG; https://www.kegg.jp.) were applied. A normalized enrichment score (NES) >1.5, a P value <0.05, and a false discovery rate (FDR) <0.25 were considered significant.

2.7 Statistical Analysis

R software (version 4.4.2; https://www.R-project.org; The R Foundation for Statistical Computing, Vienna, Austria) was used in this study to manage data, and the plots were obtained using R packages. A P value <0.05 was considered to be statistically significant.

3. Results

3.1 Different Expression of DSCC1 in Pan-cancer

Differences in mRNA expression levels of DSCC1 between pan-cancer tissues and corresponding normal tissues were analyzed on TIMER2.0 using the TCGA database; DSCC1 mRNA expression significantly upregulates in BLCA, BRCA, CESC, CHOL, COAD, ESCA, GBM, HNSC, KIRC, KIRP, LIHC, LUAD, LUSC, READ, STAD, UCEC and downregulated in KICH and PCPG (Figure 1A). For cancers lacking normal tissue controls, GEPIA combined with TCGA and GTEX databases were applied to analyze the differences in DSCC1 expression. The GEPIA2 results showed that DSCC1 was highly expressed in UCS, TGCT, THYM, LGG, OV and poorly expressed in LAML (Figure 1B). Moreover, DSCC1 is positively correlated with the high stage of ACC, BRCA, CESC, KICH, KIRC, KIRP, LUAD, SKCM and negatively correlated with the high stage of LUSC and LIHC (Figure 1C). In addition, UALCAN results exhibited DSCC1 protein was highly expressed in colon cancer, head and neck squamous carcinoma, hepatocellular carcinoma, lung adeno carcinoma, lung squamous cell carcinoma, ovarian cancer and uterine corpus endometrial carcinoma (UCEC) (Figure 1D).

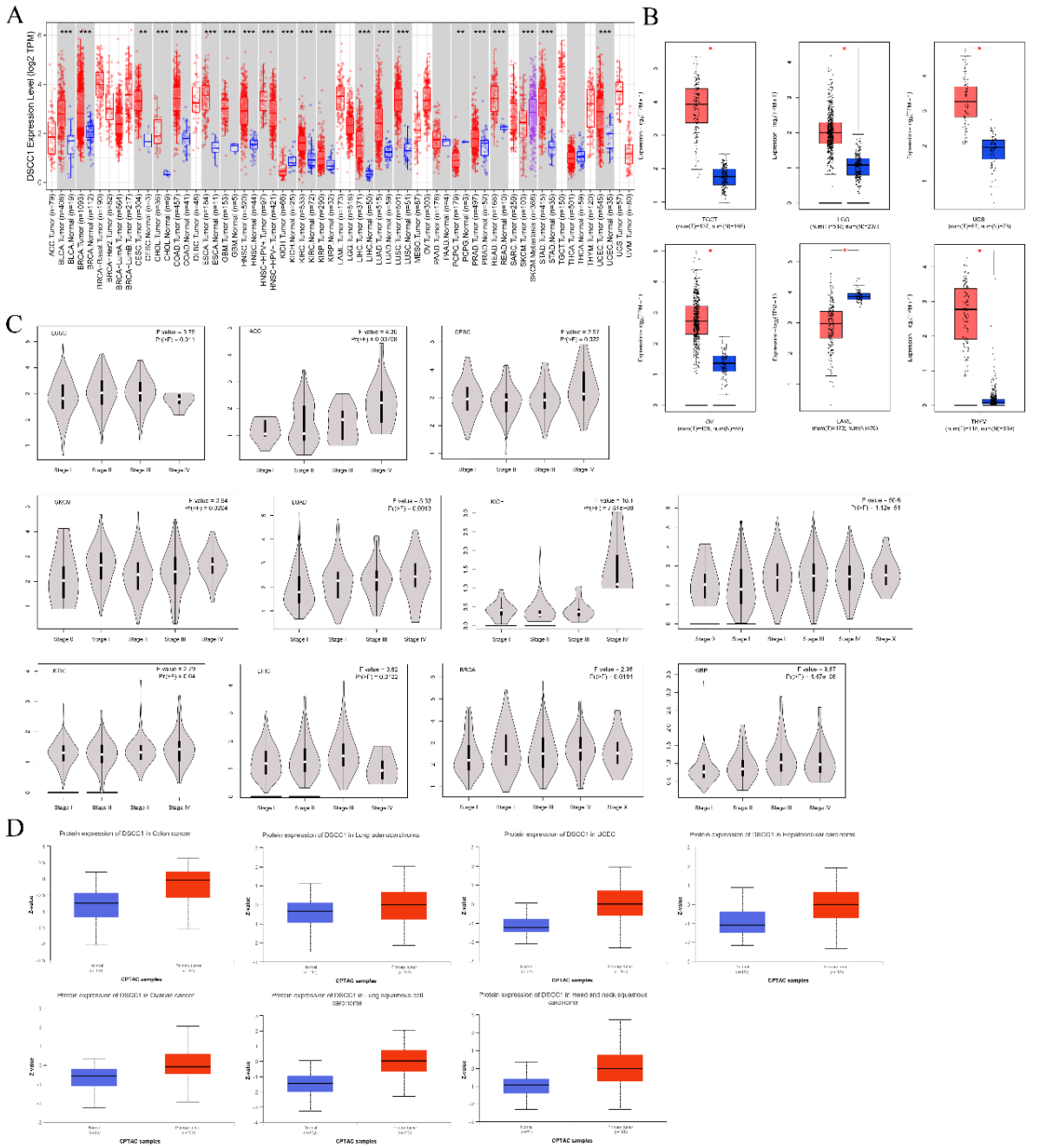

Figure 1: Expression analysis of DSCC1 in pan-cancer. (A)Analysis of DSCC1 expression levels in pan-cancer, and their corresponding control tissues with data from the TCGA database. (B)The box plots of DSCC1 mRNA log2 expression levels between tumors and normal tissues in 7 cancer types with data from the TCGA database and GTEx project database. (C)DSCC1 expression levels in different stages of 10 cancers analyzed on GEPIA2.0. (D) The protein expression differences between normal and primary tumor tissues in 7cancers compared on UALCAN.

3.2 Correlation of DSCC1 Expression and Prognosis

Univariate Cox proportional hazards regression analysis was performed to evaluate the pan cancer prognostic role of DSCC1. Results showed that DSCC1 expression was markedly correlated with OS of patients with GBMLGG(p<0.01), LGG(p<0.01), KIPAN(p<0.01), KIRP(p<0.01), KICH(p<0.01), ACC(p<0.01), LIHC(p<0.01), LUAD(p<0.01), PAAD(p<0.01), SARC(p=0.01), MESO(p=0.02), BRCA(p=0.03), UVM(p=0.03), THYM(p<0.01), DLBC(p=0.04) (Figure 2A). Moreover, DSS results exhibited that DSCC1 expression correlated with GBMLGG(p<0.01), KIRP(p<0.01), KIPAN(p<0.01), LGG(p<0.01), KICH(p<0.01), ACC(p<0.01), LIHC(p<0.01), LUAD(p<0.01), PAAD(p<0.01), MESO(p=0.01), SKCM(p=0.01), BRCA(p=0.02), PRAD(p=0.02), SARC(p=0.03), UVM(p=0.03), OV(p=0.03) (Figure 2B). In addition, DSCC1 expression is associated with the DFI of patients with KIRP(p<0.01), LIHC(p<0.01), PAAD(p<0.01), KIPAN(p<0.01), CESC(p=0.03), LUSC(p=0.03) (Figure 2C). Finally, DSCC1 expression was significantly correlated with PFI of patients with GBMLGG(p<0.01), KIPAN(p<0.01), KIRP(p<0.01), LGG(p<0.01), ACC(p<0.01), KICH(p<0.01), SKCM(p<0.01), LIHC(p<0.01), PAAD(p<0.01), PARD(p<0.01), UVM(p<0.01), CESC(p<0.01), MESO(p=0.03), PCPG(p=0.03), KIRC(p=0.04), BLCA(p=0.04) (Figure 2D).

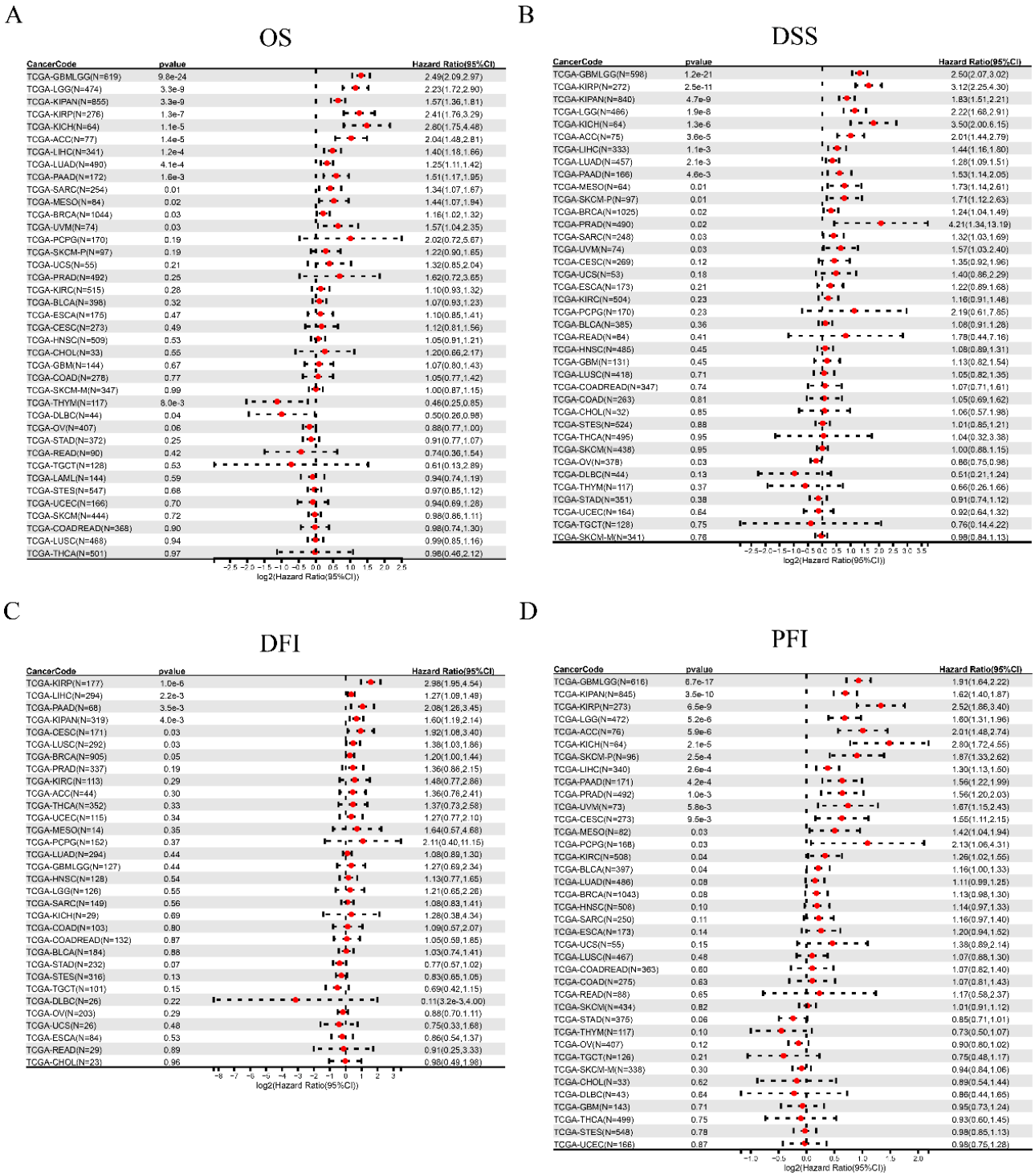

Figure 2: Forest plot of associations between DSCC1 expression and overall, disease-specific, disease-free, and progression-free survival. Association of DSCC1 with (A) OS, (B) DSS, (C) DFI, and (D) PFI. OS, overall survival; DSS, disease-specific survival; DFI, disease-free interval; PFI, progression-free interval.

3.3 Prognostic Role of DSCC1 in Pan-cancer

DSCC1 was categorized into high and low expression groups for plotting Kaplan-Meier curves to analyze OS, DSS, DFS and PFS based on DSCC1 expression in cancer patients. Results showed that high expression of DSCC1 was associated with lower overall survival (OS) percentages in ACC, BRCA, KIRP, LGG, LIHC, LUAD, MESO, THYM and UVM (Figure 3A); lower disease-specific survival (DSS) percentages of ACC, KICH, KIRP, LGG, LUAD, MESO, UCS, UVM (Figure 3B); lower disease-free interval (DFI) percentages of KIRP, LIHC and THCA (Figure 3C) and shortening of the progression-free interval (PFI) of ACC, KICH, KIRP, LGG, LIHC, LUAD, PRAD (Figure 3D).

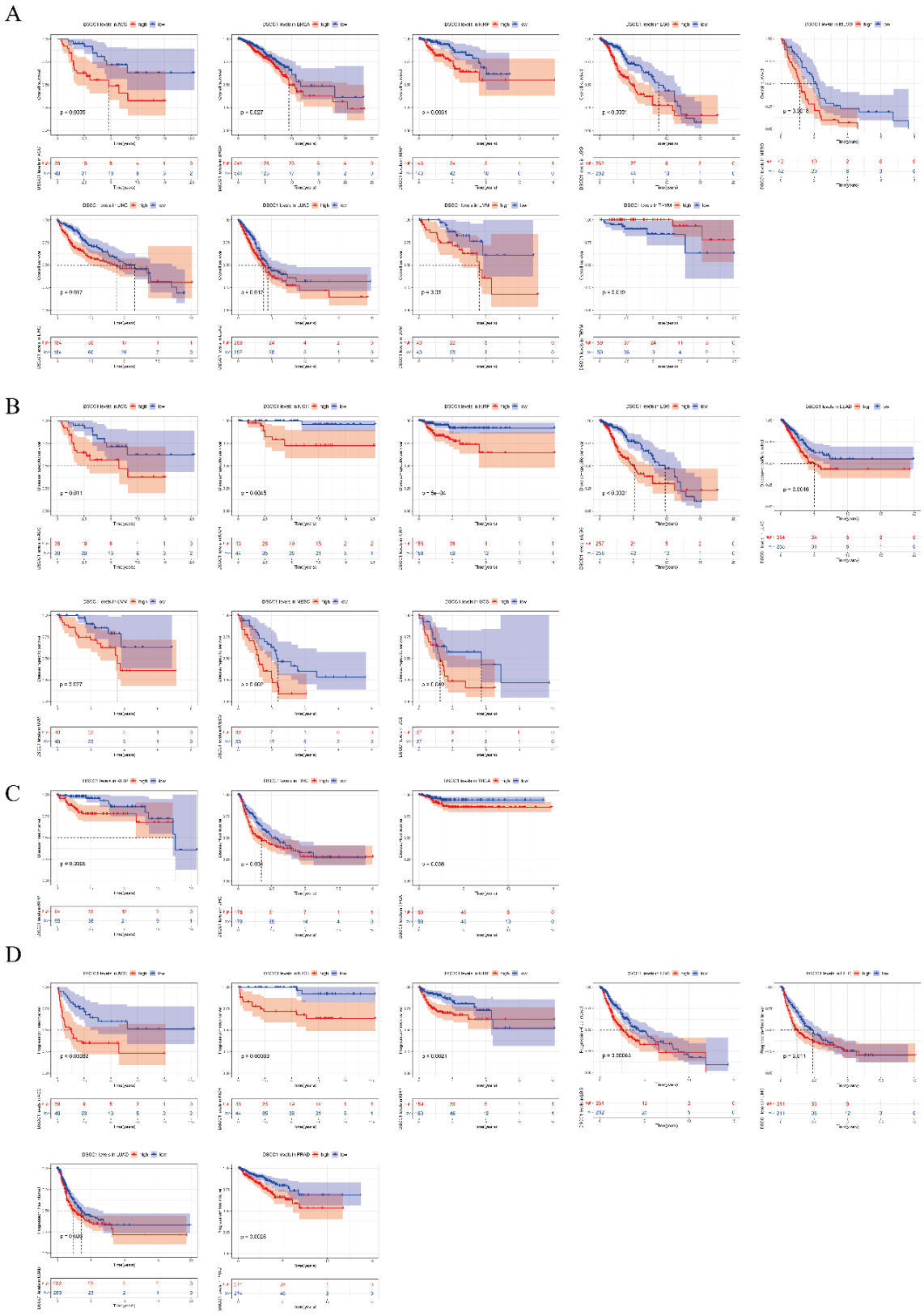

Figure 3: Kaplan-Meier analysis of overall survival, disease-specific survival, disease-free interval and progression-free interval according to DSCC1 expression level in different tumors. (A) overall survival; (B) disease-specific survival; (C) disease-free interval; (D) progression-free interval.

3.4 Correlation of DSCC1 Expression and Immunity

To explore the role of DSCC1 in tumor immunity; data of immune checkpoints, tumor-infiltrating immune cells; and immune score, stromal score, and ESTIMATE score were analyzed.

We first performed correlation analysis of DSCC1 expression and immune checkpoints, which included 24 immune inhibitors and 36 immune stimulators. Among the data of immune inhibitors in 40 common tumors, we found that DSCC1 expression was positively linked to vascular

endothelial growth factor A (VEGFA) in 29 tumors, to CD276 in 26 tumors, to lymphocyte activating 3 (LAG3) in 14 tumors, and to programmed death ligand 1 (PD-L1) in 15 tumors. Moreover, among the data of immune stimulators, DSCC1 expression was found to be positively associated with high mobility group box 2 (HMGB2) in all 40 tumors except TGCT, C-X-C motif chemokine ligand 10 (CXCL10) in 20 tumors, C-X-C motif chemokine ligand 9 (CXCL9) in 18 tumors (positively), and tumor necrosis factor superfamily member 4 (TNFSF4) in 23 tumors; conversely, DSCC1 expression was found to be negatively associated with selectin P (SELP) in 20 tumors. In addition, DSCC1 expression was positively associated with 17 of 24 immune inhibitors and with 26 of 36 immune stimulators in UVM, 12 of 24 inhibitors and 14 of 36 stimulators in OV, 18 of 24 inhibitors and 28 of 36 stimulators in LIHC, 21 of 24 inhibitors and 33 of 36 stimulators in KIPAN, 7 of 24 inhibitors and 19 of 36 stimulators in PAAD (Figure 4).

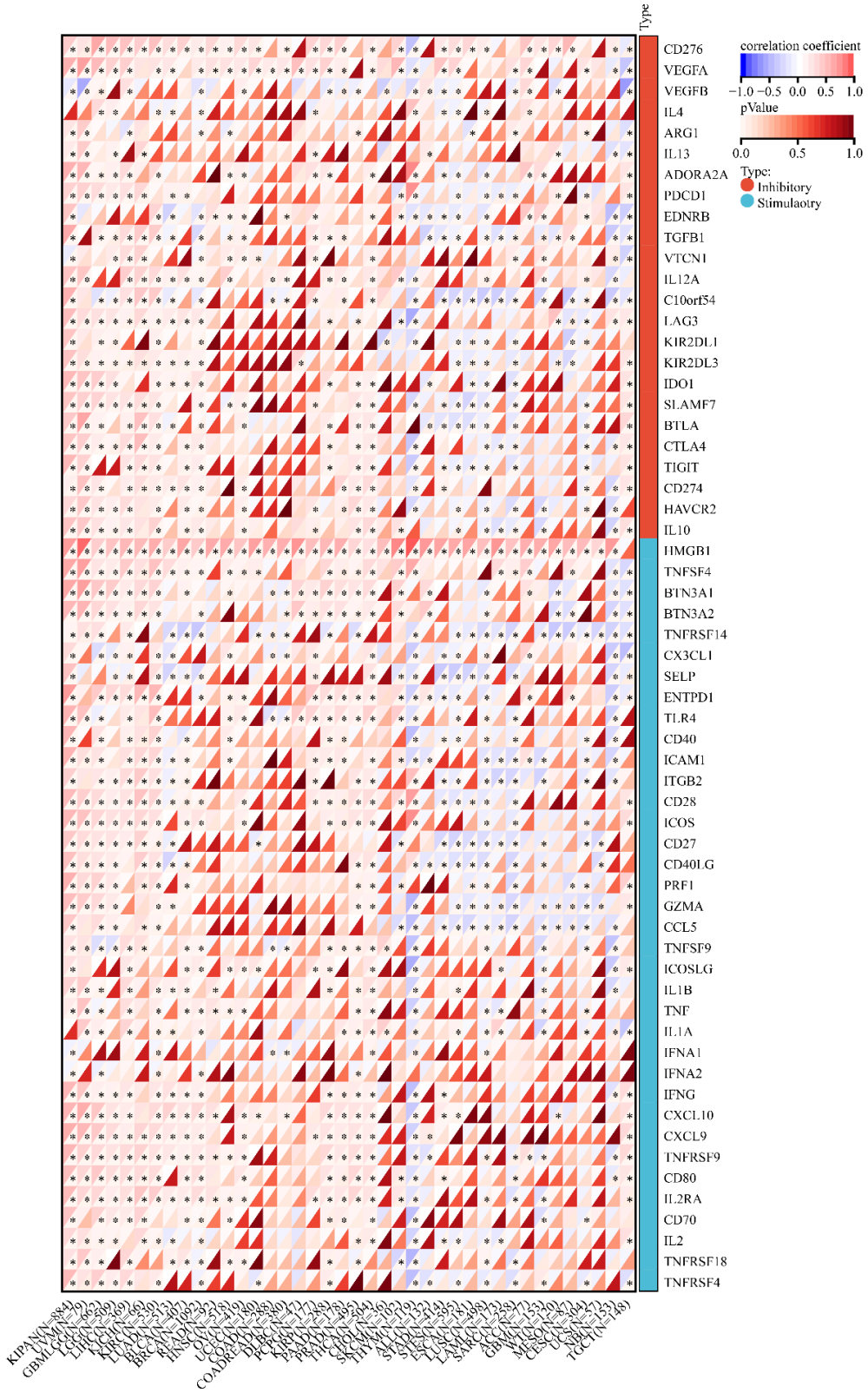

Figure 4: Pan-cancer correlations between DSCC1 expression and 24 immune inhibitors and 36 immune stimulators. *P<0.05.

Next, correlation analysis of DSCC1 expression and 6 types of immune cells of the TME, which consist of B cells, CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and DCs, was performed [23]. The results showed that in THYM, DSCC1 expression was significantly and positively correlated with B cells, CD 4 + T cells, CD 8 + T cells and DCs. Besides, DSCC1 expression was negatively correlated with B cells, CD 4 + T cells and DCs (Figure 5A). Finally, data of ESTIMATE analysis revealed correlation of DSCC1 expression with common tumor purity, infiltration and stroma (Figure 5B, C, D).

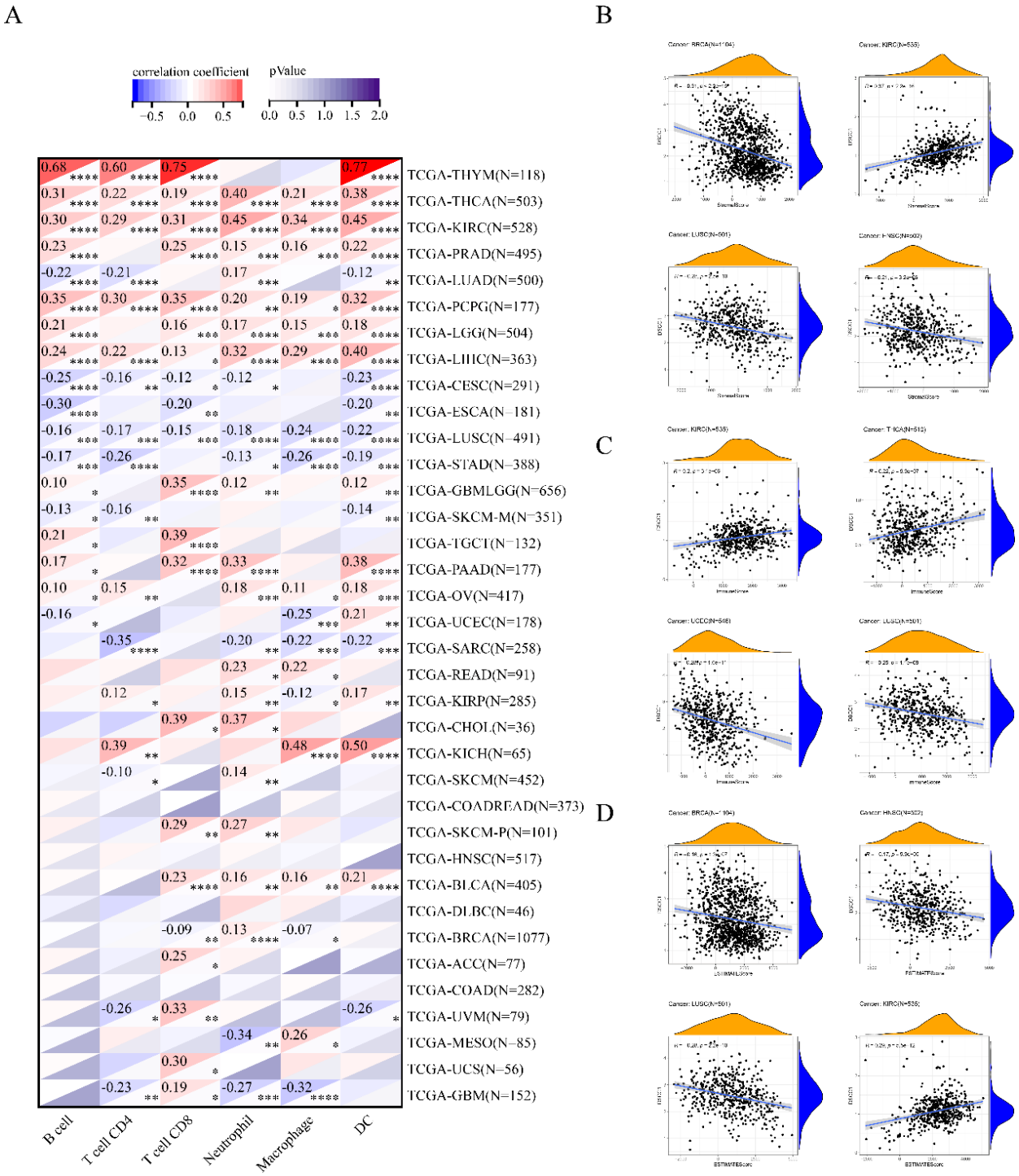

Figure 5: Correlations between DSCC1 expression and tumor-infiltrating immune cells and TME. (A) Pan-cancer correlation analysis across between DSCC1 expression and B cells, CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and DCs. (B, C, D) Representative results of correlation analysis between DSCC1 expression and stromal score(B), immune score(C) and ESTIMATE score(D). *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001.

3.5 Correlation of DSCC1 Expression with DNAss, RNAss, TMB and MSI

There is growing evidence that increased expression of stemness-related biomarkers in tumor cells is highly correlated with drug resistance, cancer recurrence, and tumor proliferation [24]. In addition, TMB and MSI have been recognized as indicators of the level of genomic instability [25]. In this study, DSCC1 expression positively correlates with DNAss (Figure 6A) and RNAss (Figure 6B) in many

tumors such as TGCT, STAD, LUAD and LUSC. The DSCC1 expression level also showed a positive correlation with TMB in many tumors, including LUAD, STAD, and LUSC (Figure 6C), but a negative correlation with THYM. In addition, the expression of DSCC1 was positively correlated with MSI in STAD, LUSC, and ESCA, but was negatively correlated with MSI in TGCT (Figure 6D).

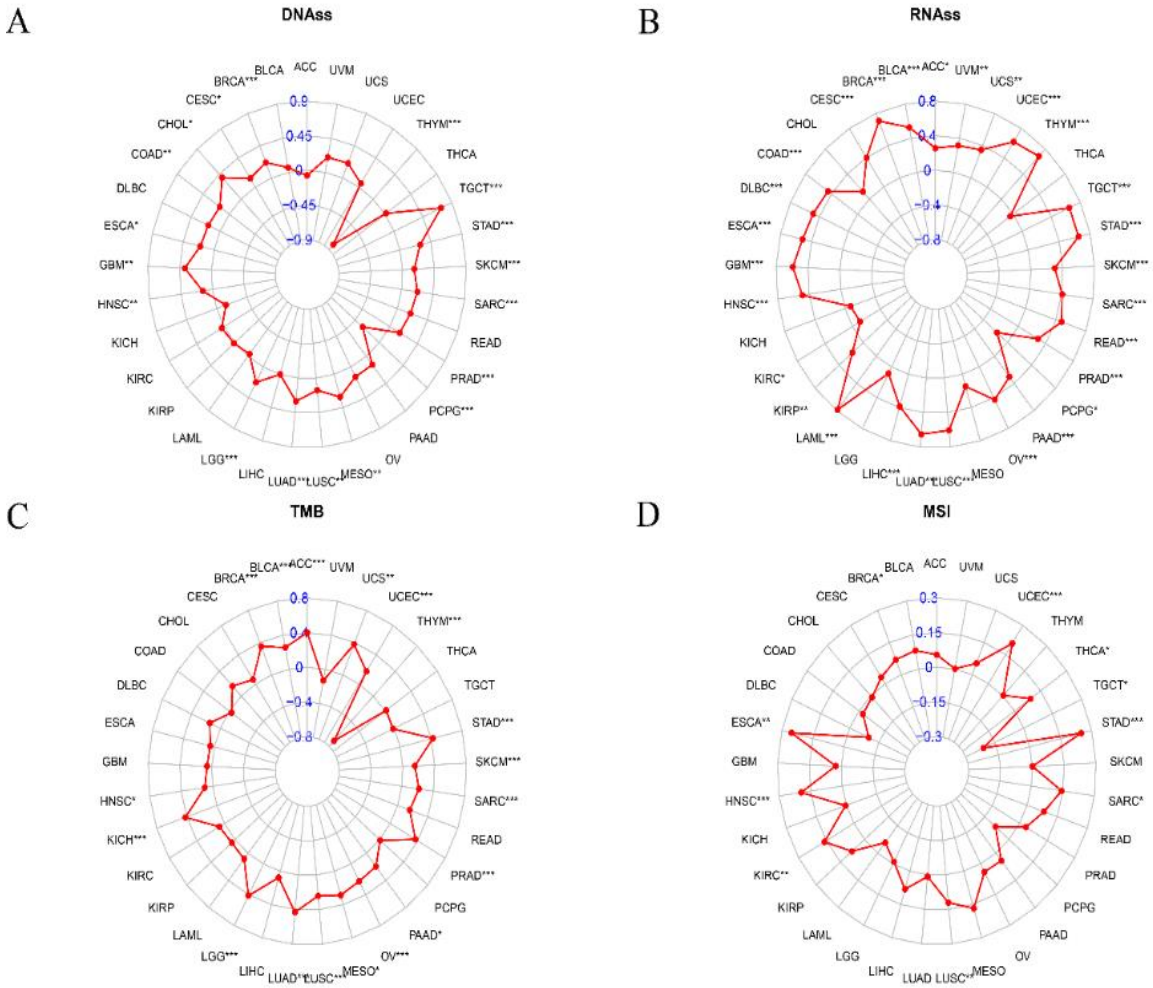

Figure 6: Correlations of DSCC1 expression levels with DNA methylation-based stemness score, mRNA expression-based stemness score, tumor mutational burden, and microsatellite instability. Radar chart of the correlations between DSCC1 expression and (A) DNA methylation-based stemness score, (B) mRNA expression-based stemness score, (C) tumor mutational burden, and (D) microsatellite instability.

3.6 GSEA

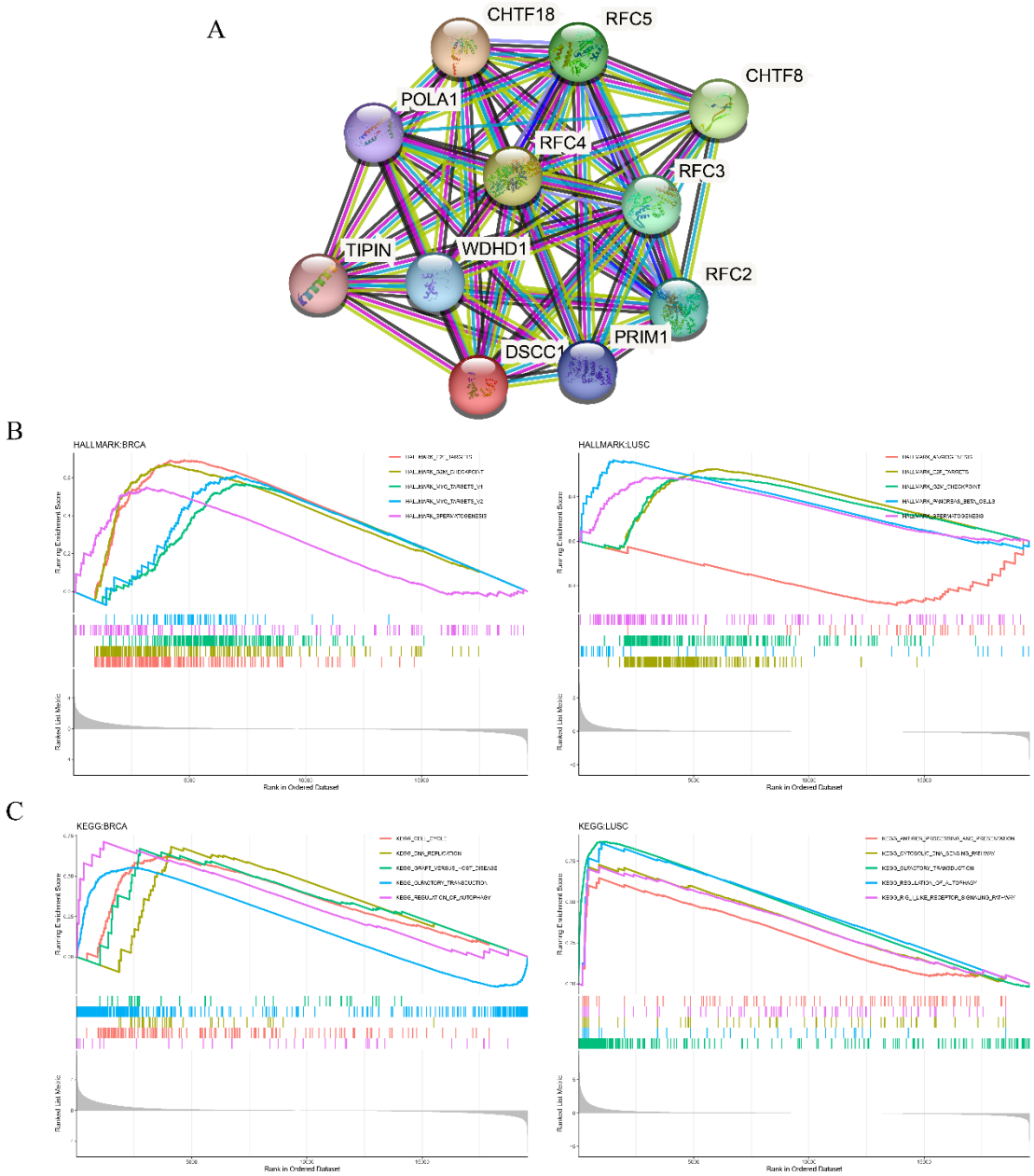

Figure 7: GSEA. (A) Protein – Protein interaction analysis of DSCC1. (B) Representative results of Hallmark analysis of DSCC1. (C) Representative results of KEGG analysis of DSCC1.

The protein-protein interaction network of DSCC1 was constructed to analyze the functional network of DSCC1, to understand its function and potential mechanisms. The results showed that DSCC1 was linked to CHTF18, RFC5, CHTF8, RFC2, RFC3, RFC4, PRIM1, TIPIN, POLA1, WDHD1, which are all mitosis-related proteins (Figure 7). In addition, DSCC1 expression levels were divided into high and low expression groups at the median value, and then compared with hallmark gene sets for GSEA analysis. The resulting data indicated DSCC1 to be highly enriched in HALLMARK_E2F_TARGETS, HALLMARK_G2M_CHECKPIONT. Meanwhile, the results of the KEGG analysis shown that DSCC1 to be highly enriched in cellular pathways such as KEGG_CELL_CYCLE and KEGG_DNA_REPLICATION.

4. Discussion

In recent years, immunotherapy has brought hope of cure to many cancer patients [2]. However, due to the heterogeneity of patients, the prognosis for most patients remains poor [26]. Therefore, there is an urgent need to develop a new and more accurate targeted therapy or combination therapy regimen. DSCC1 is a component of selective replication factor c complex (RFC) [4]. Physically associating with Ctf8 and Ctf18, RFC plays significant roles in sister chromatid cohesion, and its detection results in severe sister chromatid cohesion defects and increased sensitivity to microtubule depolymerizing drugs [9]. Moreover, it also affects in DNA replication, spindle checkpoints, DNA repair, and genome stabilization during the S-phase of the cell cycle [12]. Recently, high expression of DSCC1 has been found in many cancers and its high expression may leads to poor prognosis such as COAD, LUAD, LIHC, and BRCA [4, 13-15]. Therefore, a pan-cancer analysis of DSCC1 expression was performed to assess its role in prognosis, immunity, metabolism and its therapeutic potential in the present study.

First, we analyzed and compared the expression levels of DSCC1 in normal tissues and matched tumor tissues, and the results showed that DSCC1 expression was elevated in all tumors except ACC, KICH, LAML, MESO, PAAD, PCPG, THCA and UVM. Meanwhile, the protein level of DSCC1 showed its elevated expression in colon cancer, head and neck squamous carcinoma, hepatocellular carcinoma, lung adeno carcinoma, lung squamous cell carcinoma, ovarian cancer and uterine corpus endometrial carcinoma (UCEC) in the analysis of The Clinical Proteomic Tumor Analysis Consortium (UPTAC) data. Moreover, DSCC1 is positively correlated with the high stage of ACC, BRCA, CESC, KICH, KIRC, KIRP, LUAD, SKCM. These results corroborate the reports that DSCC1 is highly expressed in a variety of tumors and suggest that it may be closely related to tumor progression [4, 13-17]. In addition, we also analyzed the pan-cancer prognostic role of DSCC1 using clinicopathological and DSCC1 expression data. As shown by OS, DSS, DFI and PFI analysis, high expression of DSCC1 predicted poor prognosis in a variety of tumors. These results highlight the potential of DSCC1 as a new pan-cancer biomarker.

Immune checkpoint therapy has benefited many cancer patients over the past decade. However, due to tumor heterogeneity, only a subset of patients is still suitable for relevant therapy [27]. In this study, we performed a correlation analysis of DSCC1 with immune checkpoints. Within 24 immune inhibitors, we found that DSCC1 expression was positively linked to vascular endothelial growth factor A (VEGFA) in 29 tumors, to CD276 in 26 tumors, to lymphocyte activating 3 (LAG3) in 14 tumors, and to programmed death ligand 1 (PD-L1) in 15 tumors. Meanwhile, in the immune stimulators, DSCC1 expression was found to be positively associated with high mobility group box 2 (HMGB2) in all 40 tumors except TGCT, C-X-C motif chemokine ligand 10 (CXCL10) in 20 tumors, C-X-C motif chemokine ligand 9 (CXCL9) in 18 tumors (positively), and tumor necrosis factor superfamily member 4 (TNFSF4) in 23 tumors; conversely, DSCC1 expression was found to be negatively associated with selectin P (SELP) in 20 tumors. Among the immune checkpoints mentioned above, VEGFA was shown to inhibit the trafficking of cytotoxic T lymphocyte (CTL) [28], CD276 was reported as an inhibitor of T cells [29], LAG3 may inhibit activated T cells [30], PD-1/PD-L1 was reported to be involved in the acquisition of immune escape by tumor cells [31], CXCL 9 and CXCL 10 were shown to be involved in the differentiation of naïve T cells into T helper (Th) cells [32]. TNFSF4 was reported to be involved in stimulating T cell activation [33]. Collectively, these results indicate that DSCC1 plays an important role and reveal the potential of DSCC1 as a therapeutic target for tumors.

Immune cells infiltrating TME, such as DCs, macrophages, neutrophils, mast cells, monocytes, T cells and B cells regulate tumor progression [23]. To further elucidate the role of DSCC1 in tumor immunity, we performed a study of correlation analysis of DSCC1 expression and tumor-infiltrating immune cells with ESTIMATE score. In the present study, we identified a positive correlation of DSCC1 with immune infiltrating cells in THYM, THCA, KIRC and PRAD, while a negative correlation with immune cells in CESC, ESCA, LUSC, STAD. In particular, DSCC1 has a strong positive correlation with B cells, CD 4 + T cells, CD 8 + T cells and DCs in THYM, which might explain the high DSCC1 expression having high OS in THYM. In addition, DSCC1 expression was found to correlate with stromal scores in a range of tumors, suggesting that DSCC1 not only affects immune cell infiltration but may also play an important role in stromal cell infiltration, including in epithelial, fibroblast, and vascular cells [21]. Therefore, DSCC1 may affect tumor purity and has the potential to be a promising therapeutic strategy by the potential of being a crucial modulator of immunity.

TMB and MSI are important indicators of the efficacy of ICI therapy in cancer patients [25]. The level of tumor differentiation is closely related to cancer stem cell viability, which is reflected by RNAss and DNAss, where higher stemness scores indicate lower tumor differentiation [24]. In this study, we examined the relationship between DSCC1 expression and these four metrics. DSCC1 expression levels were also positively correlated with TMB but negatively correlated with THYM in many tumors including LUAD, STAD and LUSC. Meanwhile, DSCC1 expression was positively correlated with MSI in STAD, LUSC and ESCA, but negatively correlated with MSI in TGCT. In addition, DSCC1 expression positively correlates with DNAss and RNAss in many tumors such as TGCT, STAD, LUAD and LUSC. Interestingly, DSCC1 expression showed a significant negative correlation with TMB and DNAss in THYM, which explains its positive prognostic effect. To date, several cancers have been reported to be prognostically associated with DSCC1 expression. Overall, although further clinical trials are needed, DSCC1 expression may be a potential predictor of immunotherapy.

GSEA analysis was performed to understand the pathophysiological mechanisms underlying the role of DSCC1 in pan-cancer. Functional network and signaling pathway analyses revealed that DSCC1 is an important player in the cell cycle and is enriched in cell cycle, G2/M checkpoint and DNA replication. Thus, DSCC1 acts as a cell cycle regulatory participant involved in accurate distribution and replication of DNA, ultimately contributing to cell cycle and tumorigenesis.

In conclusion, this study demonstrates that DSCC1 is differentially expressed in common tumors, and can be used as a therapeutic and prognostic biomarker. However, our work still has some limitations, i only bioinformatics analysis of open accessible databases was performed and no experimental data were available. Therefore, this study provides a basis for follow-up studies and further studies are needed to validate our findings.

Abbreviations

DSCC1: DNA replication and sister chromatid cohesion1; RFC: replication factor C complex; TCGA: The Cancer Genome Atlas; GTEx: Genotype-Tissue Expression project; GSEA: gene set enrichment analysis; THYM: Thymoma; PCNA: Proliferating Cell Nuclear Antigen; Ctf18: chromosome transmission fidelity protein 18; Ctf8: chromosome transmission fidelity protein 8; UPTAC: The Clinical Proteomic Tumor Analysis Consortium; TIICs:

tumor-infiltrating immune cells; MSIs: microsatellite instability; TMB: tumor mutational load; RNAss: stemness scores based on mRNA expression; DNAss: stemness scores based on DNA methylation; TIMER: Tumor Immunity Estimation Resource dataset; OS: overall survival; DSS: disease-specific survival; DFI: disease-free interval; PFI: progression-free interval; TME: tumor microenvironment; ESTIMATE: the Estimation of Stromal and Immune Cells in Malignant Tumors Using Expression data algorithm; KEGG: the Kyoto Encyclopedia of Genes and Genomes database; NES: normalized enrichment FDR: false discovery rate; DC: dendritic cells; 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 adenocarcinoma/Rectum adenocarcinoma Esophageal carcinoma; DLBC: Lymphoid Neoplasm Diffuse Large B-cell Lymphoma; ESCA: Esophageal carcinoma; GBM: Glioblastoma multiform; GBMLGG: Glioma; HNSC: Head and Neck squamous cell carcinoma; KICH: Kidney Chromophobe; KIPAN: Pan-kidney cohort (KICH+KIRC+KIRP); 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; MESO: Mesothelioma; OV: Ovarian serous cystadenocarcinoma; PAAD: Pancreatic adenocarcinoma; PCPG: Pheochromocytoma and Paraganglioma ; PRAD: Prostate adenocarcinoma; READ: Rectum adenocarcinoma; SARC: Sarcomav; SKCM: Skin Cutaneous Melanoma; STAD: Stomach adenocarcinoma; STES: Stomach and Esophageal carcinoma; TGCT: Testicular Germ Cell Tumors; THCA: Thyroid carcinoma; THYM: Thymoma; UCEC: Uterine Corpus Endometrial Carcinoma; UCS: Uterine Carcinosarcoma; UVM: Uveal Melanoma; VEGFA: vascular endothelial growth; LAG3: lymphocyte activating 3; PD-L1: programmed death ligand 1; HMGB2: high mobility group box 2; CXCL10: C-X-C motif chemokine ligand 10; CXCL9: C-X-C motif chemokine ligand 9; TNFSF4: tumor necrosis factor superfamily member 4; SELP: selectin P; CTL: cytotoxic T lymphocyte.

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