Cancer Management and Research

Elevate Series

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ORIGINAL RESEARCH

Pan-Cancer Analysis of BST2 Expression, Prognostic Significance, and Immune Correlations

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Objective: This study aimed to investigate the expression of the bone marrow stromal cell antigen 2 (BST2) gene in malignant tumors originating from various tissues and to explore its clinical significance.

Methods: We employed the TCGA database, R software, GeneMANIA database, and biological information analysis technologies to analyze the expression of the BST2 gene across various tumor tissues at different pathological stages and to assess its association with tumor prognosis, mutations, immune invasion, immune checkpoint-related genes, and associated pathways. Validation was performed using skin cutaneous melanoma cell lines, including M14, A375, B16-F10, and A2058.

Results: The expression of the BST2 gene varied across tumors of different origins, showing both increased and decreased levels. BST2 expression was closely associated with patient prognosis. In pan-kidney cohort, renal clear cell carcinoma, pancreatic cancer, and uterine sarcoma, its expression significantly differed across pathological stages. Additionally, in most tumors, BST2 expression correlated positively with immune infiltration and was linked to immune checkpoint-related genes. Validation of skin cutaneous melanoma cell lines displayed BST2 expression was significantly elevated in melanoma cell lines compared with the normal human melanocyte line.

Conclusion: This pan-cancer analysis highlights the correlation between BST2 expression and tumor type, prognosis, pathological stage, tumor mutations, and immune invasion. The findings suggest that BST2 may serve as an effective prognostic biomarker with potential applications in clinical diagnosis and treatment.

Keywords: bioinformation, BST2, database, immune infiltration, pan-cancer

Introduction

Bone marrow stromal cell antigen 2 (BST2) is a type II transmembrane protein encoded by the BST-2 gene (Gene ID: 684, located on chromosome 19p13.2) and is also known as Tetherin and CD317.[1] BST2 is widely expressed in bone marrow stromal cells as well as B cells, T cells, and natural killer (NK) cells.[2] Several studies have detected BST2 expression in additional immune cells and malignant cell types, such as those observed in B cells, chronic lymphoid leukemia, and breast cancer.[3–5] Emerging evidence further suggests that BST2 plays a role in the initiation and progression of various tumors, including colorectal, gastric, and ovarian cancers.[6–13] However, a comprehensive pan-cancer analysis of BST2 has not yet been performed. The present study investigates BST2 expression levels, prognostic significance, gene mutations, and immune invasion across different cancer types using data from The Cancer Genome Atlas (TCGA). The novelty of this study lies in its first comprehensive investigation of BST2 across multiple cancer types, aiming to advance the development of early detection, immunotherapy, and prognostic evaluation systems for cancers.

Materials and Methods

Gene Expression Analysis

The unified and standardized TCGA pan-cancer dataset was obtained from the UCSC database (https://xenabrowser.net/) from October 2024 to March 2025 to analyze BST2 expression in a variety of tumor and normal tissue samples,

Received: 28 August 2025
Accepted: 18 November 2025
Published: 5 December 2025

including adrenal cortical carcinoma (ACC), bladder urothelial carcinoma (BLCA), invasive breast carcinoma (BRCA), cervical squamous cell carcinoma and adenocarcinoma (CESC), cholangiocarcinoma (CHOL), colon adenocarcinoma (COAD), colorectal cancer (COADREAD), esophageal carcinoma (ESCA), glioblastoma multiforme (GBM), glioma (GBMLGG), head and neck squamous cell carcinoma (HNSC), chromophobe renal cell carcinoma (KICH), pan-kidney cohort [KICH+KIRC+KIRP] (KIPAN), clear cell renal carcinoma (KIRC), papillary renal cell carcinoma (KIRP), acute myeloid leukemia (LAML), low-grade glioma (LGG), hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), ovarian serous cystadenocarcinoma (OV), pancreatic adenocarcinoma (PAAD), pheochromocytoma and paraganglioma (PCPG), prostate adenocarcinoma (PRAD), rectal adenocarcinoma (READ), stomach adenocarcinoma (STAD), skin cutaneous melanoma (SKCM), stomach and esophageal carcinoma (STES), testicular germ cell tumors (TGCT), thyroid carcinoma (THCA), uterine corpus endometrial carcinoma (UCEC), uterine sarcoma (UCS), acute lymphoblastic leukemia (ALL), and Wilms tumor (WT). To standardize the data, each expression value was transformed using Log2(x + 0.001). Moreover, cancer subtypes with fewer than three samples were excluded from the analysis to ensure statistical robustness and reliability.

Pathologic Staging Analysis

Gene expression data for BST2 were extracted from the TCGA database. The analysis included samples derived from leukemia. etc. in the peripheral blood as well as from primary tumors. Expression values were normalized using the transformation Log2(x + 0.001). Differences in BST2 expression across various clinical stages for each tumor type were evaluated using R software (version 3.6.4). Statistical comparisons between two groups were conducted using an unpaired *t*-test, while analysis of variance (ANOVA) was employed to assess differences across multiple groups.

Survival Prognosis Analysis

High-quality prognostic datasets for multiple cancer types were obtained from TCGA, and additional follow-up data from TARGET were retrieved from UCSC. Samples with a follow-up duration of less than 30 days were excluded from the analysis. A Cox regression model was constructed using the coxph function from the R survival package (version 3.2.7) to assess the relationship between gene expression and tumor prognosis. The Log rank test was employed for statistical analysis.

Immune Infiltration and Checkpoint

BST2 expression data were retrieved from The Cancer Genome Atlas (TCGA), the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) program, and the Genotype-Tissue Expression (GTEx) database (PANCAN, N = 19,131; G = 60,499). Samples were further screened based on the following criteria: primary blood-derived cancers from peripheral blood (TCGA-LAML), primary blood-derived samples from bone marrow, and primary solid tumors. Expression values were normalized using a Log2(x + 0.001) transformation. Gene expression profiles for each tumor were extracted separately and subsequently mapped to GeneSymbol identifiers. The R package ESTIMATE (version 1.0.13; available at https://bioinformatics.mdanderson.org/publicsoftware/estimate/;DOI:10.1038/ncomms3612) was utilized to compute stromal, immune, and ESTIMATE scores for each patient across tumor types based on gene expression data. Additionally, we employed the TIMER method (TIMER: A web server for comprehensive analysis of tumor-infiltrating immune cells) from the R software package to re-evaluate the infiltration scores of B cells, CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and dendritic cells (DCs) for each patient in each tumor type.

Correlation Gene Enrichment Analysis

GeneMANIA (http://genemania.org/) is a widely recognized tool for predicting gene-to-gene interactions and inferring gene functions.[14,15] In this study, GeneMANIA was employed to correlate datasets and identify genes associated with BST2. Additionally, the "Similar Gene Detection" module in GEPIA2 was used to retrieve 100 BST2-related gene datasets from The Cancer Genome Atlas (TCGA) tumor and normal tissue databases. Subsequently, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis and Gene Ontology (GO) enrichment analysis were conducted, with a significance threshold of $p < 0.05$.[16]

Gene Mutation and Gene Heterogeneity Expression Analysis

BST2 expression data were obtained from the TCGA database, and the copy number variation dataset for all TCGA samples was processed using GISTIC software from the GDC (https://portal.gdc.cancer.gov/).[17] In addition, the level 4 Simple Nucleotide Variation dataset was downloaded from the GDC and processed for all TCGA samples using MuTect2 software, with subsequent analysis conducted using the R package maftools (version 2.8.5). The tumor mutation burden (TMB) was calculated for each tumor using the TMB function, and the resulting TMB values were integrated with the corresponding gene expression data.

Clinical Analysis and Gene Expression Analysis

We downloaded the uniformly standardized pan-cancer dataset from the UCSC database (https://xenabrowser.net/), specifically the TCGA Pan-Cancer (PANCAN, N = 10,535, G = 60,499) dataset. We then extracted the expression data corresponding to the ENSG00000130303 (BST2) gene from each sample, excluding those derived from Primary Blood Derived Cancer—Peripheral Blood—and Primary Tumor. A log2(x + 0.001) transformation was applied to each expression value.

Cell Culture Conditions

Skin cutaneous melanoma cell lines M14, A375, B16-F10, A2058, and the normal human melanocyte cell line HEMn were obtained from the Shanghai Institute of Cell Biology, Chinese Academy of Sciences. All cell lines were cultured in Dulbecco's Modified Eagle Medium supplemented with 10% serum and 1% penicillin/streptomycin and maintained in a humidified incubator at 37 °C with 5% CO2. The culture medium was replaced every two days, and phosphate-buffered saline was used to wash the cell surfaces during medium changes to remove residual secreted metabolites. When cells reached 80% to 90% confluence, they were treated with 0.25% trypsin for digestion and subsequent passaging. Cells from generation 3, which exhibited stable and robust growth, were collected for further experimental procedures.

Total RNA Extraction and qPCR

Total RNA was isolated from cells using TRIzol reagent. The extracted RNA was then reverse transcribed to synthesize complementary DNA (cDNA). Gene expression was quantitatively measured in real time using a qPCR kit on the Bio-Rad CFX96™ Real-Time PCR System, with glyceraldehyde 3-phosphate dehydrogenase (GAPDH) serving as the internal control for BST2. Reverse transcription was conducted at 42 °C for 15 minutes, followed by an incubation at 95 °C for 3 minutes. Real-time PCR was performed using the Talent qPCR PreMix with an initial cycle at 95 °C for 3 minutes, succeeded by 40 cycles of 95 °C for 5 seconds and 60 °C for 15 seconds. All reactions were carried out in triplicate, and the data were analyzed using the 2^(-ΔΔCt) method.

Statistical Processing

Statistical analyses were conducted using SPSS version 22.0. Data are expressed as the mean ± standard deviation (x ± s). Comparisons between groups were performed using an independent-samples *t*-test, with a p-value of less than 0.05 considered indicative of statistical significance.

Results

Analysis of BST2 Expression Levels in Different Tumors

The BST2 expression levels in various tumors and normal tissues were analyzed using data from The Cancer Genome Atlas (TCGA) database. Expression data from 34 cancers were included. BST2 expression was significantly upregulated in 22 tumor types—including ACC, BLCA, BRCA, CESC, ESCA, GBM, GBMLGG, HNSC, KIPAN, KIRC, LAML, LGG, LIHC, LUAD, PAAD, STAD, SKCM, STES, TGCT, UCEC, ALL, and WT tumors—compared with normal tissues. In contrast, BST2 expression was significantly downregulated in several tumor types, including KICH, KIRP, LUSC, OV, PCPG, PRAD, READ, and THCA (Figure 1A).

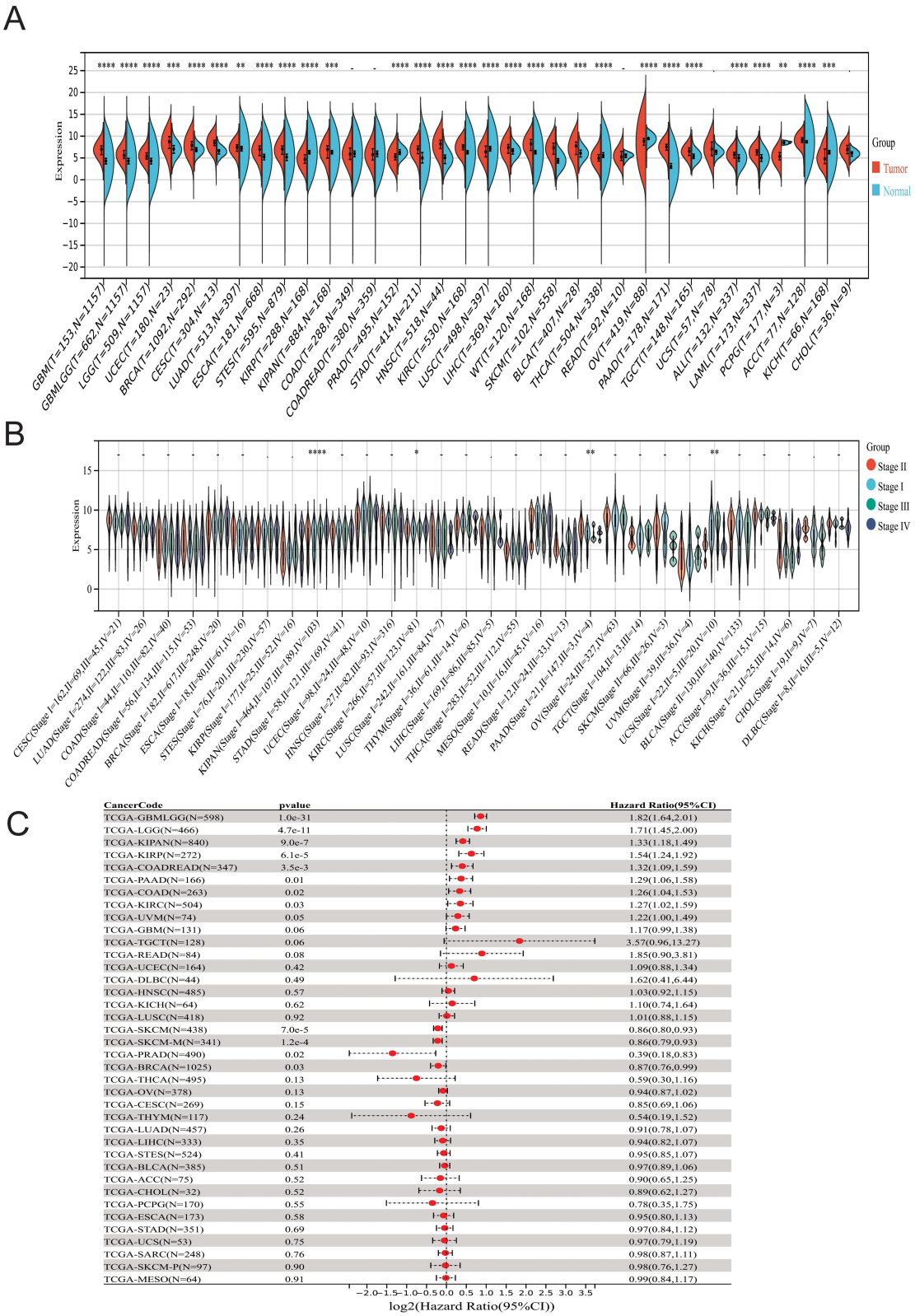

Figure 1 (**A**) Expression levels of BST2 in various tumors and corresponding normal tissues. (**B**) BST2 expression across different cancer stages. (**C**) Correlation between BST2 expression and gene expression prognosis in various tumors. (ns, ($p \geq 0.05$), *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$).

Analysis of BST2 Expression Levels in Different Cancer Stages

BST2 expression levels were analyzed across 30 tumor types at different cancer stages using the TCGA database. Statistically significant associations between BST2 expression and cancer stage were observed in KIPAN (p = 9.3e-7), KIRC (p = 0.04), PAAD (p = 4.7e-3), and UCS (p = 7.5e-3) (Figure 1B).

BST2 is a Prognostic Marker for Many Cancers

The association between BST2 expression and patient prognosis was evaluated using The Cancer Genome Atlas (TCGA) database. Tumors were categorized into high and low BST2 expression groups based on a threshold value of 50, and their correlations with clinical outcomes were subsequently examined. Cancer types with fewer than 10 samples were excluded, resulting in a total of 38 tumor types included in the analysis. Elevated BST2 expression was significantly associated with poorer prognosis in nine tumor types: PAAD, UVM, COADREAD, COAD, KIRP, KIPAN, GBMLGG, LGG, and KIRC. Conversely, diminished BST2 expression was linked to adverse outcomes in four tumor types: BRCA, PRAD, SKCM-M, and SKCM (Figure 1C). These results suggest that the prognostic implications of BST2 expression vary according to tumor type.

Immune Infiltration Analysis

Immune cells are critically involved in the tumor microenvironment and are closely linked to both the initiation and progression of tumors. These cells, which include various subtypes such as B cells and T cells, perform distinct functions in tumorigenesis. Moreover, the composition of tumor-associated immune cells differs among tumor types. In this study, immune invasion scores were computed for 10,180 tumor samples spanning 44 tumor types. We observed that BST2 expression was significantly positively correlated with immune invasion in 34 cancer types, including GBM, GBMLGG, LGG, BRCA, LUAD, ESCA, STES, SARC, KIRP, KIPAN, COAD, COADREAD, PRAD, STAD, HNSC, KIRC, LUSC, THYM, LIHC, SKCM, BLCA, SKCM-M, SKCM-P, THCA, NB, READ, UVM, MESO, ALL, PAAD, TGCT, LAML, DLBC, and PCPG (Figure 2A).

Subsequently, we determined the infiltration scores for six types of immune cells in 9,406 tumor samples across 38 cancer types. Using the R software package, we calculated the Pearson correlation coefficient between gene expression and immune cell infiltration scores for each tumor type to identify significant correlations. Significant associations between gene expression and immune infiltration were observed in 35 cancer types, including BLCA, BRCA, CESC, COAD, COADREAD, DLBC, ESCA, GBM, GBMLGG, HNSC, KIPAN, KIRC, KIRP, LGG, LIHC, LUAD, LUSC, MESO, OV, PAAD, PCPG, PRAD, READ, SARC, SKCM-M, SKCM-P, SKCM, STAD, STES, TGCT, THCA, THYM, UCEC, UCS, and UVM (Figure 2B).

Relationship Between BST2 Expression and Immune Checkpoint-Related Genes

Immune checkpoints are key regulators of signaling pathways that modulate immune responses while preserving self-tolerance. Previous studies have demonstrated that genes related to immune checkpoint regulation play a significant role in mediating tumor immune evasion. In this study, the correlation between BST2 expression and these genes was examined, revealing that BST2 is significantly associated with immune-related genes in most tumor types (Figure 3).

Enrichment Analysis of Relevant Genes

To elucidate the molecular mechanisms by which BST2 contributes to tumorigenesis and progression, the GENEMANIA database was employed to identify potential interactions (Figure 4A). Concurrently, the Gene Expression Profiling Interactive Analysis (GEPIA2) database was used to retrieve the top 100 genes correlated with BST2 expression by integrating expression data from all tumors in TCGA. These genes were then subjected to KEGG and GO enrichment analyses. The KEGG analysis revealed that a substantial number of these genes are involved in pathways related to Epstein–Barr virus infection, antigen processing and presentation, and hepatitis C (Figure 4B). Additionally, the GO enrichment analysis indicated that these genes play pivotal roles across various biological processes, cellular components, and molecular functions, including responses to biological stimuli, components of endopeptidase complexes, and double-stranded RNA binding (Figure 4C).

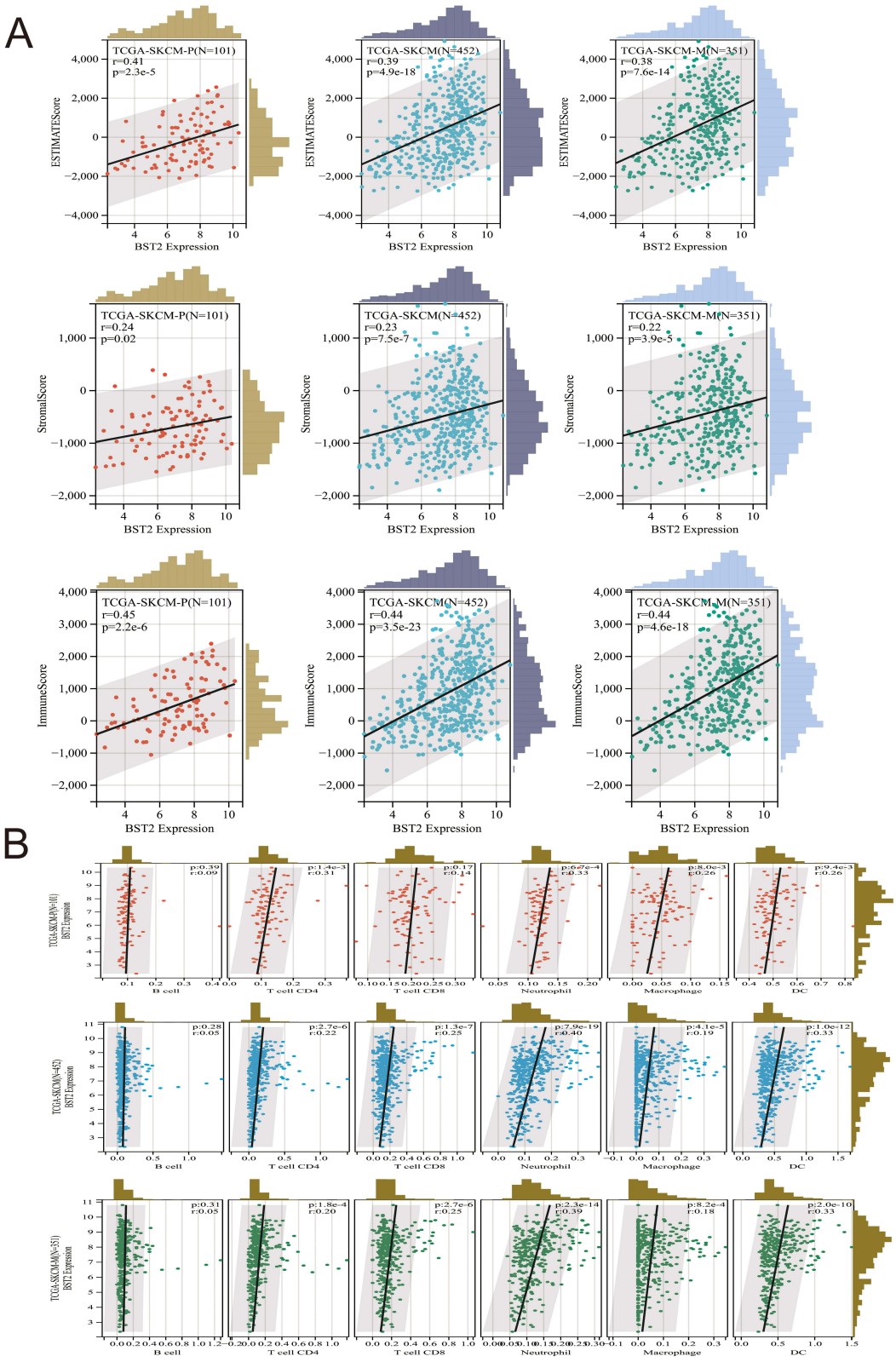

Figure 2 (**A**) Correlation between BST2 expression and immune infiltration in various tumors. (**B**) Correlation between BST2 expression and immune cells in various tumors. (only SKCM-P, SKCM, and SKCM-M are displayed).

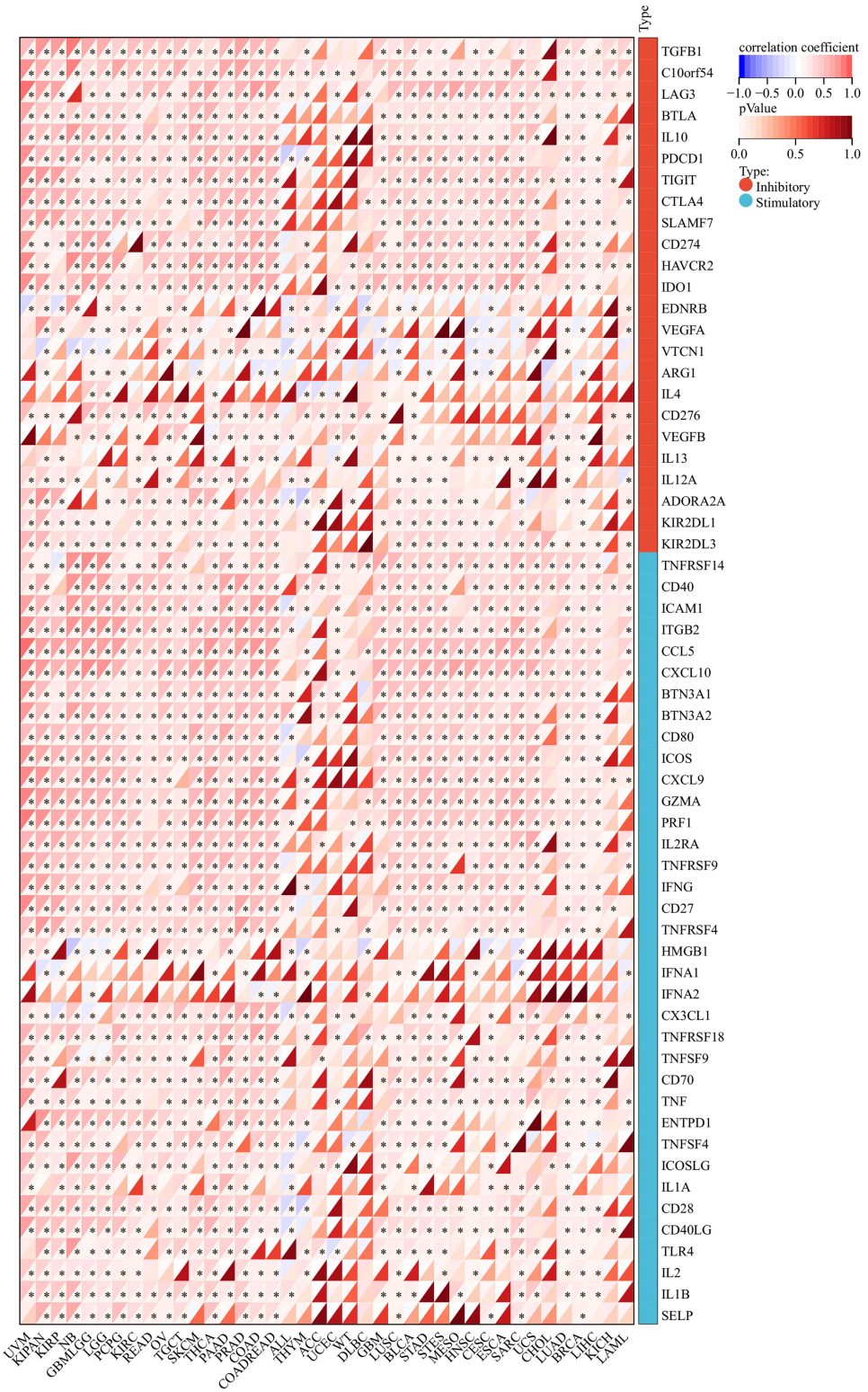

Figure 3 Correlation between BST2 and immune checkpoint-related genes across different tumors. (ns, (p ≥ 0.05), *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001).

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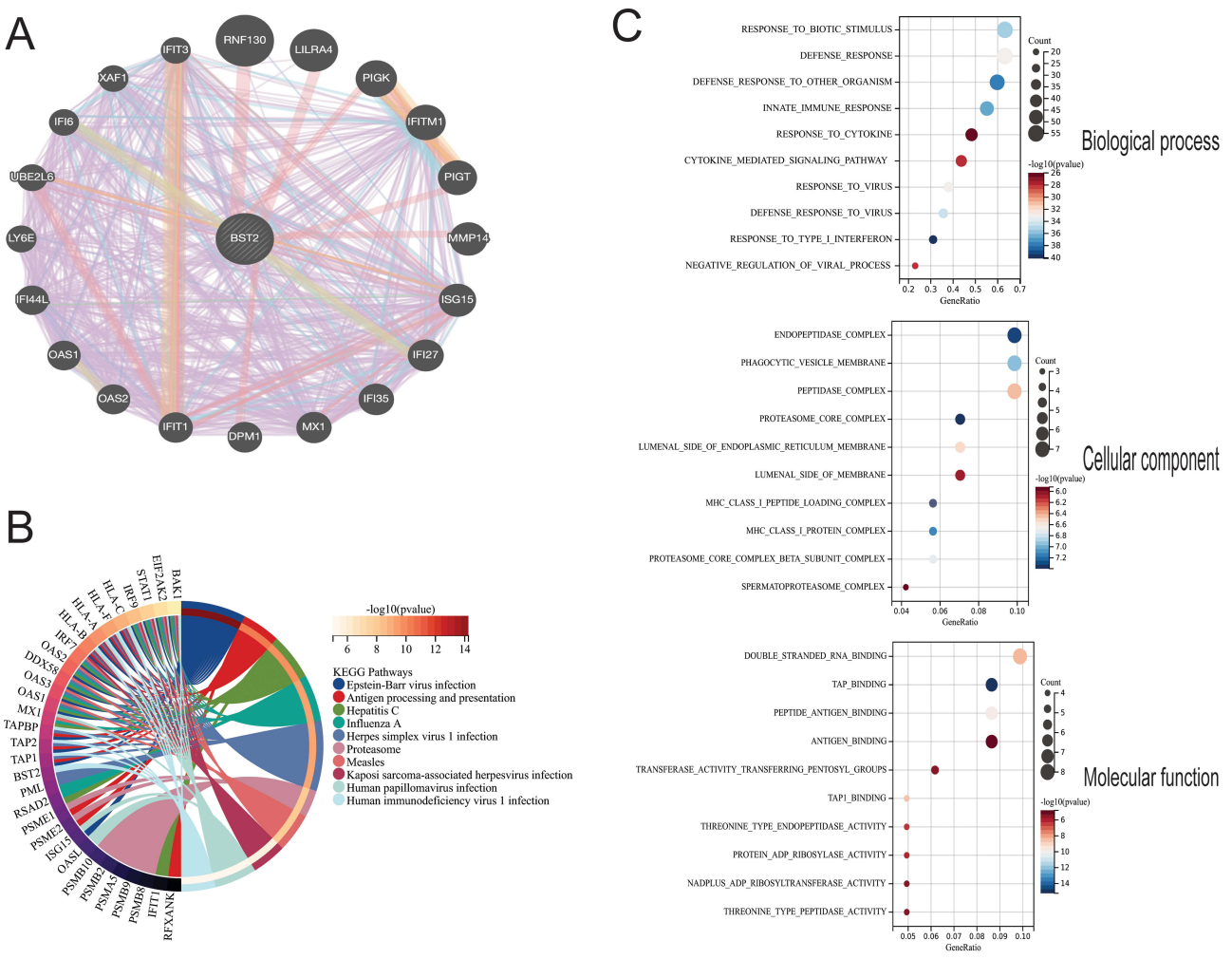

Figure 4 (**A**) Potential gene interactions of BST2. (**B**) KEGG enrichment analysis. (**C**) GO enrichment analysis.

Gene Mutation and Gene Heterogeneity Expression Analysis

R (version 3.6.4) was employed to evaluate differences in gene expression across clinical stages in various tumors. The unpaired Wilcoxon rank sum and signed rank tests were applied to compare two groups of data, while the Kruskal algorithm was utilized for analyses involving multiple groups. Significant differences were identified in six tumors: BRCA, UCEC, HNSC, LUSC, LIHC, and OV (see Figure 5A). Additionally, Pearson's correlation coefficients were computed for each tumor, revealing significant correlations in ten tumor types. Notably, six tumors—COAD, COADREAD, STES, STAD, LUSC, and READ—exhibited significant positive correlations, whereas four tumors—CESC, PCPG, LUAD, and KIRP—displayed significant negative correlations (see Figure 5B).

Clinical Analysis and Gene Expression Analysis

We utilized R software (version 3.6.4) to evaluate differences in gene expression across various clinical stages for each tumor type, including variables such as T, N, M, stage, grade, gender, and age. Statistical significance between two groups was determined using an unpaired Student's *t*-test, whereas analysis of variance (ANOVA) was employed to assess differences among multiple groups. The results are presented in Figure 6.

Validation of Skin Cutaneous Melanoma Cell Lines

BST2 expression was significantly elevated in melanoma cell lines (M14, A375, B16-F10, and A2058) compared with the normal human melanocyte line HEMn ($p < 0.05$) (Figure 7).

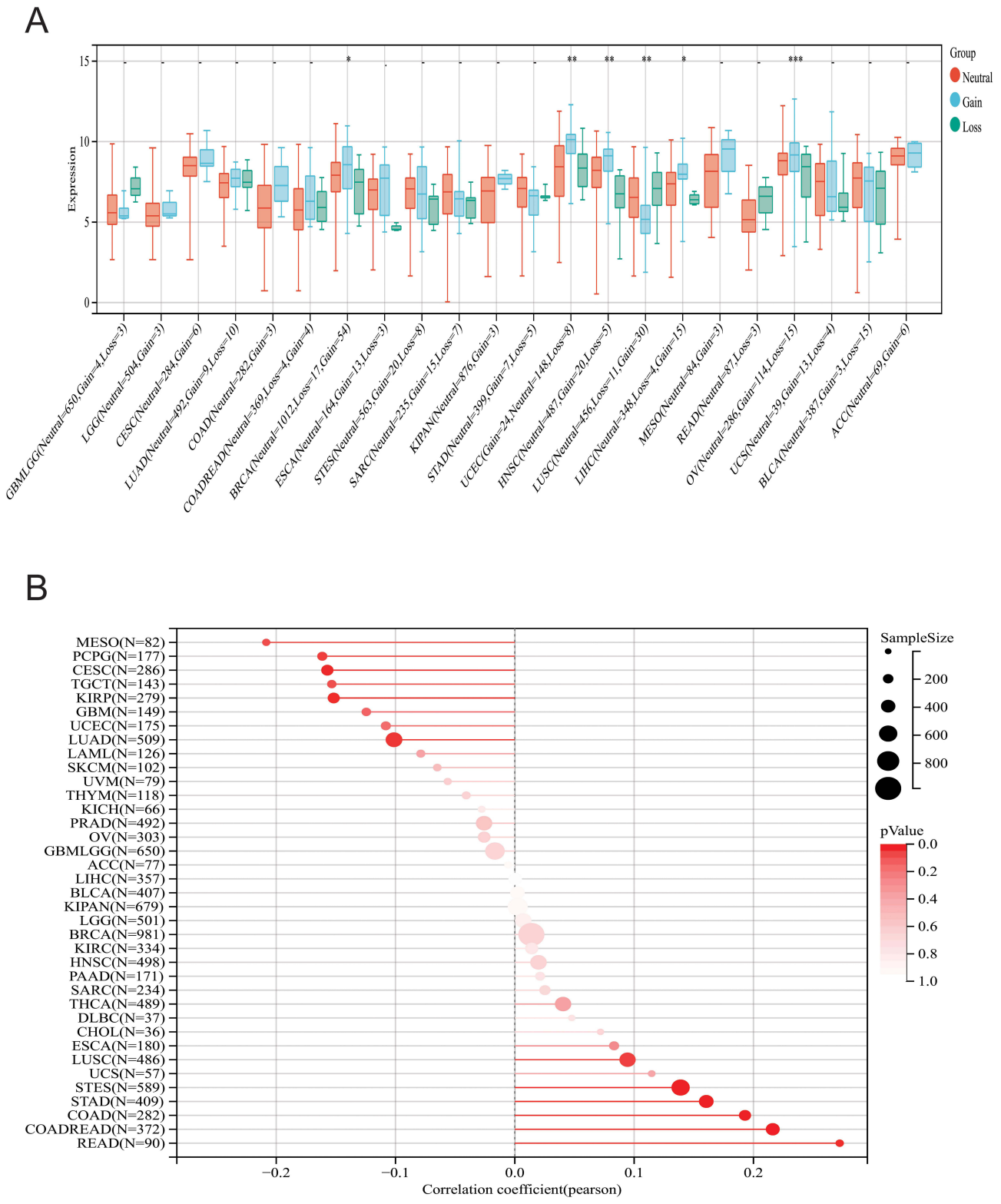

Figure 5 (**A**) Analysis of BST2 gene mutation and expression across different tumors. (**B**) Analysis of BST2 genomic heterogeneity and expression in different tumors. (ns, ($p \geq 0.05$), *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

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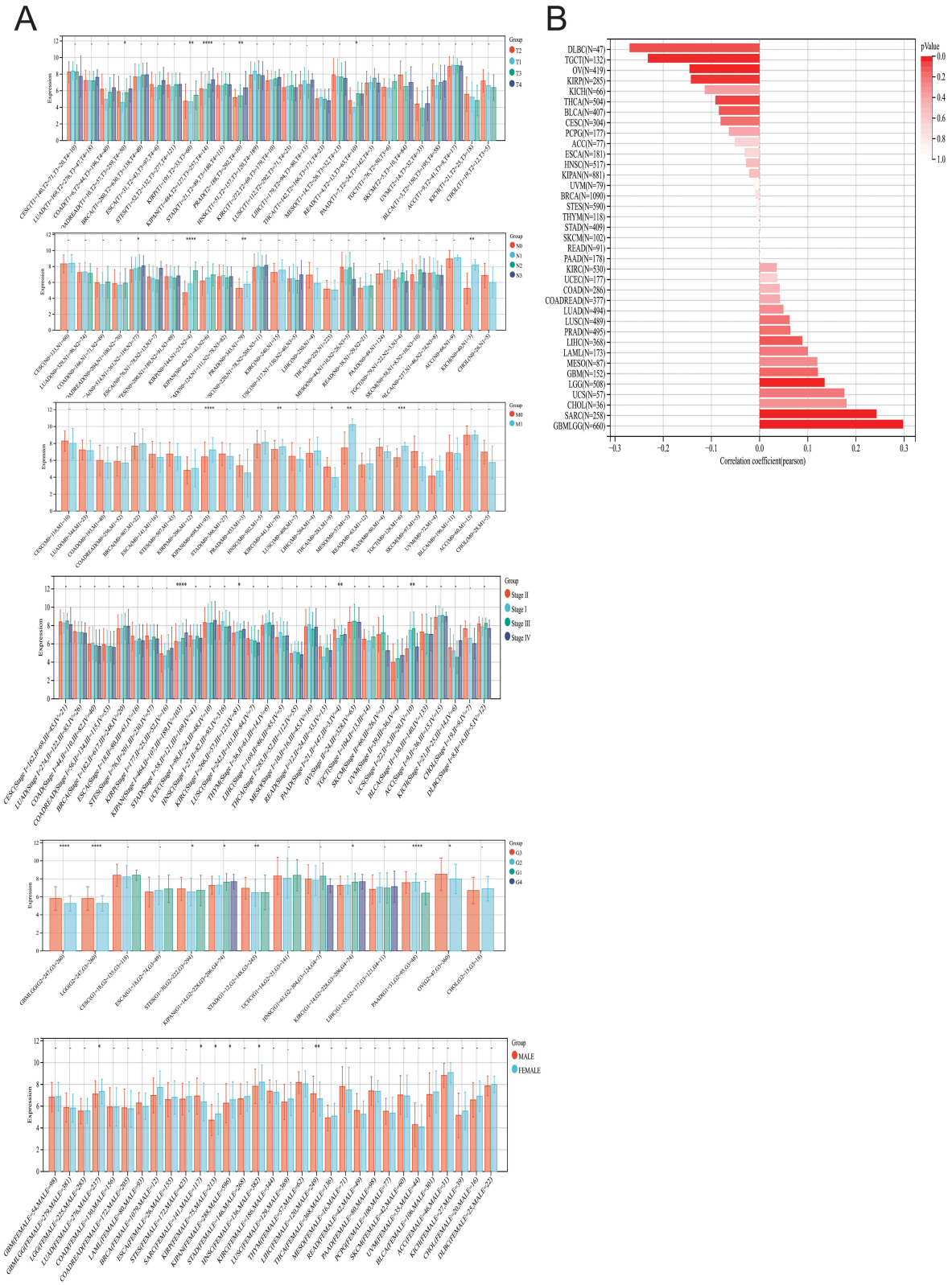

Figure 6 (**A** and **B**) Differential expression of genes across various clinical stages, including T, N, M, Stage, Grade, Gender, and Age. (ns, ($p \geq 0.05$), *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$).

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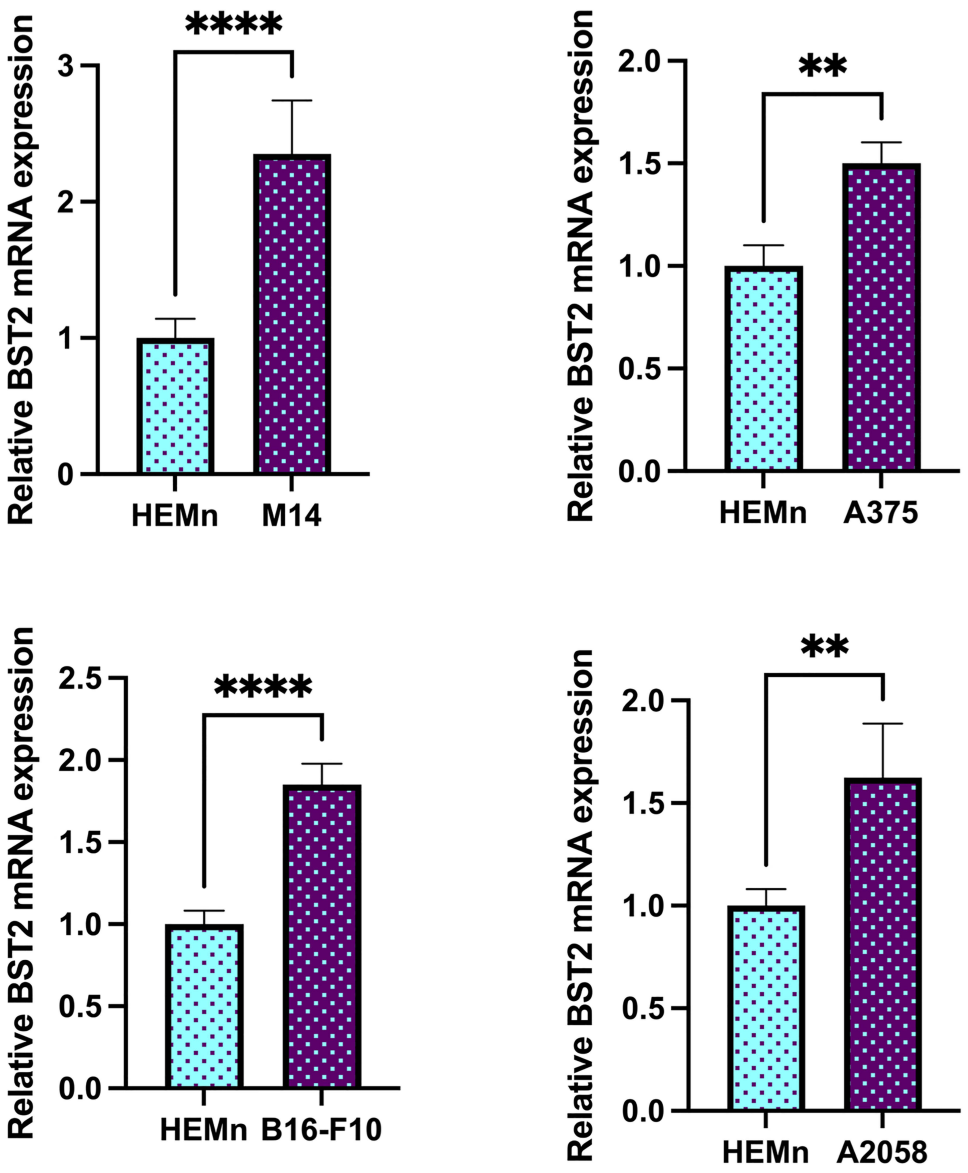

Figure 7 Relative expression of BST2 in M14, A375, B16-F10, and A2058 compared to normal human melanocyte HEMn ($p < 0.05$). (ns, ($p \geq 0.05$), **$p < 0.01$, ****$p < 0.0001$).

Discussion

Tumor immunotherapy is currently a focal area of oncological research; its core mechanism consists in potentiating the immune system's ability to recognize and eliminate malignant cells, thereby substantially improving clinical outcomes.[18,19] Accumulating evidence has revealed that the expression levels of immune-related genes are closely linked to the efficacy of immunotherapy across multiple cancers and have thus emerged as predictive biomarkers of therapeutic response.[20] BST2 (also termed CD317) is an interferon-inducible, 30–36 kDa type-II single-pass transmembrane protein that belongs to the immune-related gene repertoire.[21] Functional studies have demonstrated that BST2 actively participates in, and even propels, tumor initiation and progression; during cervical carcinogenesis it promotes neoplastic cell growth, suppresses apoptosis, and skews macrophages toward the pro-tumor M1 phenotype.[22] In gastric cancer, BST2 exerts oncogenic effects by modulating proliferation, apoptosis, and migration,[11,12] and it has further been identified as a direct target of miR-760, whose down-regulation correlates with accelerated tumor progression.[11]

To date, no study has comprehensively analyzed the role of BST2 across multiple cancer types. In this research, we leveraged TCGA, GENEMANIA, and additional databases to examine BST2 expression levels, mutation frequencies,

immune checkpoint correlations, prognoses, and potential related genes in various cancers. Our findings indicate that BST2 is highly expressed in most tumors, with previous studies confirming its tumor-promoting role in breast, gastrointestinal, lung, and nasopharyngeal cancers.

Survival prognosis analyses revealed variable outcomes related to BST2 expression. Specifically, high BST2 expression was associated with poor prognosis in PAAD, UVM, COADREAD, COAD, KIRP, KIPAN, GBMLGG, LGG, and KIRC, whereas low BST2 expression correlated with poor prognosis in BRCA, PRAD, SKCM, and SKCM-M. These differential effects underscore the need for further in-depth molecular studies to confirm these findings.

The tumor microenvironment plays a crucial role in the incidence and progression of cancers,[23–25] and tumor-infiltrating immune cells are closely linked to immune checkpoints and patient prognosis.[26–29] In our study, BST2 expression showed a positive correlation with immune invasion scores across 34 tumor types and was significantly associated with immune checkpoint-related genes. However, given that different tumor types exert distinct influences on immune cells within the tumor microenvironment, it is essential to consider additional clinical features. These findings not only offer new perspectives for tumor immunotherapy but also reinforce the prognostic significance of BST2 expression in cancer patients. In this study, BST2 exhibited significant, tumor-type–specific correlations with both immune-checkpoint genes and the abundance of infiltrating immune cells. These findings indicate that BST2 may serve as an important immunotherapeutic target and underscore the need for further investigation of its functional role within the tumor immune microenvironment and its prognostic utility across cancers.

Furthermore, this study explores genes potentially associated with BST2, providing valuable evidence for future molecular investigations. Previous research has elucidated the molecular mechanism by which the TGF-beta pathway regulates BST2, demonstrated that the methylated form of BST2 significantly influences tumor progression, and clarified the impact of the dimerized form of BST2 on tumor survival.[30] Experimental validation using four melanoma cell lines confirmed the bioinformatics analysis, suggesting that BST2 is involved in a complex network of regulatory processes. Further research is warranted to uncover additional molecular mechanisms.

Conclusions

In summary, through integrative analysis of TCGA and GeneMANIA databases, we systematically evaluated the associations of BST2 with tumor prognosis, mutational profiles, immune infiltration, immune checkpoint-related genes, and relevant signaling pathways across multiple cancer types. Our findings underscore the potential clinical translational value of BST2 as a prognostic biomarker and therapeutic target. While this study provides a comprehensive pan-cancer landscape of BST2, further experimental investigations are warranted to elucidate its specific biological functions and underlying molecular mechanisms. In-depth exploration of BST2 may facilitate the development of innovative strategies for early cancer detection, immunotherapy, and prognostic assessment.

Abbreviations

BST2, Stromal cell antigen 2; KIRC, renal clear cell carcinoma; PAAD, pancreatic cancer; UCS, uterine sarcoma; ACC, adrenal cortical carcinoma; BLCA, bladder urinary tract carcinoma; BRCA, invasive breast carcinoma; CESC, cervical squamous cell carcinoma and adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon cancer; COADREAD, colorectal cancer; ESCA, oesophageal carcinoma; GBM, polyformal glioblastoma; GBMLGG, glioma; HNSC, head and neck squamous cell carcinoma; KICH, renal chromophobia carcinoma; KIPAN, pan-kidney cohort [KICH+KIRC +KIRP]; KIRC, renal clear cell carcinoma; KIRP, renal papillary cell carcinoma; LAML, acute myeloid leukaemia; LGG, low-grade brain glioma; LIHC, hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, squamous cell carcinoma of the lungs; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic cancer; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate cancer; READ, rectal adenocarcinoma; STAD, gastric cancer; SKCM, melanoma; STES, stomach and oesophageal cancer; TGCT, testicular cancer; THCA, thyroid adenocarcinoma; UCEC, endometrial cancer; UCS, uterine sarcoma; ALL, leukaemia; WT, Wilms tumour.

Data Sharing Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Ethics Approval

This study utilized exclusively de-identified, publicly available data from The Cancer Genome Atlas (TCGA) and other cited databases. In accordance with the "Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects", the use of such pre-existing, anonymized data is exempt from ethical approval by an Institutional Review Board (IRB). The original data sources obtained necessary ethical approvals and patient consent.

Acknowledgments

We are particularly grateful to all the people who have given us help on our article.

Funding

No external funding received to conduct this study.

Disclosure

The authors declare no conflict of interest.

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