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Abnormal Expression of WSB1 in Lung Adenocarcinoma: A Potential Prognostic and Immunotherapeutic Sensitivity Biomarker

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Abstract

This study aimed to conduct a pan-cancer analysis of WD40 Repeat-Containing SOCS Box Protein 1 (WSB1) through bioinformatics, detect its expression in lung adenocarcinoma (LUAD) tissues and adjacent normal tissues by immunohistochemistry (IHC), analyze its correlation with clinical indicators, and explore its diagnostic and prognostic value. We performed WSB1 bioinformatics analysis using data from multiple public databases (including TCGA, GTEx, HPA, CPTAC, etc.). IHC was used to detect the expression difference of WSB1 in LUAD tissues and adjacent normal tissues, followed by statistical processing and clinicopathological data analysis. Kaplan-Meier plotter was used to analyze the relationship between WSB1 expression and survival, and GO and KEGG pathway enrichment analyses were conducted to explore its functions. WSB1 was differentially expressed between various cancers and normal tissues. Specifically, WSB1 mRNA levels were downregulated in LUAD, while protein levels were significantly upregulated ($P < 0.05$). WSB1 expression was negatively correlated with LUAD distant metastasis ($P < 0.05$) and promoter methylation, and positively correlated with overall survival (OS), tumor immunity, and PDCD1. The genetic variation frequency of WSB1 was >4% (3.18% in LUAD), and there was no correlation with gender, age, etc. IHC validation (80 LUAD samples and 80 adjacent normal tissues) confirmed that WSB1 expression in LUAD tissues was significantly higher than that in

adjacent normal tissues. WSB1 is upregulated at the protein level in LUAD and serves as a potential prognostic marker. It correlates with tumor immunity/PDCD1 (as a marker of immunotherapy sensitivity) and promoter methylation (through epigenetic regulation), and its abnormal expression may be caused by high-frequency mutations.

Keywords: Lung Adenocarcinoma; WSB1; Pan-Cancer Analysis; Immunohistochemistry

1. Introduction

Cancer is a major public health issue. Over three - quarters of the 20.4 million premature deaths (aged 30 - 70) are from non - communicable diseases, with 3/10 of these deaths caused by cancer (Bray et al., 2021). China's 2022 National Cancer Report shows a rising incidence and mortality of malignant tumors, along with a 40.5% 5-year survival rate (Zheng et al., 2024). IARC's GLOBOCAN 2022 (2024) recorded 20 million new cancer cases and 10 million deaths in 2022 (Cao et al., 2024), with lung cancer the most common (2.5 million cases, 12.4%) and leading cause of cancer death (1.8 million, 18.7%) (Cao et al., 2024). Lung cancer incidence is highest in East Asian men and a top cancer death cause in women in 23 countries (Siegel et al., 2024); it is divided into small cell (15%) and non-small cell (85%) subtypes (Megyesfalvi et al., 2023).

Lung adenocarcinoma (LUAD), a non-small cell subtype (40% of lung cancer cases (Cao et al., 2020)), originates from small airway epithelial and type II alveolar cells (Alamri et al., 2024). Its incidence rises in smokers and non-smokers, with a low 5-year survival rate (5%-20%) (Zhang et al., 2024), despite advances in PD-L1 immunotherapy (Fehrenbacher et al., 2016) and targeted therapies for specific gene mutations (Blumenschein et al., 2015). Personalized LUAD treatment follows 2025 NCCN Guidelines, with current research focusing on novel targeted drugs, antibody-drug conjugates, and immune microenvironment optimization (Chinese Society of Oncology, 2024).

WSB1, an E3 ubiquitin ligase with N-terminal WD40 repeats and C-terminal SOCS box, enables specific substrate degradation (Fong et al., 1986). WD repeats were first identified in bovine transducin β (Fong et al., 1986); WSB1 has 6 (Wang et al., 2015), 7 (Dentice et al., 2005), and 8 (Vasiliauskas et al., 1999) WD40 repeats (Villamil et al., 2013). Its SOCS box interacts with E3 ligase complex members (e.g., elongin B/C, VHL tumor suppressor protein) (Bullock et al., 2006); high-resolution structural information, which may clarify its functional diversity, remains undetermined (Haque et al., 2016).

This study used TCGA, HPA, TIMER, cBioPortal, and Sangerbox 3.0 to evaluate WSB1's expression, prognosis, mutation, function, and correlation with tumor immune infiltration. Kaplan-Meier plotter analyzed WSB1 expression and survival; GO and KEGG pathway enrichment analyses explored its functions. Gene chip and immunohistochemical staining detected WSB1 in LUAD/normal tissues, with statistical analysis to verify differences and clinicopathological correlations, assessing its feasibility as a LUAD prognostic predictor.

2. Materials and Methods

2.1. Bioinformatics Analysis

2.1.1. GEPIA2 Database

Developed by the team of Professor Zhang Zemin from Peking University, GEPIA2 integrates data from The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx), offering multiple analytical functions. As a convenient online tool for cancer research (Li et al., 2021), it was utilized for the enrichment analysis of WSB1.

2.1.2. HPA Database (https://www.proteinatlas.org)

This database focuses on gene expression at both mRNA and protein levels in human tissues, with data obtained from 44 normal tissues and Swedish cancer tissues (anonymized in accordance with ethical approval). It was used to analyze the protein expression of WSB1 in cancer and adjacent normal tissues.

2.1.3. Kaplan-Meier Plotter (http://kmplot.com/analysis/)

This platform integrates data from GEO, EGA, and TCGA, covering more than 35,000 samples across 21 tumor types. It enables Kaplan-Meier survival analysis and log-rank tests (with $P<0.05$ indicating statistical significance) for verifying prognostic biomarkers.

2.1.4. cBioPortal (http://www.cbioportal.org/)

Integrating multi-omics data, this database supports the systematic analysis of gene mutation frequencies and molecular characteristics. It was employed to analyze the genetic variation characteristics of WSB1 in pan-cancer.

2.1.5. UALCAN Database

As an interactive database based on TCGA for cancer omics analysis (Wang et al., 2015), it was used to identify gene expression patterns, tumor staging, and the impact of genes on patient survival in specific cancers.

2.1.6. Clinical Proteomic Tumor Analysis Consortium (CPTAC) Database

This database focuses on large-scale proteomic analysis of cancer tissues and integrates multi-omics data to reveal the molecular mechanisms of cancer development, thereby supporting the discovery of cancer biomarkers and therapeutic targets.

2.1.7. Xiantao Academic (https://www.xiantao.love/):

Comprising 5 modules, this platform features core bioinformatics tools that facilitate statistical analysis and data visualization for various diseases.

2.1.8. Sangerbox 3.0

Developed by the team of Professor Song Xiang, this platform integrates over 100 analytical methods and databases (including GEO and TCGA), supporting data processing, analysis, and interactive visualization.

2.2. Construction of Clinical Information Database

Lung adenocarcinoma tissue microarrays (160 samples: 80 LUAD, 80 adjacent tissues) were provided by Shanghai Xiabukang Biotechnology Co., Ltd. Experimental data included all antibody-derived results from immunohistochemical experiments. Eighty LUAD patients were grouped by age, gender, tumor size, invasion depth, lymph node/distant metastasis, and IASLC 8th edition staging criteria, providing a basis for analyzing WSB1's differential expression and clinical significance.

2.3. Statistical Analysis

Statistical analyses were conducted using GraphPad Prism 8.2.1, and group comparisons were performed via Student's t-test. A P value < 0.05 was considered statistically significant.

3. Results

3.1. Expression of WSB1 Across Human Cancers

To investigate the differential expression of WSB1 between tumor and normal tissues, we performed a pan-cancer paired analysis using the Xiantao Academic platform, comparing WSB1 expression in 33 cancer types and their adjacent normal tissues. WSB1 was found to be significantly upregulated in five cancer types, including cholangiocarcinoma (CHOL), head and neck squamous cell carcinoma (HNSC), kidney renal clear cell carcinoma (KIRC), liver hepatocellular carcinoma (LIHC), and thyroid carcinoma (THCA). In contrast, WSB1 was downregulated in breast invasive carcinoma (BRCA), kidney chromophobe carcinoma (KICH), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and uterine corpus endometrial carcinoma (UCEC) (Figure 1A). When normal tissue samples from TCGA combined with GTEx were used as the reference control, WSB1 was confirmed to be downregulated in BRCA, KICH, LUAD, and LUSC, and upregulated in CHOL (Figure 1B).

According to data from the CPTAC database, WSB1 protein expression was increased in LUAD and BRCA (Figure 1C). Immunohistochemistry images from the HPA database showed no specific staining of WSB1 in normal lung or breast tissues, whereas moderate staining was observed in LUAD and BRCA tumor tissues (Figure 1D).

These results revealed a decoupling between WSB1 mRNA and protein expression in LUAD and BRCA: (1) WSB1 mRNA levels were significantly decreased in tumor tissues compared with normal tissues ($P<0.05$); (2) in contrast, proteomic data showed that WSB1 protein levels were abnormally elevated in tumor samples ($P<0.05$).

Notably, WSB1 exhibits significant mRNA-protein expression decoupling in LUAD: mRNA levels are downregulated, while protein levels are abnormally elevated. This contradictory pattern may stem from tissue-specific epigenetic regulation and post-translational modifications.

Epigenetic regulation such as promoter methylation may inhibit WSB1 transcription, reducing mRNA levels—though region-specific methylation or histone acetylation could also be involved, despite lower overall promoter methylation in LUAD tissues than adjacent normal tissues.

Post-translational modifications may stabilize WSB1 protein to prevent degradation and promote accumulation. As an E3 ubiquitin ligase in the ubiquitin-proteasome system (UPS), WSB1's stability may be regulated by UPS components like deubiquitinases, which can remove ubiquitin chains to reduce proteasomal degradation. Additionally, translational regulation via microRNAs or long non-coding RNAs may contribute to the mRNA-protein inconsistency. Collectively, these bioinformatic analyses indicate a significant divergence between WSB1 mRNA and protein expression patterns during tumorigenesis.

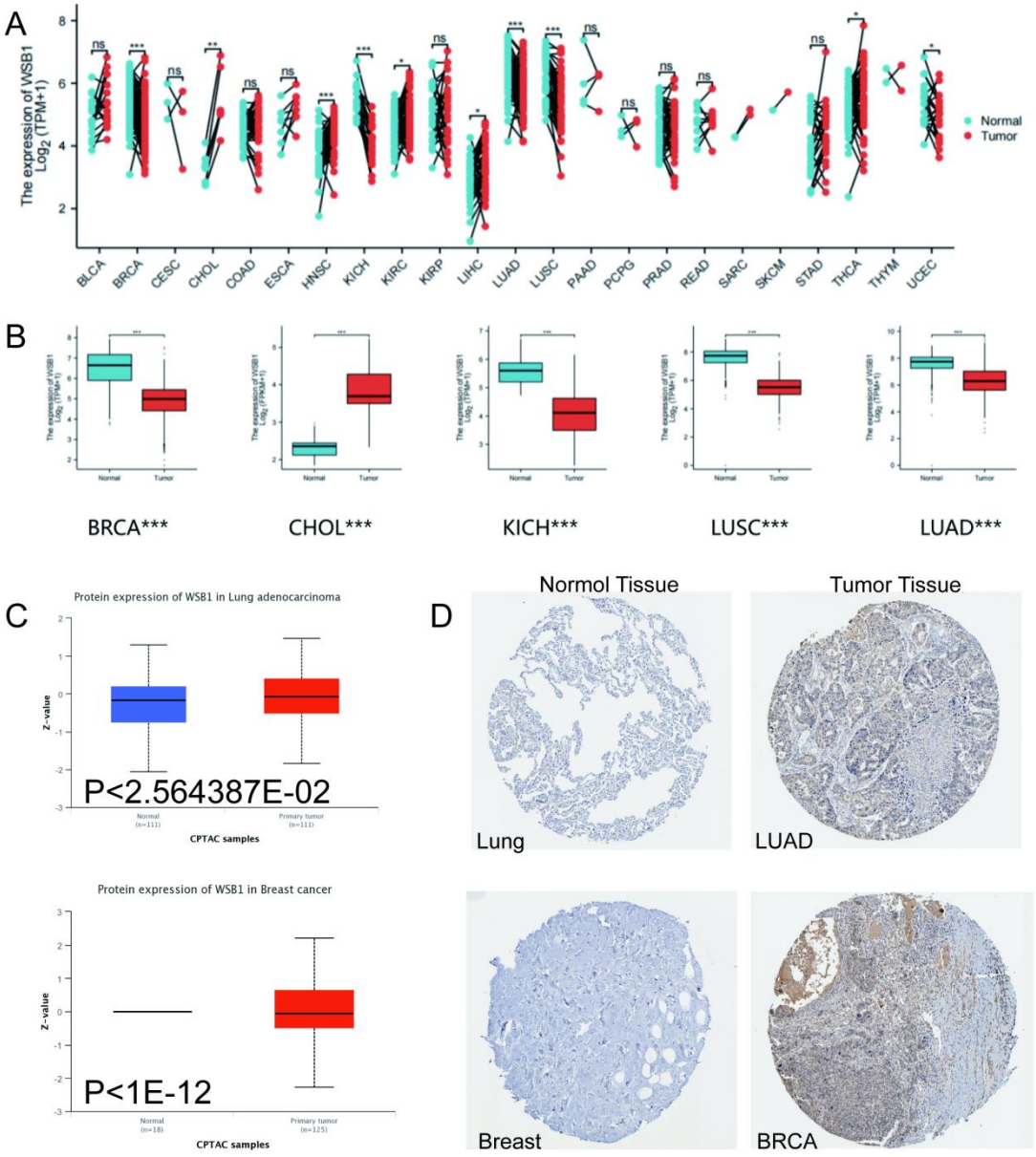

Figure 1. Expression levels of WSB1 in normal and tumor tissues

Notes: (A) Expression differences of WSB1 between various tumor tissues and their adjacent normal tissues. (B) Expression differences of WSB1 in cancer tissues and normal tissues in unpaired samples. (C) Analysis of WSB1 protein expression differences between normal and tumor tissues based on the CPTAC database. (D) Analysis of WSB1 protein expression differences between normal and tumor tissues based on the HPA database. *P < 0.05, **P < 0.01, ***P < 0.001.

3.2. Prognostic Potential of WSB1 in Human Cancers

Pan-cancer survival analysis using the Kaplan-Meier Plotter database revealed that the expression level of WSB1 was associated with the overall survival (OS) of cancer patients in a tissue-specific manner. High WSB1 expression significantly shortened OS in patients with KIRC, LIHC, and BRCA ($P < 0.001$). In contrast, WSB1 expression was significantly positively correlated with OS in patients with pheochromocytoma and paraganglioma (PCPG), thymoma (THYM), and LUAD ($P < 0.05$), suggesting that WSB1 may bidirectionally regulate tumor progression through tissue-specific molecular mechanisms (Figure 2A).

Receiver operating characteristic (ROC) curve analysis showed that the area under the curve (AUC) of WSB1 was consistently above the clinically relevant threshold of 0.7 in LUAD, KIRC, KICH, BRCA, OV, and THYM, indicating that WSB1 may serve as a novel pan-cancer diagnostic biomarker with potential for translational applications (Figure 2B).

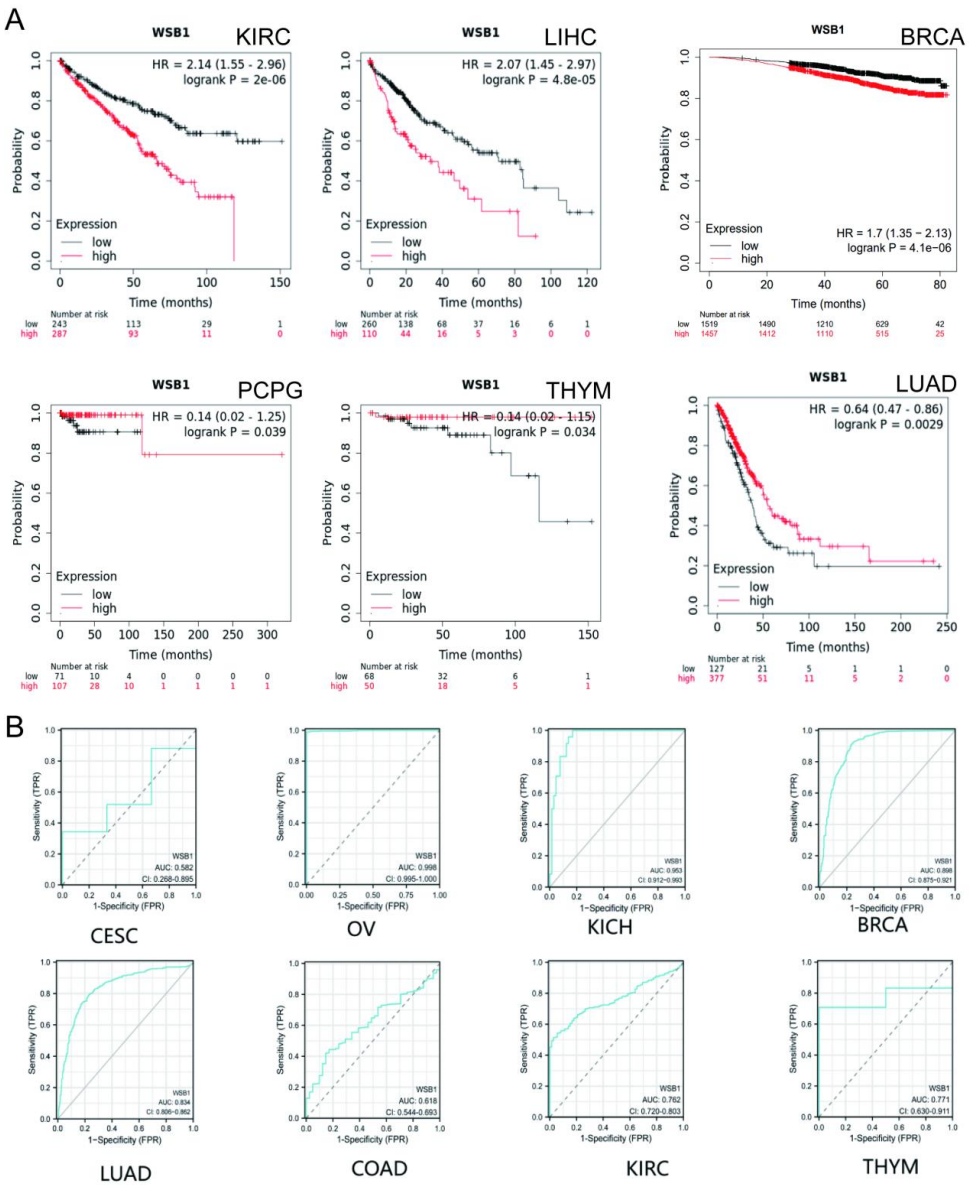

Figure 2. Prognostic potential of WSB1 in human cancers

Notes: (A) Pan-cancer survival curves of WSB1 based on the TCGA database. (B) Pan-cancer receiver operating characteristic (ROC) curves of WSB1.

3.3. Analysis of the Correlation between WSB1 Expression and Genetics

cBioPortal database analysis showed WSB1 had a genetic alteration frequency >4%, mainly mutations. Its mutation frequency exceeded 2% in ESCA, BLCA, LUAD, CHOL, LUSC, BRCA, STAD, MESO and SKCM, with varied alteration types among cancers. The highest frequency was in esophageal adenocarcinoma (predominantly amplification). In LUAD (n=566) and BRCA (n=1084), WSB1 alteration frequencies were 3.18% (mutations/amplifications) and 2.58% (mainly amplifications), respectively; amplification was the only type in CHOL (Figure 3A). Missense mutations were the major alteration, with R17C/H hotspot detected in 3 UCEC and 1 STAD cases (Figure 3B). UALCAN analysis (Figure 3C) revealed significantly lower WSB1 promoter methylation in tumor than adjacent normal tissues in 14 cancers ($P<0.05$), but higher methylation in CHOL and PRAD ($P<0.05$). WSB1 shows frequent genetic/epigenetic dysregulation with tissue-specific patterns, suggesting potential as a pan-cancer diagnostic biomarker and therapeutic target, requiring further validation.

3.4. Immune in Filtration Analysis of WSB1

Based on pan-cancer omics data from the SangerBox 3.0 bioinformatics platform, this study systematically evaluated the correlation between WSB1 expression and immune cell infiltration characteristics in the tumor microenvironment using multivariate Spearman correlation analysis. Pan-cancer analysis showed that WSB1 transcriptional levels were significantly positively correlated with six major immune cell types ($P<0.05$), suggesting a potential broad-spectrum role in regulating immune infiltration. Notably, in PRAD, LIHC, COAD, READ, BRCA, COAD, and PAAD, WSB1 expression was significantly positively correlated with the infiltration of six core immune effector cells, including CD8+ T cells, CD4+ T cells, B cells, natural killer cells, dendritic cells, and macrophages ($P<0.05$). However, a distinct regulatory pattern was observed in LUAD: WSB1 expression was positively correlated with CD4+ T cells and tumor-associated macrophages, but negatively correlated with cytotoxic CD8+ T cell infiltration ($P<0.05$), indicating significant heterogeneity in its immune-modulatory functions across different tumor types (Figure 4).

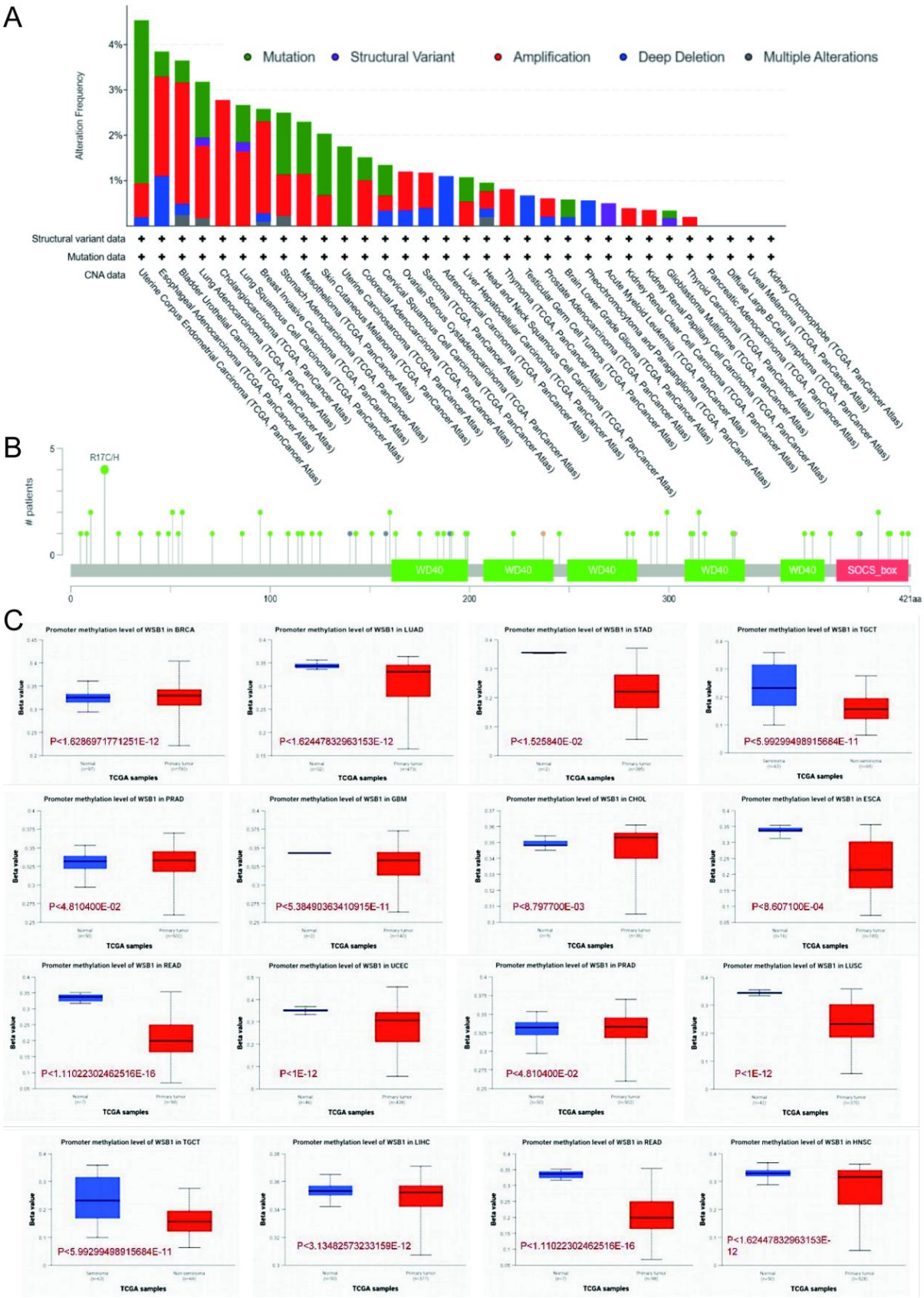

Figure 3. Analysis of WSB1 expression and its genetic correlates

Notes: (A) Frequency of genetic alterations of WSB1 across human cancers(B) Somatic mutation sites of WSB1(C) Methylation levels of the WSB1 promoter

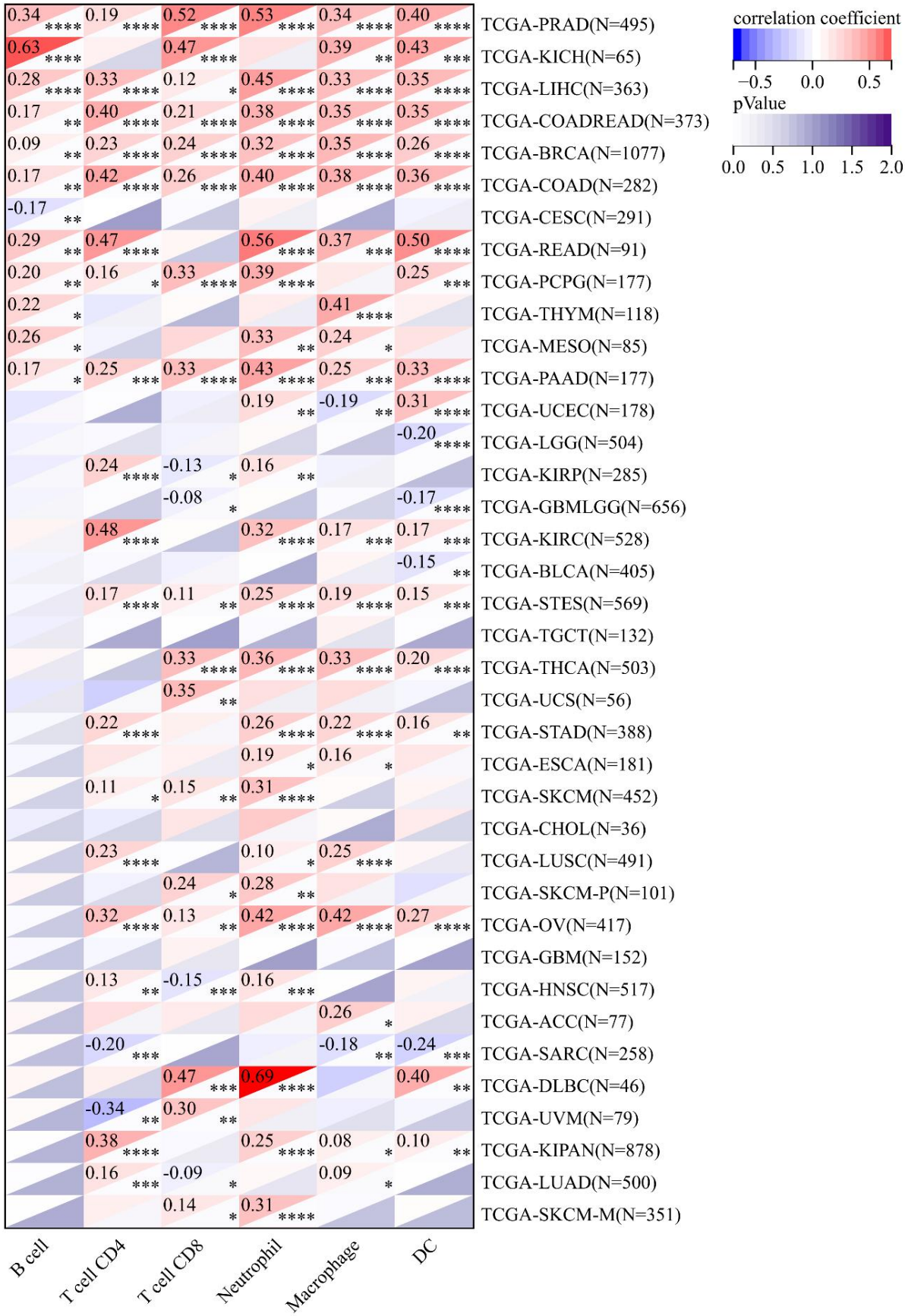

Figure 4. Correlation between WSB1 expression and immune cell infiltration levels across human cancers

3.5. WSB1 and Immune Checkpoint Analysis

Immune checkpoints (ICPs) are key regulators of immune activation and suppression that play a critical role in tumor immune evasion. To explore the potential clinical value of WSB1 in cancer immunotherapy, we analyzed its correlation with ICP gene expression across human cancers using the SangerBox 3.0 platform. Our results showed that WSB1 expression was closely associated with 60 ICP-related genes across 40 cancer types (Figure 5). In COAD, COAD, READ, neuroblastoma (NB), OV, LIHC, PAAD, READ, KICH, PRAD, pan-kidney cohort (KIPAN), KIRC, uveal melanoma (UVM), and LUAD, WSB1 was positively correlated with most ICP genes. Notably, in KIPAN, WSB1 expression correlated with 59 ICP genes. WSB1 was significantly positively correlated with PDCD1 (PD-1) in 14 cancers, with CD274 (PD-L1) in 24 cancers, and with CTLA-4 in 20 cancers (all $P<0.05$). In LUAD specifically, WSB1 was positively correlated with CTLA-4. These findings suggest that WSB1 may coordinate the activity of multiple ICP pathways and could serve as a promising immunotherapeutic target. High WSB1 expression may predict favorable responses to ICP-based immunotherapy in relevant cancer types.

3.6 Enrichment Analysis of the WSB1 Gene

To explore WSB1-related functions and protein interactions, we constructed a protein–protein interaction (PPI) network using the STRING database, which included 20 co-expressed genes (Figure 6A). The most strongly associated protein was Cullin 5 (CUL5), with a correlation score of 0.952. Using GEPIA2, we identified the top 100 genes significantly correlated with WSB1 expression and selected the top 50 based on Pearson correlation coefficients. These genes were combined with the STRING-predicted WSB1 interaction network for further analysis.

GO and KEGG enrichment analyses were performed using the Xiantao Academic platform, and results were visualized with ggplot2 in R. GO analysis showed that WSB1-related genes were enriched in RNA metabolism, RNA splicing, mRNA processing (biological process); transcription elongation factor complexes and CUL2-ring ubiquitin ligase complexes (cellular component); and transcriptional coactivator binding, cyclosporin A binding, and peptidyl-prolyl isomerase activity (molecular function). KEGG analysis indicated involvement in ubiquitin-mediated proteolysis and other pathways (Figure 6B).

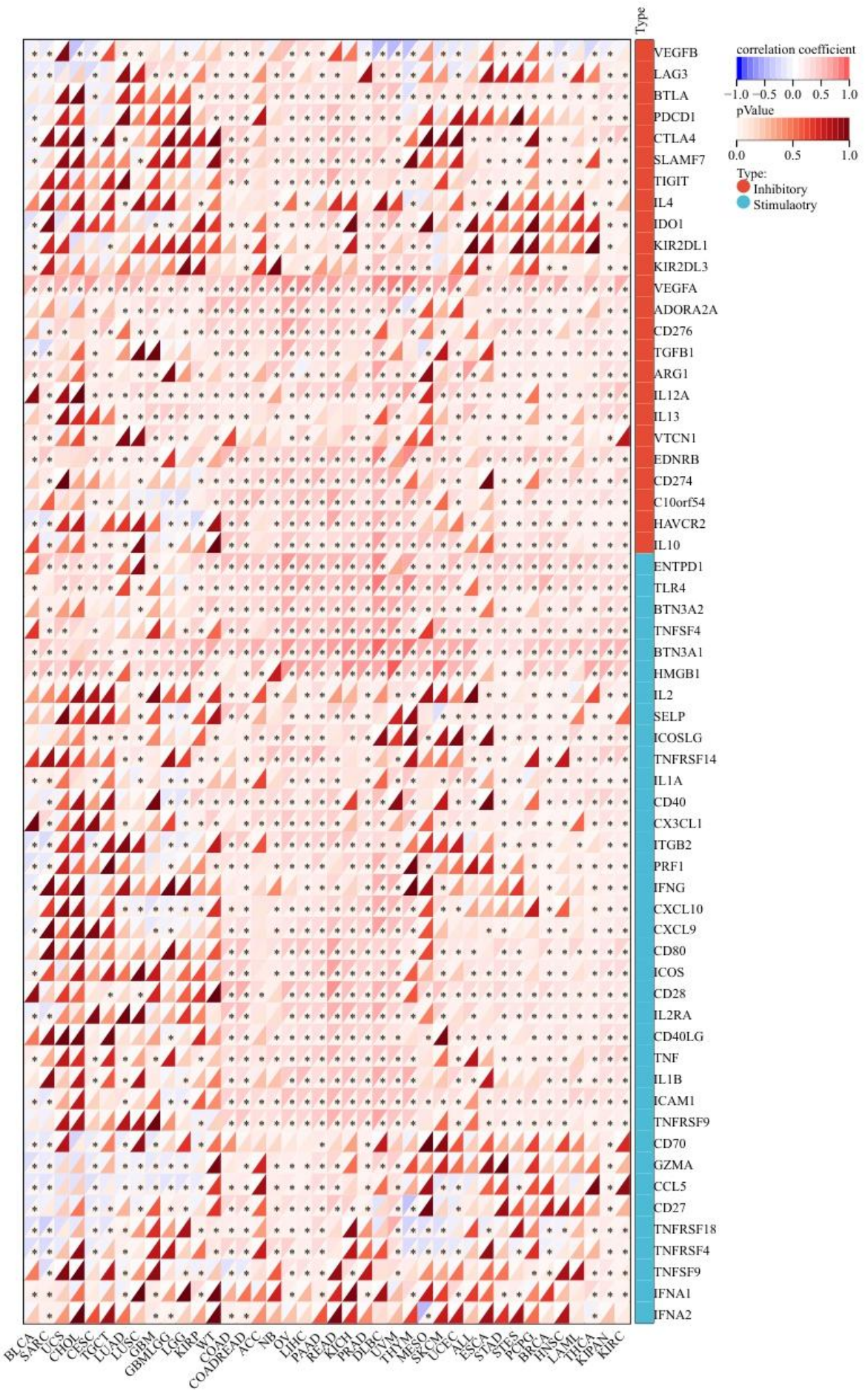

Figure 5. Relationship between WSB1 expression and immune checkpoint (ICP) genes in human cancers

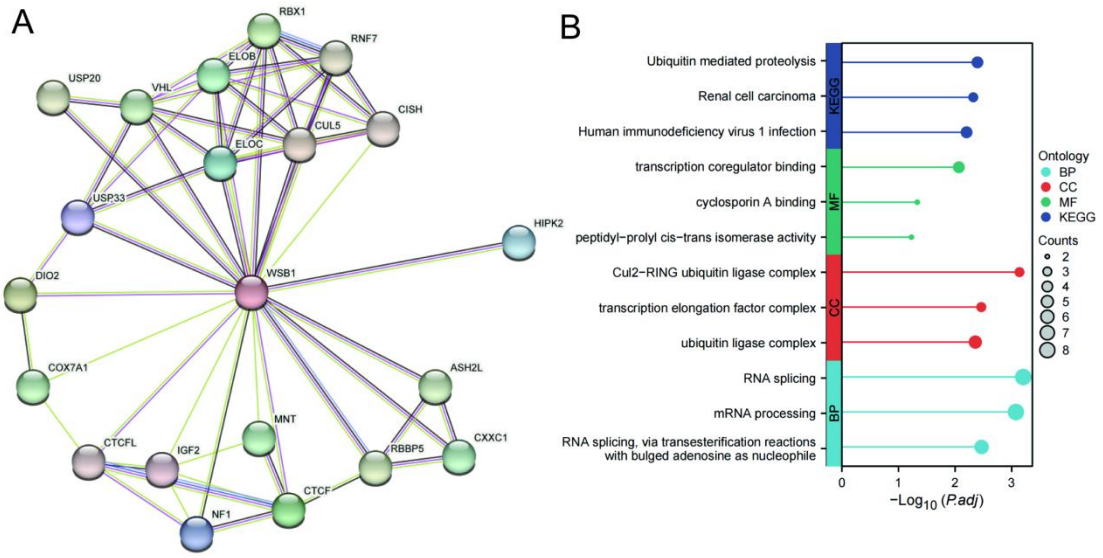

Figure 6. Enrichment analysis of the WSB1 gene

Notes: (A) Protein–protein interaction network between WSB1 and other proteins. (B) KEGG and GO enrichment analysis of WSB1 co-expressed genes.

3.7. WSB1 Expression in LUAD and Its Correlation with Clinicopathological Features

The LUAD tissue microarray included 80 tumor cores and 80 adjacent normal tissue cores, totaling 160 samples; among the 80 LUAD patients, 46 (57.5%) were male, 34 (42.5%) were female, 36 (45%) were <55 years old, 44 (55%) were ≥55 years old, 42 (52.5%) were at clinical stages I–II, 37 (47.5%) at stages III–IV, 61 (76.25%) at T1–T2 stage, 19 (23.75%) at T3–T4 stage, 47 (60.3%) without lymph node metastasis, 31 (39.7%) with lymph node metastasis (2 cases unknown), 70 (74.6%) without distant metastasis, and 7 (9.09%) with distant metastasis (3 cases unknown). WSB1 protein expression in LUAD and paired adjacent normal tissues was evaluated by immunohistochemistry (Figure 7A) using a semi-quantitative scoring system (0–300 points) combining staining intensity (0–3 points) and positive cell percentage (0–100%), and the results showed that high WSB1 expression (score ≥200) was observed in 7.5% of LUAD samples but in none of the adjacent normal tissues (100% low expression), with chi-square and rank-sum tests confirming significantly higher WSB1 expression in LUAD tissues than in adjacent normal tissues (Figure 7B, Table 1); further analysis of the correlation between WSB1 expression and clinicopathological features indicated that WSB1 expression was significantly higher in patients without distant metastasis (M0) than in those with metastasis (M1) ($P<0.05$), while no significant correlations were found with gender, age, clinical stage, T stage, or N stage (Table 2).

Table 1. Differential expression of WSB1 in cancer and adjacent normal tissues

Sample	Total	WSB1 expression		χ2	P value
		High expression	Low expression		
Lung adenocarcinoma tissue	80	6	74	4.43	0.04
Adjacent normal tissue	80	0	80		

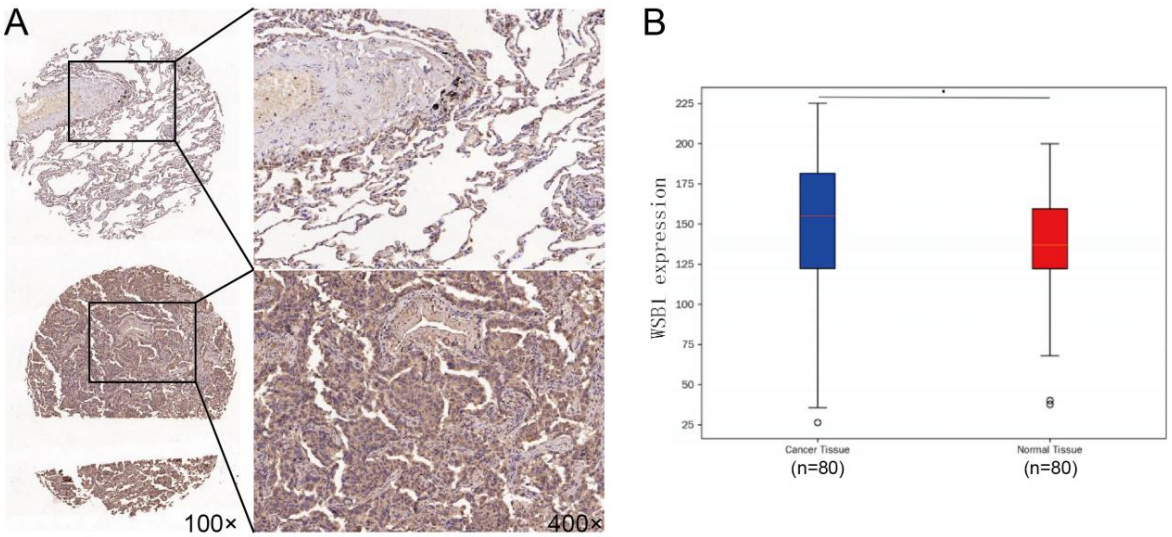

Figure 7. Differential expression of WSB1 in lung adenocarcinoma tissues and adjacent normal tissues

Notes: (A) Immunohistochemical staining showing the localization and expression intensity of WSB1 in lung adenocarcinoma and adjacent tissues (100× and 400× magnification). (B) Boxplot of WSB1 expression levels in lung adenocarcinoma (n=80) and adjacent normal tissues (n=80).

Table 2. Correlation analysis between WSB1 expression and clinicopathological characteristics in patients with lung adenocarcinoma

Clinicopathological Features	Variables	WSB1 Expression		Total	χ2	P value
		Low Expression	High Expression			
Age	＜55years	35	1	36	2.468	0.1162
	≥55years	50	5	55		
Gender	Male	43	3	46	0.149	0.6991
	Female	31	3	34		
Clinical Stage	Stage I-II	38	4	42	0.475	0.4905
	Stage III-IV	35	2	37		
Invasion Depth (T Stage)	T1-T2	57	4	61	0.329	0.5663
	T3-T4	17	2	19		
Lymph Node Metastasis (N Stage)	Yes	28	3	31	0.915	0.3887
	No	45	2	47		
Distant Metastasis (M Stage)	Yes	7	1	7	-	0.0002
	No	65	5	70		

4. Discussion

The ubiquitin-proteasome system (UPS) plays a crucial role in regulating cellular physiological functions. As the core recognition component of the UPS, E3 ubiquitin ligases are closely associated with tumorigenesis and development due to their abnormal expression, and their functions exhibit tumor type- and microenvironment-specific characteristics. As a member of the E3 ubiquitin ligase family, WSB1 exerts complex roles in cancer. It can affect cancer cell survival and proliferation by regulating proteins such as HIPK2 and VHL as well as related signaling pathways. Additionally, WSB1 is dysregulated in various types of tumors, and its different transcripts exert distinct functions.

This study focused on the role of WSB1 in pan-cancer and lung adenocarcinoma (LUAD), and conducted investigations by combining bioinformatics analysis and immunohistochemical experiments. Bioinformatics analysis showed that WSB1 mRNA expression was significantly different between various tumors and corresponding normal tissues; specifically, WSB1 mRNA was downregulated while its protein level was upregulated in LUAD, and this discrepancy may be related to mechanisms such as post-translational modification. Survival analysis indicated that high WSB1 expression in LUAD was associated with longer overall survival of patients. Moreover, WSB1 expression was negatively correlated with promoter methylation, and positively correlated with CD4+ T cells and most immune checkpoint (ICP) genes in LUAD, suggesting its potential in immune regulation. Protein-protein interaction analysis revealed that WSB1 had the strongest association with CUL5, and might form a dual regulatory network by participating in RNA metabolism and the ubiquitin-proteasome system.

Immunohistochemical experiments (80 LUAD tissue samples and 80 adjacent normal tissue samples) verified that WSB1 expression was significantly higher in LUAD tissues than in adjacent normal tissues, and its expression in the M0 group was significantly higher than that in the M1 group. However, WSB1 expression had no significant correlation with other clinicopathological factors such as patient gender and age.

In conclusion, WSB1 is highly expressed in LUAD and associated with better prognosis. It may be involved in the regulation of tumor metastasis and tumor immune microenvironment, and its functional mechanism and clinical application value require further exploration.

Furthermore, this study is primarily based on public databases and IHC validation, and the functional mechanism of WSB1 has not yet been verified through in vitro or in vivo experiments. In the future, it will be necessary to construct WSB1 overexpression/knockout models to further clarify its role in LUAD metastasis and tumor immune microenvironment regulation. Additionally, the sample size is relatively limited, and subsequent studies can expand the clinical cohort and conduct multi-center validation.

Author Contributions:

Y. L. and S. W. conceived and designed the study; J. X. and T. H. prepared the experimental materials; J. X. analyzed the data and wrote the manuscript; T. H. confirmed the authenticity of all

raw data. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement:

The study follows the principles of the Declaration of Helsinki. All studies performed with human tissue specimens were approved by the Ethics Committee of North China University of Science and Technology (Csya20260125). Cancer samples and clinical data were collected from patients undergoing surgery at Affiliated Hospital of North China University of Technology, and informed consent was obtained from all patients included in this study.

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Data Availability Statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Informed Consent Statement:

All patients provided their informed consent.

Conflict of Interest:

The authors declare no competing interests.

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