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Research article

Identification of SSBP1 as a prognostic marker in human lung adenocarcinoma using bioinformatics approaches

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Abstract: Objective: Single-stranded DNA-binding protein 1 (SSBP1) plays an important role in DNA repair processes and the maintenance of genomic stability. The aim of this study was to evaluate the expression of SSBP1 and its prognostic value in lung adenocarcinoma (LUAD) using bioinformatics approaches. Methods: We applied databases including UALCAN, Kaplan-Meier plotter, LinkedOmics, Webgestalt, cBioPortal and TIMER2.0 in this study. Results: We found that SSBP1 expression was up-regulated in LUAD samples and was correlated with clinicopathological features including age, cancer stage, and nodal metastasis status by the UALCAN analysis. Multivariate Cox regression analysis by the Kaplan-Meier plotter showed that high SSBP1 expression was independently correlated with poor overall survival (hazard ratio = 1.63, 95% confidence interval: 1.08−2.46, logrank P = 0.02). The LinkedOmics analysis showed that 5078 genes were positively correlated with SSBP1 expression, whereas 7905 genes were negatively correlated with SSBP1 in LUAD. Functional enrichment analysis using the Webgestalt tool showed that for SSBP1 and the genes positively correlating with it, the significantly enriched biological process was ribosomal large subunit biogenesis, and the significantly enriched pathway was proteasome. According to the cBioPortal database, the frequency of SSBP1 alterations was 1.7% in LUAD patients, and patients with SSBP1 alterations had worse prognosis (logrank P = 4.26e-05) compared with those unaltered for SSBP1. Finally, SSBP1 expression was negatively correlated with B cell infiltration level (Rho = −0.193, P = 1.54e-05) and the expression of B cell biomarkers including CD79A and CD19. Conclusion: Our results suggest that SSBP1 may be a prognostic marker for human LUAD.

Keywords: SSBP1; LUAD; prognosis; bioinformatics

1. Introduction

Lung cancer is the most common cancer and the leading cause of cancer mortality in the world, resulting in over 1.5 million deaths every year. Lung adenocarcinoma (LUAD) is the most frequently diagnosed subtype of lung cancer and comprises about 40 percent of all cases. LUAD is derived from the mucosal glands and is usually located in the lung periphery. It is the most common subtype of lung cancer found in never-smokers [1]. Despite advancement in medical imaging and treatment options, the 5-year survival rate of LUAD remains very poor. This raises the urgent need for the development of novel targeted therapies as well as novel prognostic markers.

Single-stranded DNA-binding protein 1 (SSBP1) is a member of the SSBP family that is characterized by the presence of an oligonucleotide/oligosaccharide binding fold (OB-fold). SSBP1 is known to play an important role in DNA repair processes and the maintenance of genomic stability. After DNA damage, SSBP1 localizes at sites of double-strand DNA breaks (DSBs) extremely rapidly (within 10 s) and participates in homologous recombination (HR)-dependent repair of DSBs [2]. Richard et al found that SSBP1 may be essential for DSB stability and the recruitment of other repair factors such as the MRN (Mre11, Rad50, NBS1) complex [3]. In addition, SSBP1 controls the activation of ataxia telangiectasia mutated (ATM) signaling and is required for ATM-mediated DSB signaling events [2,3]. Although repairing DNA damage is the known role of SSBP1, it also exerts other important functions including cell cycle regulation and telomere end protection [4,5]. In recent years, aberrant SSBP1 expression has been reported in some cancers including ovarian cancer, liver cancer, and colorectal cancer, suggesting that SSBP1 may be a participant in the development of these cancers [6−8]. However, the role of SSBP1 in LUAD development remains largely unknown. In the present study, we evaluated the clinical significance and prognostic role of SSBP1 in LUAD using a comprehensive bioinformatics analysis.

2. Materials and methods

2.1. UALCAN analysis

UALCAN is a web-based tool for analyzing the RNA sequencing expression data based on The Cancer Genome Atlas (TCGA) database [9]. The mRNA expression of SSBP1 in LUAD and normal tissues was evaluated using the UALCAN (http://ualcan.path.uab.edu/analysis.html) database. In addition, the correlation between SSBP1 expression and LUAD clinical characteristics was also assessed through the UALCAN database. To validate the mRNA expression of SSBP1 in LUAD samples, we used two Gene Expression Omnibus (GEO) datasets (GSE7670 and GSE43458) [10,11].

2.2. SSBP1 expression and LUAD prognosis

The correlation of SSBP1 expression with LUAD patients' prognosis was estimated using the UALCAN and Kaplan-Meier plotter (www.kmplot.com) databases [12]. The Kaplan Meier plotter is an interactive web application for survival analysis, which is established with gene expression data

and survival information of cancer patients. Both univariate and multivariate Cox regression analyses were performed using the Kaplan Meier plotter.

2.3. LinkedOmics analysis

The LinkedOmics database (http://www.linkedomics.org/login.php) contains multi-omics data and clinical information from the TCGA portal for 32 cancer types [13]. The LinkFinder module of the LinkedOmics database was used to analyze the differentially expressed genes (DEGs) related to SSBP1. A volcano plot was generated for the DEGs. The Pearson's correlation coefficient was used to test the correlation of results. For the DEGs whose Pearson's correlation coefficient ≥ 0.70 or ≤ -0.70, the Kaplan Meier plotter was applied to estimate whether their expressions were correlated with LUAD prognosis. The gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis for the DEGs were performed using WebGestalt (http://www.webgestalt.org/) [14].

2.4. Hub gene analysis

A protein-protein interaction (PPI) network of SSBP1 and its co-expressed genes was constructed using STRING (http://string-db.org/). The Cytoscape software was used to identify the top 10 hub genes of the network. WebGestalt (http://www.webgestalt.org/) was applied to perform the GO and KEGG pathway enrichment analysis for the hub genes. MiRNet (https://www.mirnet.ca/) was utilized to identify the microRNAs and lncRNAs that were linked with the top 10 hub genes [15].

2.5. cBioPortal analysis

We evaluated the correlation of SSBP1 alterations with LUAD prognosis at cBioPortal (http://www.cbioportal.org/) based on nine datasets with a total of 2670 LUAD patients. For overall survival analysis, LUAD patients with SSBP1 alterations were compared with those unaltered for SSBP1, and log-rank test was carried out. We also evaluated the association of SSBP1 alterations with alterations of major oncogenic drivers including Kirsten rat sarcoma viral oncogene homolog (KRAS), epidermal growth factor receptor (EGFR), tumor protein p53 (TP53), ROS proto-oncogene 1 (ROS1), anaplastic lymphoma kinase (ALK), MET proto-oncogene (MET), purposePhosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), B-Raf proto-oncogene serine/threonine-protein kinase (BRAF), Kelch-like ECH-associated protein 1 (KEAP1), and serine/threonine kinase 11 (STK11). Finally, the top 5 genes with highest alteration event frequency in the SSBP1-altered group and their correlation with LUAD patients' prognosis were evaluated.

2.6. TIMER2.0 analysis

TIMER2.0 (http://timer.cistrome.org/) is a web-based bioinformatics tool for systematical assessment of immune infiltrates (B cells, CD4+ T cells, CD8+ T cells, macrophages, dendritic cells, neutrophils) in diverse cancer types [16]. The correlation between SSBP1 expression and immune infiltration levels in LUAD was evaluated using the TIMER2.0 database. In addition, the correlation between immune infiltrates and LUAD patients' overall survival was also assessed.

2.7. Statistical analysis

Wilcox rank sum test was utilized for continuous variables between pairs of groups. The Kaplan-Meier method with log-rank test was used for survival analysis. To evaluate genes that were correlated with SSBP1 expression, the Pearson's correlation coefficient was applied. The Spearman method was used for analyzing the correlation coefficients of immune infiltrates. A two-sided $p < 0.05$ was set as statistically significant.

2.8. Ethical approvals

Since this study was performed on publicly available data sets provided by online databases, the institutional review board approval was waived.

3. Results

3.1. Correlation between SSBP1 expression and LUAD clinicopathological features

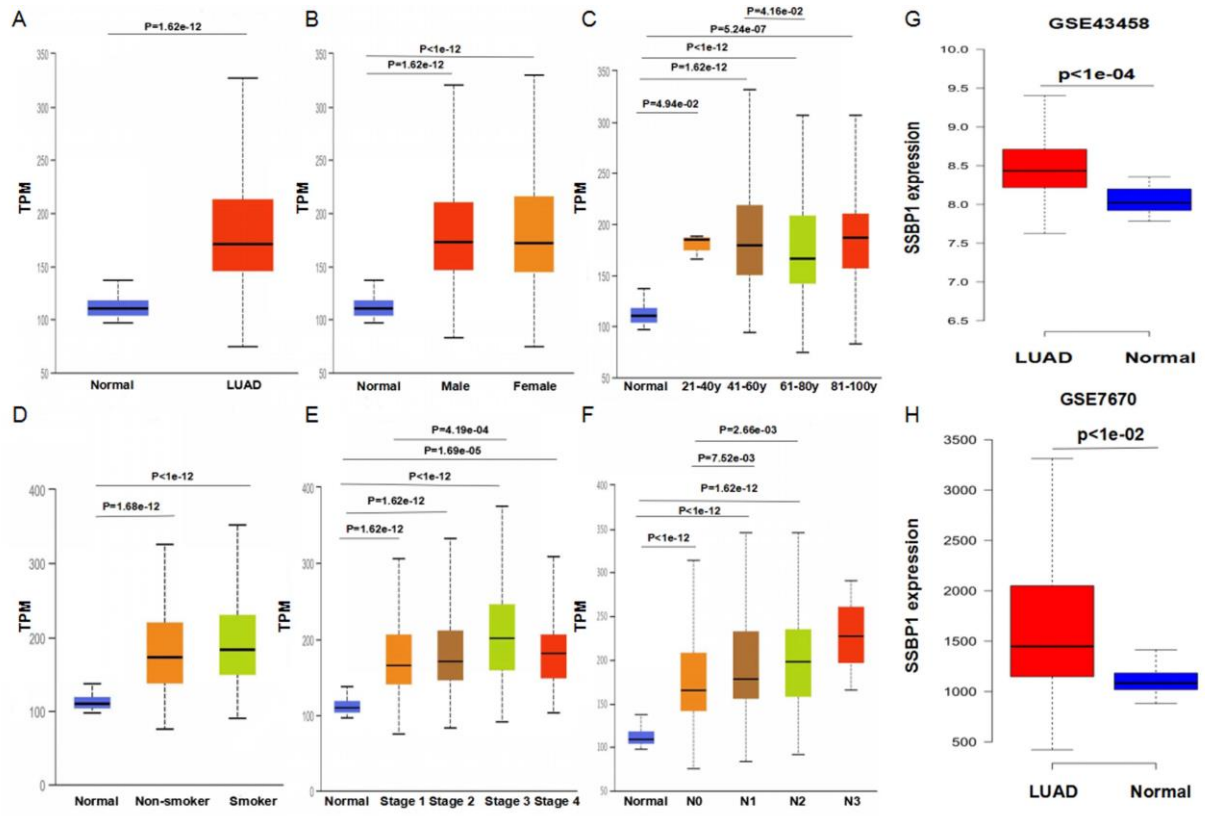

Figure 1. SSBP1 mRNA expression was evaluated using the UALCAN database. (A) Up-regulation of SSBP1 mRNA expression in lung adenocarcinoma samples. (B) The mRNA expression of SSBP1 in subgroups of gender. (C) The mRNA expression of SSBP1 in subgroups of age. (D) The mRNA expression of SSBP1 in subgroups of tobacco smoking. (E) The mRNA expression of SSBP1 in subgroups of cancer stage. (F) The mRNA expression of SSBP1 in subgroups of nodal metastasis status. (G) Evaluation of SSBP1 mRNA expression in GSE43458. (H) Evaluation of SSBP1 mRNA expression in GSE7670.

The mRNA expression of SSBP1 was significantly up-regulated in LUAD samples compared with normal samples based on the UALCAN analysis (Figure 1A). Subsequently, the correlation between SSBP1 expression and LUAD clinicopathological features was estimated (Figure 1B-F). The UALCAN analysis showed that SSBP1 expression was correlated with LUAD patients' age, cancer stage and nodal metastasis status (Figure 1C,E,F). We validated the mRNA expression of SSBP1 in two GEO datasets (GSE43458 and GSE7670); the results showed that SSBP1 expression was significantly up-regulated in LUAD samples (Figure 1G,H).

3.2. Correlation between SSBP1 expression and poor prognosis

The correlation between SSBP1 expression and LUAD patients' prognosis was evaluated based on the UALCAN and Kaplan-Meier plotter databases. The UALCAN analysis demonstrated that the high-SSBP1 expression group had considerably worse overall survival than the medium/low-SSBP1 expression group (logrank P = 0.037) (Figure 2A). The Kaplan-Meier plotter analysis also showed that high SSBP1 expression was significantly correlated with poor overall survival (hazard ratio (HR) = 1.46, 95% confidence interval (CI): 1.15−1.86, logrank P = 0.002) (Figure 2B). To verify the correlation, we further performed multivariate Cox regression analysis based on the Kaplan-Meier plotter, finding that high-SSBP1 expression group was correlated with worse overall survival (HR = 1.63, 95% CI: 1.08−2.46, logrank P = 0.02) after adjusting for gender and cancer stage (Figure 2C).

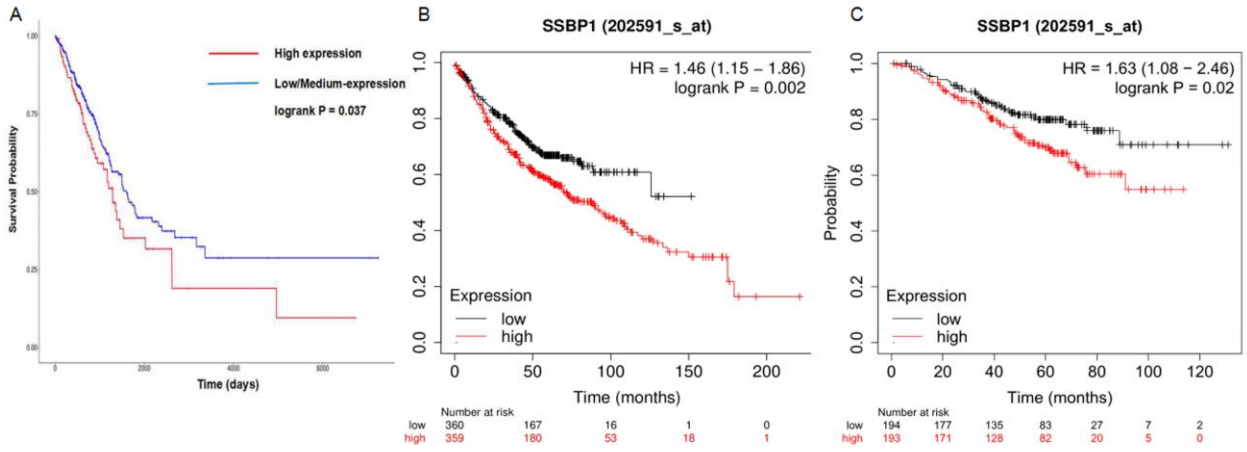

Figure 2. The correlation between SSBP1 expression and lung adenocarcinoma prognosis. (A) The high-SSBP1 expression group had considerably worse overall survival than the medium/low-SSBP1 expression group according to the UALCAN database. (B) The high-SSBP1 expression group had considerably worse overall survival than the low-SSBP1 expression group according to the Kaplan-Meier plotter. (C) Multivariate Cox regression analysis showed that the high-SSBP1 expression group was correlated with poor overall survival.

3.3. Genes correlating with SSBP1 expression

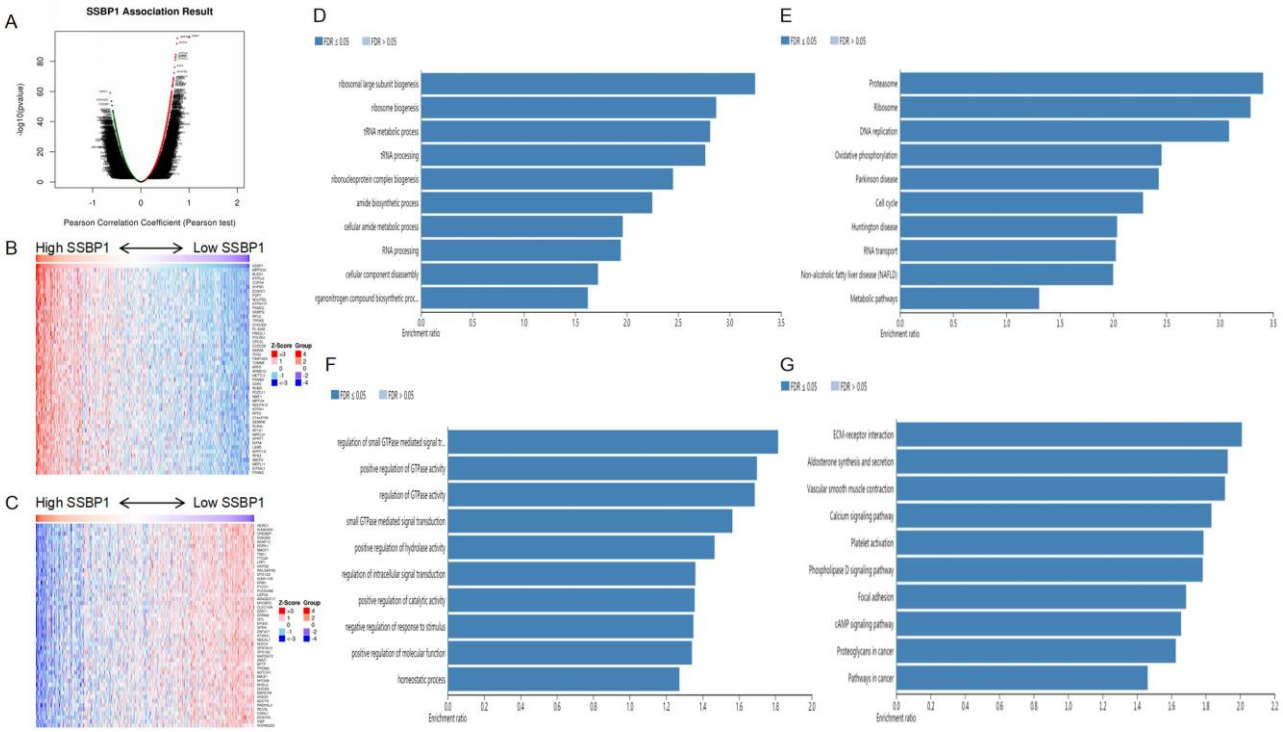

Figure 3. SSBP1 co-expressed genes and functional enrichment analysis (A) A volcano plot demonstrated that 5078 genes were positively correlated with SSBP1 expression, whereas 7905 genes were negatively correlated with the expression of SSBP1. (B) The heat map showed the top 50 genes that were positively correlated with SSBP1 expression. (C) The heat map showed the top 50 genes that were negatively correlated with SSBP1 expression. (D) The gene ontology analysis (biological process) for SSBP1 and the genes that were positively correlated with it. (E) The Kyoto Encyclopedia of Genes and Genomes pathway analysis for SSBP1 and the genes that were positively correlated with it. (F) The gene ontology analysis (biological process) for the genes that were negatively correlated with SSBP1. (G) The Kyoto Encyclopedia of Genes and Genomes pathway analysis for the genes that were negatively correlated with SSBP1.

We used the LinkFinder module of the LinkedOmics database to evaluate the SSBP1 co-expression network in LUAD. The volcano plot demonstrated that 5078 genes were positively correlated with SSBP1 expression, whereas 7905 genes were negatively correlated with the expression of SSBP1 (Figure 3A). The heat map of Figure 3B showed the top 50 genes that were positively correlated with SSBP1, while Figure 3C demonstrated the top 50 genes that were negatively correlated with SSBP1. The GO analysis indicated that SSBP1 and the genes positively correlating with it were mainly involved in biological processes including ribosomal large subunit biogenesis, ribosome biogenesis, tRNA metabolic process, tRNA processing, ribonucleoprotein complex biogenesis, amide biosynthetic process, cellular amide metabolic process, RNA processing, cellular component disassembly and organonitrogen compound biosynthetic process (Figure 3D). The KEGG pathway analysis showed that SSBP1 and the genes positively correlating with it were

mainly enriched in proteasome, ribosome, DNA replication, oxidative phosphorelation, Parkinson disease, cell cycle, Huntington disease, RNA transport, non-alcoholic fatty liver disease and metabolic pathways (Figure 3E). The genes that were negatively correlated with SSBP1 were mainly enriched in biological processes involving regulation of small GTPase mediated signal transduction, positive regulation of GTPase activity, regulation of GTPase activity, small GTPase mediated signal transduction, positive regulation of hydrolase activity, regulation of intracellular signal transduction, positive regulation of catalytic activity, negative regulation of response to stimulus, positive regulation of molecular function, and homeostatic process (Figure 3F). The KEGG pathway analysis showed that the genes negatively correlating with SSBP1 were mainly enriched in ECM-receptor interaction, aldosterone synthesis and secretion, vascular smooth muscle contraction, calcium signaling pathway, focal adhesion, cAMP signaling pathway, proteoglycans in cancer, and pathways in cancer (Figure 3G).

Among the co-expressed genes (positively or negatively correlated with SSBP1), six genes showed the strongest correlation (Pearson's correlation coefficient $|\geq 0.70$); all of them were positively correlated with SSBP1 expression. They were mitochondrial ribosomal protein S33 (MRPS33), BUD31 homolog (BUD31), ATP synthase, H+ transporting, mitochondrial Fo complex subunit F2 (ATP5J2), COP9 signalosome subunit 6 (COPS6), split hand/foot malformation type 1 (SHFM1) and zinc finger, C3HC-type containing 1 (ZC3HC1) (Figure 4A). We used the Kaplan-Meier plotter to analyze whether these six genes affected LUAD patients' prognosis. The results showed that BUD31, ATP5J2 and SHFM1 were significantly correlated with poor overall survival of LUAD patients (BUD31: HR = 1.53, 95% CI = 1.01−2.31; ATP5J2: HR = 2.75, 95% CI = 1.76−4.30; SHFM1: HR = 1.64, 95% CI = 1.08−2.48) (Figure 4B).

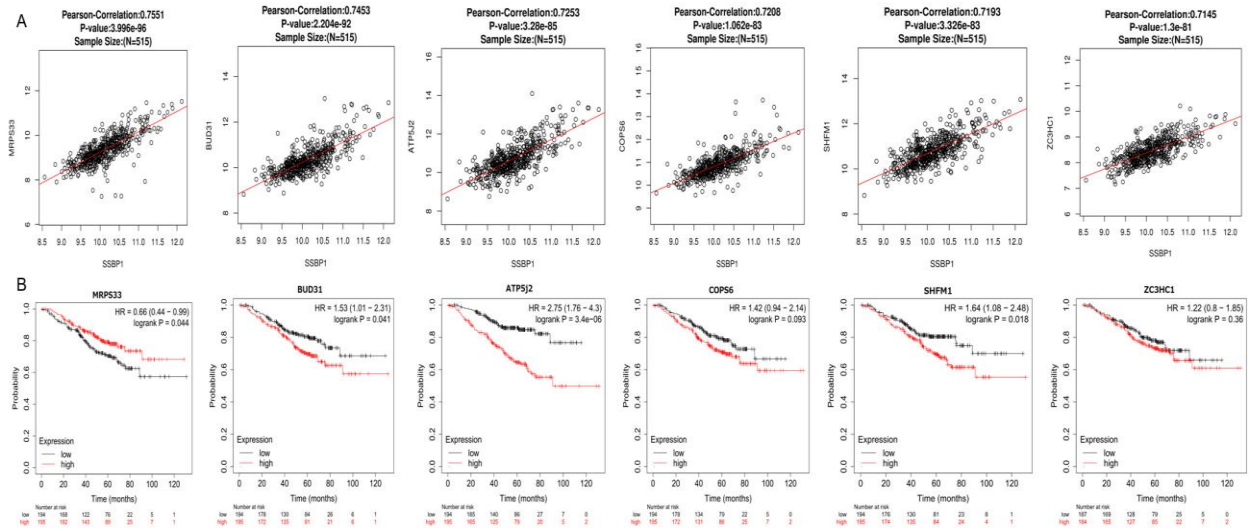

Figure 4. The genes that showed the strongest correlation with SSBP1 expression and their correlation with lung adenocarcinoma prognosis. (A) The genes that showed the strongest correlation with SSBP1 expression. (B) The correlation between the genes that showed the strongest correlation with SSBP1 expression and lung adenocarcinoma prognosis.

3.4. Hub gene analysis

Using STRING (http://string-db.org/), the PPI network of SSBP1 and its correlated genes was constructed (Figure S1). The top 10 hub genes of the network were identified using the Cytoscape software (Figure S1). We performed functional annotation including GO and KEGG enrichment analyses for these hub genes (Figure S2). Using miRNet (https://www.mirnet.ca/) and the Cytoscape software, we identified 10 hub microRNAs and 325 lncRNAs that were linked with the hub genes (Figure S3).

3.5. SSBP1 alterations and LUAD patients' prognosis

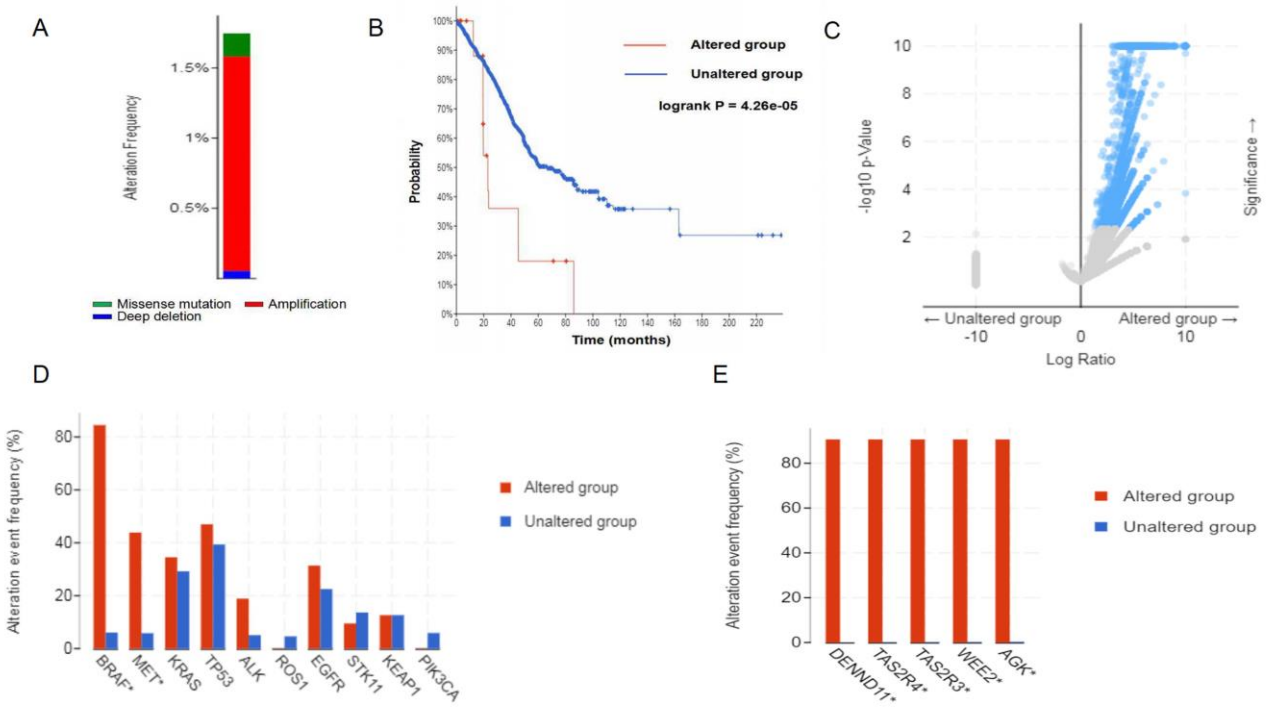

Figure 5. cBioPortal analysis for SSBP1. (A) The frequency of SSBP1 alterations in lung adenocarcinoma patients. (B) Lung adenocarcinoma patients with SSBP1 alterations had worse prognosis compared with those unaltered for SSBP1. (C) Genes in the SSBP1 altered group had significantly higher altered frequency than the SSBP1 unaltered group. (D) Association of SSBP1 alterations with alterations of major oncogenic drivers. (E) The top 5 genes with highest frequency in the SSBP1 altered group.

To assess the correlation between SSBP1 alterations and LUAD patients' prognosis, the analysis was carried out using the cBioPortal database, which included nine LUAD datasets containing 2670 LUAD patients. We found that the frequency of genetic alterations in the SSBP1 gene was 1.7% and the majority of SSBP1 alterations in LUAD were represented by amplifications (Figure 5A). Next, the cBioPortal database was queried to assess whether SSBP1 alterations impacted LUAD prognosis. The results indicated that LUAD patients with SSBP1 alterations had worse prognosis compared with those unaltered for SSBP1 (logrank P = 4.26e-05) (Figure 5B). Figure 5C showed that genes in

the SSBP1 altered group had significantly higher altered frequency than the SSBP1 unaltered group. Among the major oncogenic drivers for LUAD, BRAF and MET had higher alteration event frequency in LUAD patients with SSBP1 alterations than those unaltered for SSBP1 (BRAF: 84.38% vs 5.92%, P = 9.24e-28; MET: 43.75% vs 5.69%, P = 1.15e-09) (Figure 5D). According to the cBioPortal database, the top 5 genes with highest frequency in the SSBP1 altered group were DENND11, TAS2R4, TAS2R3, WEE2 and AGK (Figure 5E). The alterations of these genes were correlated with poor prognosis in LUAD (Figure 6).

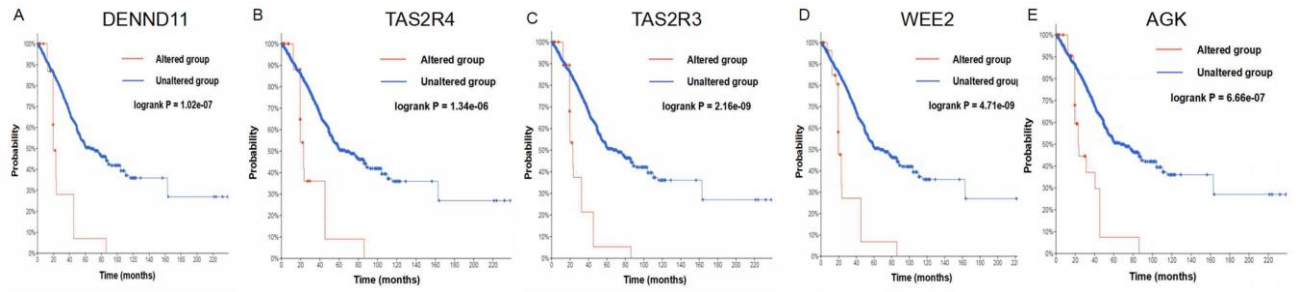

Figure 6. Survival analysis for the top 5 genes with highest frequency in the SSBP1 altered group. (A-E) The top 5 genes with highest frequency in the SSBP1 altered group were DENND11, TAS2R4, TAS2R3, WEE2 and AGK; the alterations of these genes were correlated with poor prognosis in lung adenocarcinoma.

3.6. SSBP1 expression and immune cell infiltration

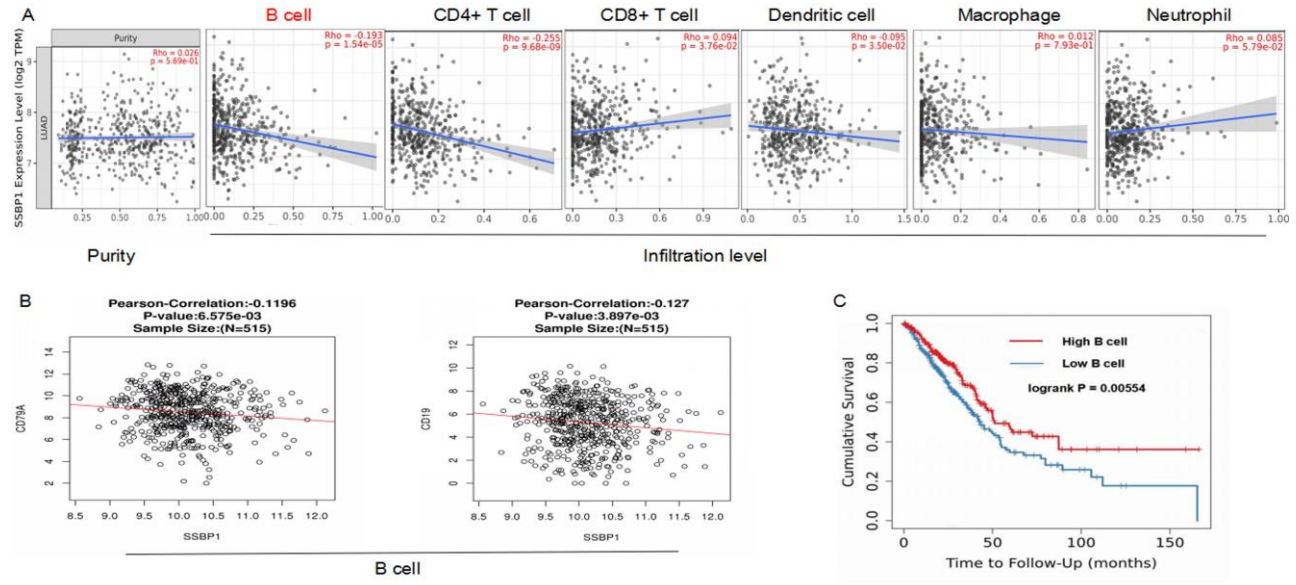

Figure 7. The correlation of SSBP1 expression with immune cell infiltration in lung adenocarcinoma. (A) SSBP1 expression was negatively correlated with B cell infiltration level. (B) SSBP1 expression was negatively correlated with the expression of B cell biomarkers including CD79A and CD19. (C) The low B cell group had considerably worse prognosis than the high B cell group.

We used the TIMER2.0 database to estimate the effect of SSBP1 expression on the infiltration of immune cells including B cells, CD4+ T cells, CD8+ T cells, macrophages, dendritic cells and neutrophils in LUAD. We found that SSBP1 expression was negatively correlated with B cell infiltration level (Rho = −0.193, P = 1.54e-05) (Figure 7A). However, there was no correlation of SSBP1 expression with the infiltration levels of CD4+ T cells, CD8+ T cells, macrophages, dendritic cells and neutrophils (Figure 7A). Next, we assessed the correlation between SSBP1 expression and the biomarkers of B cells including CD79A and CD19, finding that SSBP1 expression was negatively correlated with the expression of CD79A (Pearson's correlation coefficient: −0.1196, P = 6.575e-03) and CD19 (Pearson's correlation coefficient: −0.127, P = 3.897e-03) (Figure 7B). Finally, we evaluated the correlation between B cells and LUAD prognosis. The low B cell group had considerably worse prognosis than the high B cell group (logrank P = 0.00554) (Figure 7C).

4. Discussion

LUAD is the most common subtype of lung cancer, representing 35−40% of all cases. The high mortality of LUAD underlies the need for identifying useful prognostic markers that can aid in the prediction of patients' outcome and the development of targeted therapy. The human SSBP1 gene located at chromosome 7q34 encodes a protein that is a subunit of a single-stranded DNA (ssDNA)-binding complex [4]. SSBP1 is involved in many important biological processes, including mitochondrial biogenesis, DNA repair processes, cell cycle, transcription termination, and the maintenance of genomic stability. Although SSBP1 has been implicated in many cancer types such as colorectal cancer and cervical cancer, few studies have evaluated the correlation between SSBP1 and lung cancer. The studies by Chen et al. [9] and Kabbout et al. [10] demonstrated elevated SSBP1 mRNA expression in LUAD samples. Chen et al. [17] found that in clinical lung cancer samples and lung cancer cells lines, SSBP1 was negatively regulated by an Fbxl5-containing Skp1-Cul1-F box E3 ligase. They further showed that down-regulating the expression of SSBP1 by inducing fbxl5 overexpression made A549 cells (non-small cell lung cancer cells) exhibit enhanced radiosensitivity and chemosensitivity. Using a different non-small cell lung cancer cell line (H1299 cells), the study by Wang et al. [18] obtained similar findings. They observed that SSBP1 was a radioresistance-related protein in non-small cell lung cancer. Knockdown of SSBP1 resulted in prolonged G2/M phase arrest, abnormal copy number of mitochondrial DNA and mitochondrial dysfunction, and increased the radiosensitivity of human non-small cell lung cancer cells. In addition, Wang et al. demonstrated that SSBP1 was an important regulator of non-small cell lung cancer cell proliferation and apoptosis; SSBP1 knockdown suppressed H1299 cell proliferation and induced cell apoptosis [18].

In the present study, we found that the mRNA expression of SSBP1 was significantly up-regulated in LUAD samples when compared to normal samples. At the transcriptomic level, SSBP1 was significantly correlated with clinicopathological parameters including age, cancer stage, and nodal metastasis status. Moreover, the expression of SSBP1 was independently correlated with poor prognosis in multivariate Cox regression analysis. The frequency of genetic alterations in the SSBP1 gene was 1.7% among 2670 LUAD patients, and the majority of SSBP1 alterations were represented by amplifications. Survival analysis showed that SSBP1 alterations were correlated with worse prognosis in LUAD. These results suggested that SSBP1 may be a prognostic factor for LUAD.

Our functional enrichment analysis showed that SSBP1 and the genes positively correlating with it were mainly involved in biological processes involving ribosomal large subunit biogenesis, ribosome biogenesis, tRNA metabolic process, tRNA processing, ribonucleoprotein complex biogenesis. Among the six genes showing the the strongest correlation with SSBP1 expression, BUD31, ATP5J2 and SHFM1 were significantly correlated with poor overall survival of LUAD patients. BUD31 is a core spliceosomal protein. It plays an important role in spliceosome pathway and affects focal adhesion and extracellular matrix components [19]. The expression of BUD31 was found to be up-regulated in hepatocellular carcinoma and was essential for cancer cell migration [19,20]. Knockdown of BUD31 dramatically inhibited the proliferation of MYC-driven cancer cells [21]. The ATP5J2 gene encodes a subunit of the mitochondrial proton channel [22]. ATP5J2 knockdown resulted in alterations in ATP synthase assembly and in dimer stability in haploid HAP1 human cells [23]. In addition, ATP5J2 plays a key role in crista morphology and the modulation of permeability transition pore (PTP) [24]. SHFM1 has been shown to participate in various biological processes including DNA repair, genome stability, cell cycle, cell proliferation and cell differentiation. Its expression was up-regulated in some cancers including ovary cancer, breast cancer and head and neck cancer [24]. Tamilzhalagan et al. demonstrated that SHFM1 facilitated gastric carcinogenesis by significantly suppressing p53 activity [25]. SHFM1 was also involved in the activation of MAPK/ERK, Src and PI3K/Akt signaling pathways. Previous experimental data and our survival analysis suggested that these genes may be potential candidates for cancer development. We further evaluated the PPI network of SSBP1 and its correlated genes. Functional annotation including GO and KEGG enrichment analyses suggested that the 10 hub genes of the PPI network were mainly involved in mitochondrion morphogenesis and mismatch repair. Pokrzywinski et al. [26] reported that SSBP1 was critical for the survival of non-small cell lung cancer cells as it was necessary for maintaining mitochondrial DNA stability and mitochondrial homeostasis. Future studies are needed to elucidate the underlying mechanisms by which SSBP1 regulates LUAD development.

In addition to SSBP1 co-expressed genes, we assessed genes with highest frequency in the SSBP1 altered group and their correlation with LUAD prognosis. We found that the top 5 genes with highest frequency in the SSBP1 altered group were DENND11, TAS2R4, TAS2R3, WEE2 and AGK. All of them were positively correlated with poor prognosis. Furthermore, SSBP1 alterations were found to be correlated with the alterations of BRAF and MET, which were oncogenic drivers for LUAD [27].

As an important component of the tumor microenvironment, infiltrating host immune cells are significantly involved in the development, progression, and metastasis of lung cancer [28]. For instance, tumor-infiltrating CD8+ T cells can inhibit cancer cell growth and metastasis [29]. On the contrary, tumour-associated macrophages can suppress the function of CD8+ T cells and promote cancer cell expansion [30]. Elucidating the composition and function of tumor-infiltrating immune cells is an active research area over the past 10 years. In this study, we assessed the correlation between SSBP1 expression and immune infiltration in LUAD. We found that SSBP1 expression was negatively correlated with B cell infiltration level in LUAD. In addition, we found that SSBP1 expression was negatively correlated with the expression of B cell biomarkers including CD79A and CD19. Previous studies demonstrated that tumor-infiltrating B cells could exert anti-tumor immunity by secreting antibodies, enhancing the cytolytic effect of CD8+ T cells, and behaving as regulatory cells, which supports better prognosis for LUAD [31]. Using the TIMER2.0 database, we estimated

the correlation of B cells with LUAD prognosis. The results showed that the high B cell group had considerably better prognosis than the low B cell group. This indicated that the positive correlation between SSBP1 expression and poor LUAD prognosis may partly be owing to a negative correlation of SSBP1 with B cell infiltration level.

5. Conclusions

In summary, we found that SSBP1 expression was up-regulated in LUAD samples and was correlated with clinicopathological features including age, cancer stage, and nodal metastasis status. High SSBP1 expression was significantly correlated with poor prognosis. In addition, there was a negative correlation of SSBP1 expression with B cell infiltration level, CD79A expression and CD19 expression. Among 2670 LUAD patients, the frequency of SSBP1 alterations was 1.7%. LUAD patients with SSBP1 alterations had worse prognosis compared with those unaltered for SSBP1. These results suggested that SSBP1 may be a prognostic marker for LUAD. Future studies are needed to elucidate the underlying mechanisms by which SSBP1 promotes LUAD development.

Acknowledgments

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Conflict of interest

The authors declare there is no conflict of interest.

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