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PTPRC as a Predictive Marker Related to PD-L1 for Prognosis and Immunotherapy Efficacy in LUAD and SKCM

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1. Abstract

1.1. Background: The expression of programmed cell death protein 1 (PD-L1) has been found to be closely related to the efficacy of immunotherapy. The aim of our study is to explore biomarkers associated with PD-L1 expression that might influence the efficacy of immunotherapy.

1.2. Methods: We downloaded transcriptome data and clinical data of lung adenocarcinoma (LUAD) and skin cutaneous melanoma (SKCM) patients from the TCGA database. Differentially expressed genes (DEGs) between the high and low PD-L1 expression groups were identified. Subsequently, univariate Cox regression was performed to pinpoint potential key genes. We then analyzed the relationship between PTPRC expression and immune cell infiltration. Finally, using the GEO database, we determined the predictive value of PTPRC expression for immunotherapy in LUAD and SKCM.

1.3. Results: In this study, we observed that PD-L1 expression did not influence the prognosis of LUAD. However, high expression of PD-L1 was associated with improved prognosis in SKCM. Furthermore, there was no significant correlation between PD-L1 expression and clinical characteristics. By intersecting PD-L1-related DEGs with immune genes, we identified 591 immune-related DEGs. Using univariate COX regression analysis, we screened and identified PTPRC, CYBB, ICOS, and TRAV21. PTPRC expression was higher in normal tissues and exhibited a significant positive correlation with PD-L1. Additionally, Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) analyses indicated that genes related to PTPRC were predominantly enriched in immune-related pathways. Patients with high PTPRC expression displayed heightened sensitivity to immunotherapy and had a more predictive value for prognosis than PD-L1.

1.4. Conclusions: Our research indicated that PTPRC is a gene associated with PD-L1 expression. High expression of PTPRC in SKCM and LUAD is predictive of longer survival and increased sensitivity to immunotherapy.

2. Introduction

Over the past few decades, the incidence of skin cutaneous melanoma (SKCM) has been on the rise worldwide, making it one of the most aggressive and alarming types of skin cancer [1]. Recent research on advanced SKCM indicates that targeted therapy can significantly enhance the prognosis; however, the 5-year survival rate remains low [2-4]. Lung adenocarcinoma (LUAD) represents a primary histological subtype of lung cancer, accounting for approximately 60% of all lung cancer cases [5]. While targeted therapy has notably improved the progression-free survival (PFS) for LUAD patients with EGFR mutations, the overall survival (OS)

remains less than optimal [6-8]. Consequently, there is an imperative need to identify new biomarkers and potential biological targets to improve the prognosis for both SKCM and LUAD.

The emergence of immunotherapy, particularly immune checkpoint inhibitors, has dramatically transformed the landscape of cancer treatment. Immunotherapy works by enhancing or restoring the patient's immune system to target and eliminate cancer cells [9]. With the advent of the immunotherapy era, immune checkpoint inhibitors first achieved remarkable success in treating lung cancer and melanoma, boasting both high efficacy and minimal toxicity [10-12]. These inhibitors have revolutionized the approach to tumor treatment and can even be applied in both preoperative neoadjuvant therapy and postoperative adjuvant therapy [13-15]. While numerous studies have shown that PD-L1 expression and tumor mutation burden (TMB) can somewhat predict the efficacy of immunotherapy, their predictive value is not consistently reliable [16,17]. Hence, the discovery of novel biomarkers is essential to better predict the outcomes of immunotherapy.

Protein tyrosine phosphatase receptor type C (PTPRC) is a transmembrane protein, which is considered to be an important regulator of T cell and B cell antigen receptor-mediated activation and plays a vital role in the innate immune system18. PTPRC controls immune function by regulating lymphocyte survival, cytokine response and phosphorylated T cell receptor complex (TCR) signal transduction [19]. Increasing evidence suggests that PTPRC can modulate the immune system's signaling pathways. As a result, it has been explored as a therapeutic target for various immune diseases [20,21]. However, no research currently demonstrates whether PTPRC can serve as a biomarker to predict immunotherapy responses.

The aim of this study is to identify immunotherapy biomarker associated with PD-L1 expression. We obtained transcriptome data and clinical characteristics of LUAD patients and SKCM patients from the TCGA database. We identified PD-L1 related DEGs, and used univariate Cox regression analysis to screen the candidate gene-PTPRC. Furthermore, we assessed the predictive value of PTPRC for immunotherapy response in SKCM and LUAD immunotherapy cohorts.

3. Methods

3.1. Extraction of Data

We collected transcriptome profiles (HTSeq Fragments Per Kilobase of transcript per Million mapped reads [FPKM]) and clinical data for SKCM (471 tumor samples and 1 healthy sample) and LUAD samples (535 tumor samples and 59 healthy samples) from The Cancer Genome Atlas (TCGA) database (https://portal.gdc.cancer.gov/). Additionally, transcriptome data and clinical data for LUAD (GSE126044, GSE93157) and SKCM (GSE93157) immunotherapy cohorts were obtained from the GEO database (https://www.ncbi.nlm.nih.gov/geo/).

3.2. Associations of PD-L1 Expression with Survival And Clinical Features

The samples were divided into two groups based on the median gene expression. OS served as the primary prognostic endpoint, and survival curves were generated using the "survival" and "survminer" R packages. We used the log-rank test to compare the subgroups, considering a p value < 0.05 as significant. Additionally, the Kruskal-Wallis rank sum test was employed to assess the associations between gene expression and TNM staging, utilizing the "ggpubr" R package.

3.3. Identification of PD-L1 Related DEGs

Differentially expressed genes (DEGs) were identified between the groups with high and low PD-L1 expression. We used the "limma" R package to perform the differential expression analysis. Statistically significant DEGs were defined defined as $|\log2FC|>1$ and a false discovery rate (FDR) <0.05. The results were plotted in heatmaps using the "pheatmap" R package. We intersected DEGs with immune genes to obtain immune-related DEGs.

3.4. Univariate COX Regression Analysis

To identify which of the immune-related DEGs were associated with survival in both SKCM and LUAD, we used the "survival" R package to perform a univariate Cox regression analysis. From our analysis, the genes PTPRC, CYBB, ICOS, and TRAV21 were screened. Of these, the target gene PTPRC was selected for further study. We used the Kaplan-Meier analysis to generate the survival curve. $p<0.05$ was considered significant difference

3.5. PTPRC Differential Expression and Survival Analysis

We used GEPIA2 to compare the mRNA expression of PTPRC between LUAD tumor tissues and normal tissues. Additionally, we determined the correlation between PTPRC expression and PD-L1 using GEPIA2. Survival analysis based on low and high PTPRC expression was performed using the "survival" R package. The "ggpubr" R package was employed to analyze the relationship of PTPRC expression with age, sex, T stage, N stage, and M stage.

3.6. Enrichment Analysis

We intersected the DEGs related to PTPRC in both SKCM and LUAD to identify common DEGs. These genes were subsequently subjected to Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis and Gene Ontology (GO) functional enrichment analysis. We used the "clusterProfiler", "enrichplot", and "ggplot2" R packages for the enrichment analyses ($p < 0.05$, $q < 0.05$). The results were then visualized using bubble diagrams.

3.7. PTPRC Expression and Immune Cells Infiltration

The Tumor Immune Estimation Resource (TIMER) was used to evaluate the relationship between the expression of PTPRC and the infiltration of B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells in SKCM and LUAD, respectively.

3.8. PTPRC Expression and Immunotherapy

We obtained gene expression profiles and clinical data for LUAD (GSE126044, GSE93157) and SKCM (GSE93157) immunotherapy cohorts from GEO. Patients were stratified into high and low expression groups based on PTPRC and PD-L1 expression levels. We then compared the immunotherapy efficacy between these groups.

4. Results

4.1. Analysis Process of Patients and Data Sets

The flow chart summarizing our study was shown in Figure 1. We downloaded transcriptome profiles and clinical data of SKCM (471 tumor samples and 1 healthy sample) and LUAD samples (535 tumor samples and 59 healthy samples) from the TCGA database. We identified DEGs between groups with low and high PD-L1 expression. Using univariate Cox regression analysis on immune-related DEGs, we identified hub genes, including PTPRC, CYBB, ICOS, and TRAV21. Subsequently, we conducted a detailed analysis of PTPRC, encompassing its expression, survival, enrichment analysis, clinical characteristics, and its correlation with immune cell infiltration. We evaluated the immunotherapy predictive value of PTPRC using GEO datasets (LUAD: GSE126044, GSE93157; SKCM: GSE93157).

4.2. PD-L1 Expression Was Associated with SKCM Patients' Prognosis

Based on the median expression of PD-L1, the SKCM and LUAD patients were divided into two groups: high PD-L1 expression and low PD-L1 expression. We evaluated the associations between PD-L1 expression and the overall survival (OS) of SKCM and LUAD patients by constructing K-M survival curves. PD-L1 expression was not significantly associated with LUAD patients' OS ($p= 0.593$, Figure 2A). However, SKCM patients with high PD-L1 expression had a longer OS ($p < 0.001$, Figure 2B). These results suggest that PD-L1 expression is a potentially positive factor affecting the prognosis of SKCM patients.

4.3. Associations of PD-L1 Expression with Clinical Characteristics Among LUAD And SKCM Patients

We obtained clinical data from the TCGA database and analyzed the correlation between PD-L1 expression and various factors, including age, gender, T stage, N stage, M stage, and clinical stage, for both SKCM and LUAD patients. As depicted in Figure 3, there was no significant relationship between PD-L1 expression and most of these factors. However, male LUAD patients had lower PD-L1 expression compared to females (Figure 3A), and T stage was negatively correlated with PD-L1 expression in SKCM patients (Figure 3B). In summary, our findings indicate a lack of significant association between PD-L1 expression and several clinical features, particularly age, N stage, M stage, and clinical stage.

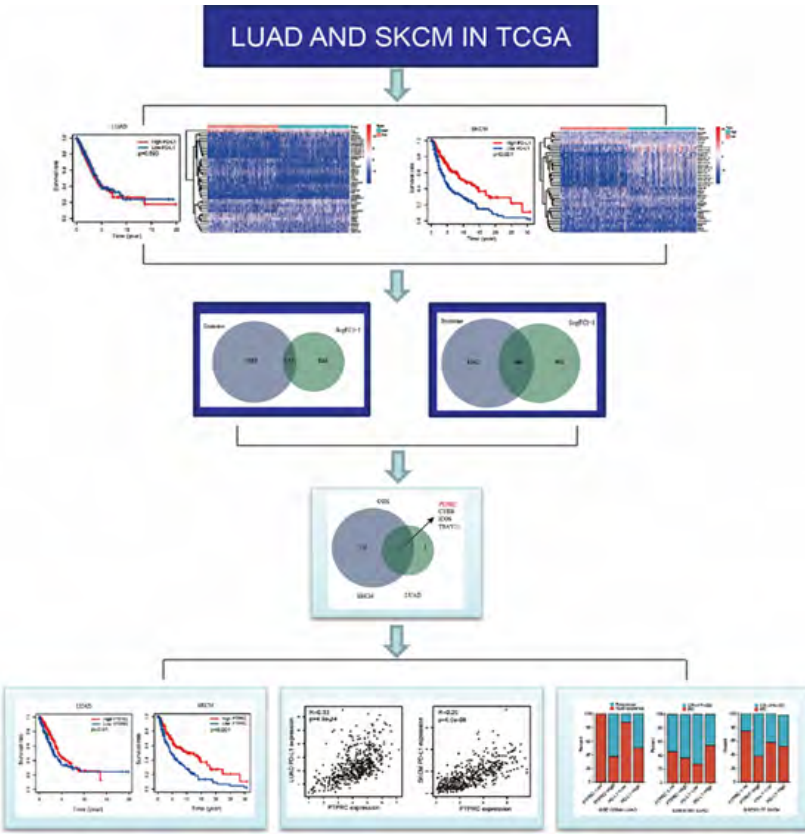

Figure 1: Analytical flowchart of this study.

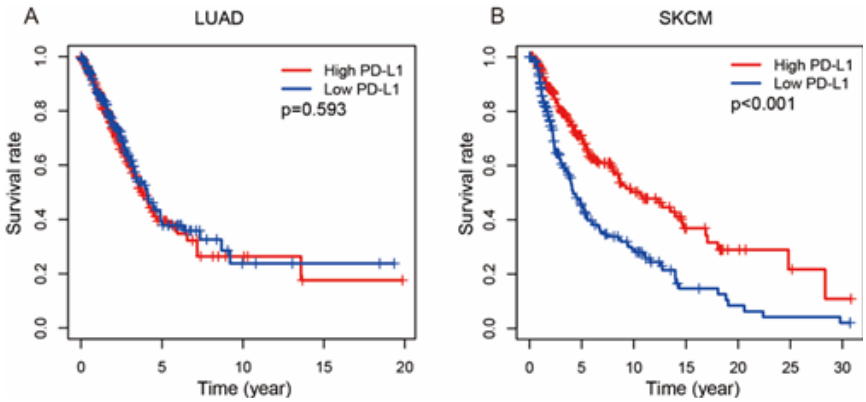

Figure 2: Associations of PD-L1 expression with survival among LUAD (A) and SKCM (B) patients.

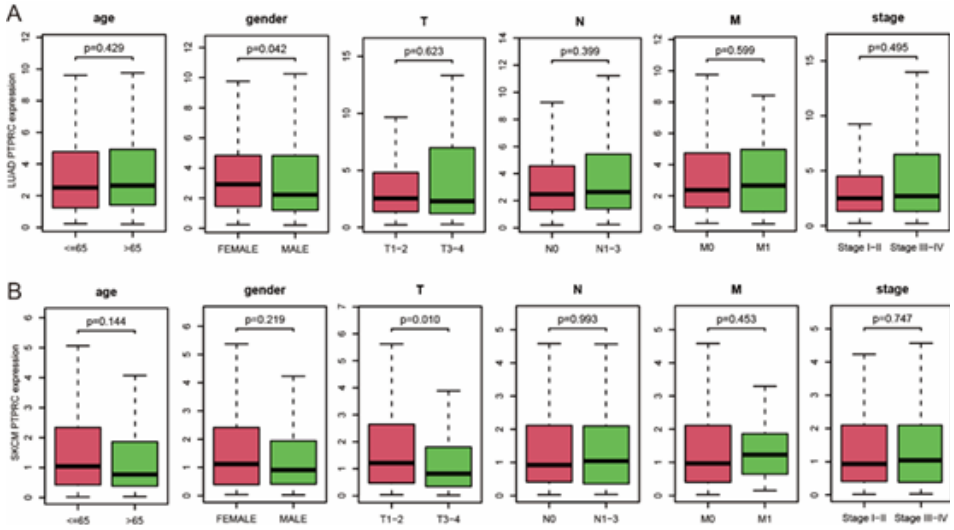

Figure 3: Associations of D-L1 expression and clinical characteristics in LUAD (A) and SKCM (B).

4.4. DEGs Between the High and Low PD-L1 Expression Groups Among LUAD And SKCM Patients

To analyze gene expression profiles related to PD-L1 DEGs in LUAD and SKCM patients, we categorized patients based on high or low PD-L1 expression. The PD-L1 related DEGs for both LUAD and SKCM were visualized in heatmaps (Figure 4A, C), with 968 genes found in LUAD and 1430 in SKCM (Figure 4B, D). By intersecting the PD-L1 related DEGs with immune genes, we identified 591 immune-related DEGs (Figure 4B, D). A univariate analysis highlighted 224 genes in SKCM and 7 in LUAD as being associated with prognosis (Figure 4E). Intersection analysis of these gene sets revealed 4 common genes: PTPRC, CYBB, ICOS, and TRAV21. We then honed in on the key gene, PTPRC. Survival analysis indicated that LUAD (p=0.01, Figure 4F) and SKCM (p<0.001, Figure 4G) patients with high PTPRC expression had longer overall survival (OS) than those with low expression.

4.5. Associations of PTPRC Expression with Clinical Characteristics

In both normal tissues and paired tissues (derived from the same patient) of LUAD patients, PTPRC expression was significantly higher than in tumor tissues (p<0.001 for both, Figure 5A). Unfortunately, we could not compare PTPRC expression between melanoma tumor tissue and its adjacent normal tissue due to the absence of such data in the TCGA database. We utilized a scatter plot to depict the relationship between PD-L1 and PTPRC expressions in LUAD and SKCM. This plot revealed a significant positive correlation between PTPRC and PD-L1 expression (Figure 5B-C). Further analysis showed that in LUAD, PTPRC expression negatively correlated with T stage and clinical stage (Figure 5D). Similarly, PTPRC expression in SKCM was negatively associated with age and T stage (Figure 5E). In conclusion, PTPRC expression positively correlates with PD-L1 expression but negatively correlates with T stage.

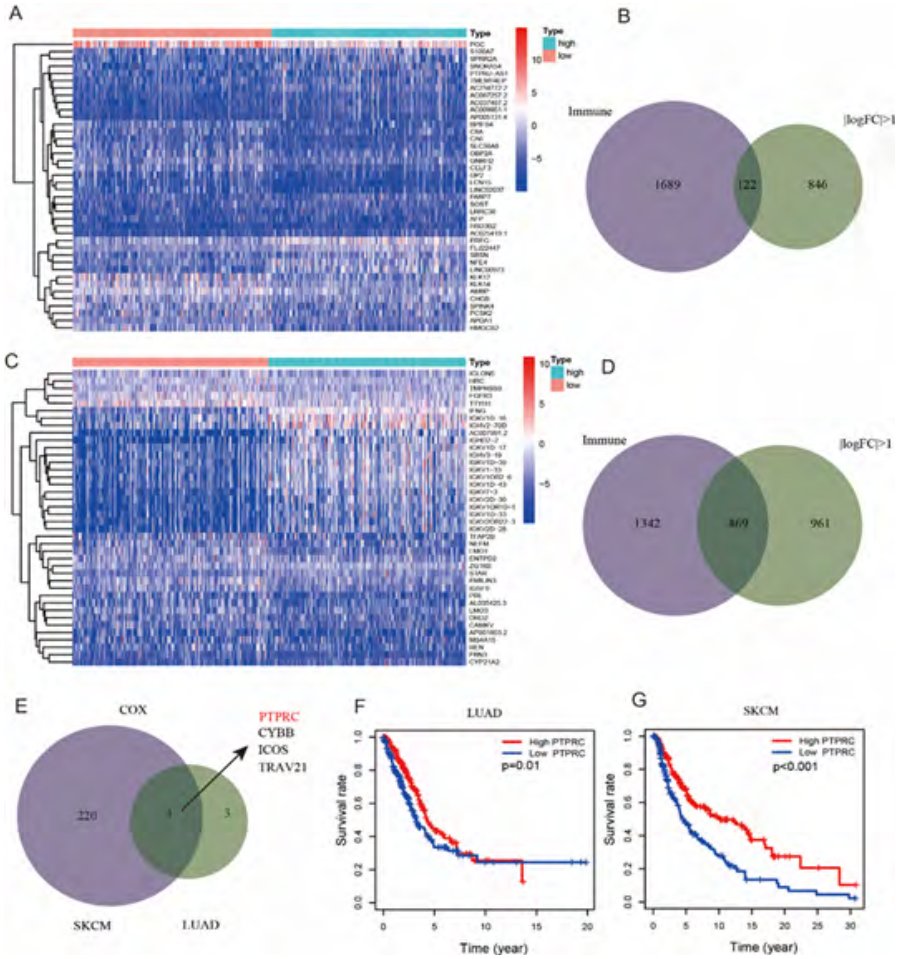

Figure 4: (A) Heatmap of DEGs generated in LUAD. (B) Venn diagram of the intersection between immune genes and DEGs in LUAD. (C) Heatmap of DEGs generated in SKCM. (D) Venn diagram of the intersection between immune genes and DEGs in SKCM. (E) Venn diagram of the intersection between prognostic related genes in LUAD and SKCM. (F) Survival analysis of LUAD patients with low and high PTPRC expression (based on median expression) in the TCGA database (p=0.01). (G) Survival analysis of SKCM patients with low and high PTPRC expression (based on median expression) in the TCGA database (p<0.001).

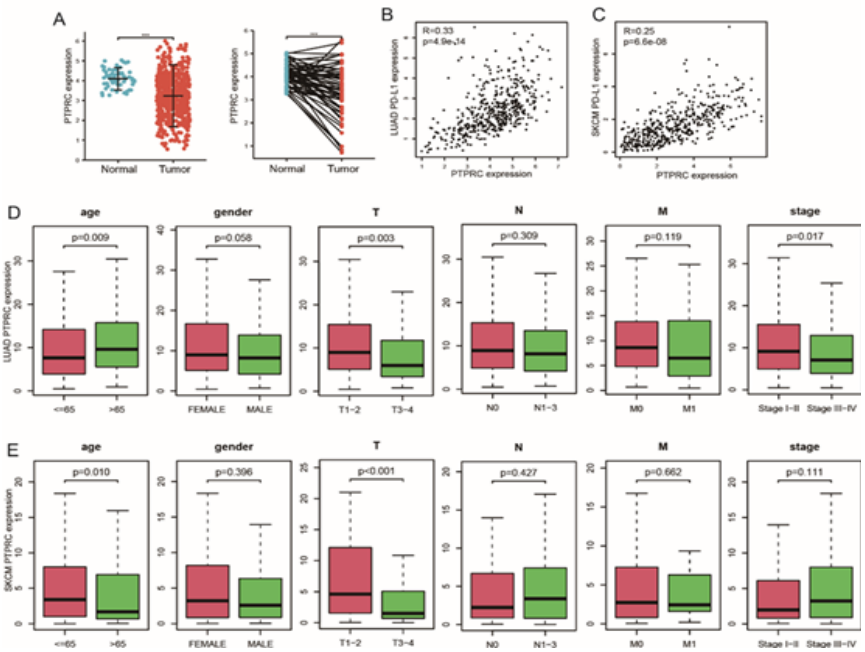

Figure 5: (A) PTPRC expression in LUAD tumor tissues compared to normal tissues. (B-C) Correlation between PD-L1 and PTPRC expression in LUAD and SKCM. (D-E) Correlation analysis of PTPRC expression with clinical characteristics in LUAD and SKCM.

4.6. Functional Enrichment Analysis of PTPRC Expression Related DEGs

We identified DEGs related to PTPRC expression, comprising 1,403 genes from LUAD (1,287 up-regulated and 116 down-regulated) and 1,733 genes from SKCM (1,613 up-regulated and 120 down-regulated). Intersection analysis of these genes revealed 731 up-regulated and 8 down-regulated genes shared between both sets (Figure 6A-B). Subsequent functional enrichment analysis on the shared DEGs indicated that, based on gene ontology (GO) analysis, these genes were predominantly involved in immune responses, such as activating cell surface receptors, signaling pathways, lymphocyte-mediated immunity, and humoral immune responses (Figure 6C). The Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis revealed that these DEGs were mainly enriched in pathways like cytokine-cytokine receptor interaction, chemokine signaling, hematopoietic cell lineage, and B cell receptor signaling (Figure 6D).

4.7. Correlation of PTPRC Expression with Immune Cells Infiltration And Immunotherapy Response

To further explore the interaction between PTPRC expression and the tumor microenvironment (TME), we examined tumor-infiltrating immune cells in LUAD and SKCM samples using TIMER2. Our correlation analysis revealed that PTPRC expression was significantly positively correlated with the infiltration of various immune cells, including B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells (Figure 7A). These findings suggest that PTPRC plays a pivotal role in influencing the immune state of both SKCM and LUAD.

Moreover, we assessed the differences in PTPRC and PD-L1 expression in relation to immunotherapy response. Notably, patients with high PTPRC expression demonstrated a significant response to immunotherapy. As illustrated in Figure 7B-D, a high PTPRC expression correlates with a higher immunotherapy response rate compared to high PD-L1 expression. Conversely, low PTPRC expression correlates with a lower response rate to immunotherapy compared to low PD-L1 expression. In conclusion, PTPRC expression is strongly linked with immunotherapy response and appears to have greater predictive value than PD-L1 expression.

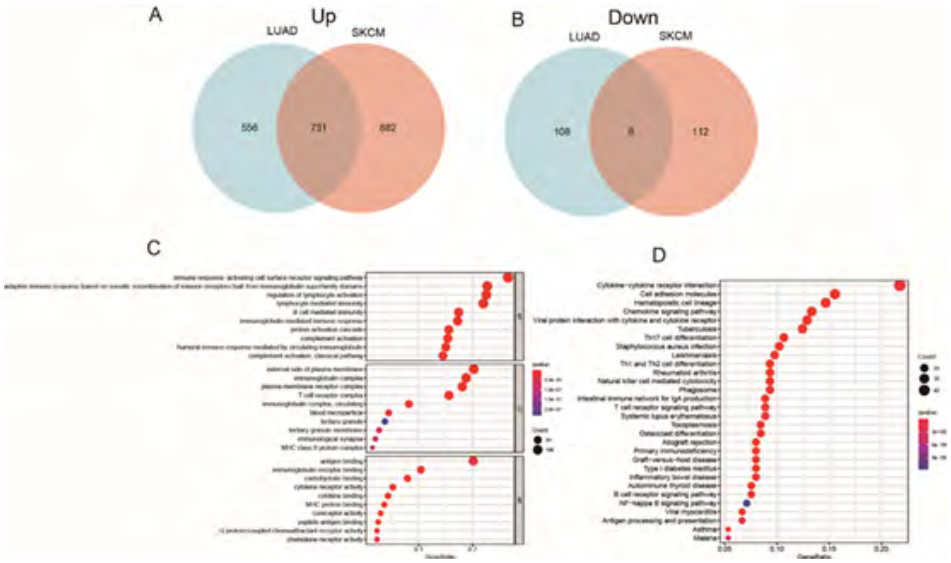

Figure 6: (A) Venn plots showing the shared up-regulated DEGs between LUAD and SKCM. (B) Venn plots showing the shared down-regulated DEGs between LUAD and SKCM. (C-D) GO and KEGG enrichment analyses of the shared DEGs.

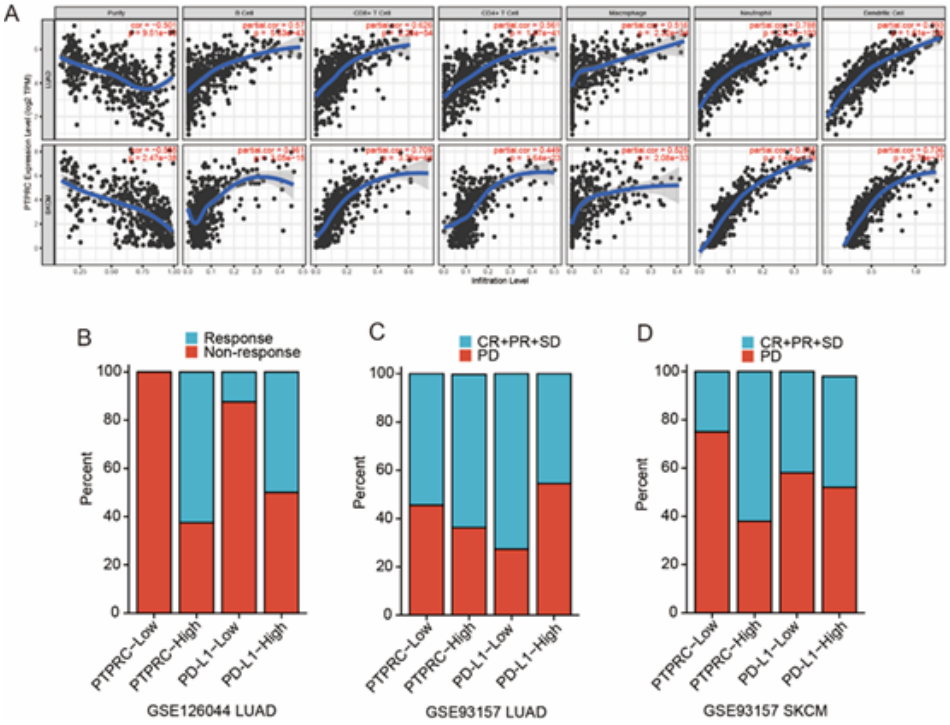

Figure 7: (A) Scatter plots illustrating the correlation between the proportions of six types of immune cells and PTPRC expression in LUAD and SKCM. (B-D) Differences in PTPRC and PD-L1 expression in relation to immunotherapy response.

5. Discussion

While PTPRC has been recognized as a pan-leukocyte marker and is involved in the immune response-activating cell surface receptor signaling pathway, its precise role in cancer and the TME remains uncertain. Studies comparing PTPRC expression in metastatic and primary tumors have suggested that increased PTPRC expression is linked to colorectal cancer metastasis22. Furthermore, PTPRC expression was found to be significantly down-regulated in non-small cell lung cancer and Parkinson's disease23,24. In other tumor types, higher PTPRC expression appears to correlate with a better prognosis, suggesting that PTPRC might play varying roles across different tumors 25,26. Our study revealed that PTPRC expression in tumor tissues was notably lower than in normal tissues, and patients with elevated PTPRC expression experienced longer OS. Further analyses demonstrated a significant positive correlation between PTPRC expression and immune cell infiltration within the TME. Additionally, a high PTPRC expression was linked to a more favorable response to immunotherapy. Collectively, these findings imply that PTPRC plays a role in shaping the TME and might act as both a prognostic marker and an immunotherapy biomarker for SKCM and LUAD.

The immune checkpoint inhibitor has achieved notable success in tumor treatment, most tumors utilize PD-L1 as a predictor of immunotherapy response27,28. While PD-1/PD-L1 blockade therapy offers significant clinical benefits for various cancer types, the response rates remain below 40%29. PTPRC is expressed in nearly all hematopoietic cells and serves as a vital regulator of B cell and T cell antigen receptor-mediated activation18,30. It is one of the most prevalent proteins in the T cell plasma membrane. Its activity is crucial for the normal function of immune cells, acting as a signaling gatekeeper in T cells31,32. The role of the TME in tumorigenesis and cancer progression has been elucidated recently33,34. Immune components within the TME can mediate anti-tumor effects, and studies have highlighted a correlation between TME and immunotherapy response35,36. Our study reveals that PTPRC is linked with immune cell infiltration and can serve as an indicator of TME status in SKCM and LUAD, consistent with prior research37. We further examined the relationship between PTPRC and PD-L1 expression in immunotherapy. Our findings affirm that high PTPRC expression suggests an augmented response to immunotherapy and offers a more potent predictive value than high PD-L1 expression alone. Therefore, PTPRC significantly influences the efficacy of immunotherapy in SKCM and LUAD patients and, subsequently, the prognosis of these diseases.

In summary, our findings suggest a close relationship between PTPRC and PD-L1 expression that affects both prognosis and the infiltration of immune cells. Specifically, high expression of PTPRC enhances the sensitivity of immunotherapy in SKCM and LUAD patients. PTPRC high expression can serve as a biomarker to predict the response to immunotherapy, offering a novel therapeutic target for both LUAD and SKCM.

6. Author Contributions

Kunwei Peng: original idea, manuscript writing. Deyi Liu: data acquisition and analysis, prepared the fgures and tables. Huaxing

Huang: manuscript editing. Haifeng Song and Jun Dong: project development, manuscript editing. All authors read and approved the final manuscript.

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