PTPN14 remodels the inflammatory immune microenvironment of clear cell renal cell carcinoma by inhibiting the β-catenin signaling pathway

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Abstract

The occurrence and progression of kidney renal clear cell carcinoma (KIRC) are closely associated with chronic inflammation triggered by tissue injury. PTPN14 is a protein tyrosine phosphatase that is closely related to cell adhesion linkage and proliferation. In this study, we found that PTPN14 is lowly expressed in tumors from patients with KIRC, whereas upregulation of its expression can significantly reduce the infiltration of inflammatory factors in the tumor immune microenvironment of KIRC and markedly prolong the survival of patients with KIRC. Mechanistic investigations showed that PTPN14 expression is positively correlated with that of cell adhesion–related proteins (TGFBR1 and CTNNB1), thereby promoting cell adhesion junctions and tissue repair, while inhibiting activation of the β-catenin signaling pathway and consequently suppressing the expression of inflammatory factors driven by this pathway. This study, for the first time, reveals that PTPN14 functions as a central regulatory node that, by integrating tissue adhesion capacity and restraining inflammatory responses, significantly improves the local tumor immune microenvironment and provides a new potential therapeutic target for KIRC.

Full Text

PTPN14 Reshapes the Inflammatory Immune Microenvironment of Kidney Renal Clear Cell Carcinoma by Inhibiting the β-catenin Signaling Pathway

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Abstract

Kidney renal clear cell carcinoma (KIRC) development is closely associated with chronic inflammation triggered by tissue injury. PTPN14 is a protein tyrosine phosphatase linked to cell adhesion and proliferation. This study reveals that PTPN14 is expressed at low levels in KIRC tumors, while its upregulation significantly reduces inflammatory cytokine infiltration in the tumor immune microenvironment and markedly extends patient survival. Mechanistic investigations demonstrate that PTPN14 expression positively correlates with cell adhesion-associated proteins (TGFBR1 and CTNNB1), promoting cell adhesion junction formation and repair while simultaneously inhibiting β-catenin signaling pathway activation, thereby suppressing inflammation factor expression driven by this pathway. Our findings identify PTPN14 as a core regulatory node that significantly improves the local immune microenvironment by integrating tissue adhesion capacity and curbing inflammatory responses, offering a novel potential therapeutic target for KIRC.

Introduction

Kidney renal clear cell carcinoma (KIRC) represents the predominant subtype of renal cell carcinoma, and its pathogenesis is intimately linked to a chronic inflammatory microenvironment (1). Tissue damage disrupts the physical cellular barrier and initiates inflammatory responses. When tissue injury remains unresolved, persistent inflammation can transform into a dysregulated chronic state that becomes a critical tumor-promoting factor (2). During the initial inflammatory phase, various pro-inflammatory cytokines (such as IL-6 and IL-1β) and chemokines (such as CXCL8) recruit macrophages and other immune cells to eliminate pathogens, facilitate tissue repair, and suppress tumor growth —representing a protective mechanism for maintaining homeostasis. However, a chronically inflamed microenvironment induces functional exhaustion of cytotoxic CD8+ T cells and synergizes with the accumulation of immunosuppressive cells, collectively reshaping the tumor microenvironment (TME) and influencing disease progression (3). In summary, extensive crosstalk exists among inflammatory signaling pathways, tissue repair mechanisms, and the immune microenvironment, forming complex feedback loops that constitute a core regulatory network influencing ccRCC development from initiation to progression.

PTPN14 is a non-receptor tyrosine phosphatase localized at epithelial cell adhesion junctions. Studies have shown that lipopolysaccharide (LPS) stimulation of PTPN14 expression promotes restoration of intercellular junctions and repair of endothelial barrier function (4). PTPN14 mutations correlate with progression in multiple cancers, and PTPN14 deficiency leads to developmental defects and lymphedema phenotypes (5). These findings suggest that PTPN14 not only participates in tissue repair processes but may also possess important regulatory functions in the immune microenvironment. Based on this evidence, we propose the scientific question: What is the role and mechanism of PTPN14 in KIRC?

Our study demonstrates that high PTPN14 expression significantly extends survival in KIRC patients. Concurrently, elevated PTPN14 expression promotes infiltration of immunosuppressive cells while reducing levels of key pro-inflammatory factors such as CCL5. These results indicate that PTPN14 may reduce inflammation by repairing cellular structures, thereby reshaping the immune microenvironment and improving patient outcomes. Although we have observed associations between PTPN14 and specific immune phenotypes, the precise molecular mechanisms mediating this remote regulation within tumor cells require further elucidation.

Results

1: PTPN14 Functions as a Tumor Suppressor in Kidney Renal Clear Cell Carcinoma

To investigate the impact of PTPN14 expression on patient survival in KIRC, we first analyzed survival data, cancer stage, and tumor grade using the TISIDB database. In pan-cancer analyses from TISIDB, we identified non-receptor protein tyrosine phosphatase 14 (PTPN14) as a potential protective factor in kidney renal clear cell carcinoma. Survival analysis revealed that high PTPN14 expression is strongly associated with significantly improved overall survival in KIRC patients, an effect that is the most pronounced among all analyzed cancer types (Figure 1 [Figure 1: see original paper]A, D).

We further examined the relationship between PTPN14 expression and clinicopathological features. In KIRC, PTPN14 expression showed significant negative correlations with both cancer stage (Figure 1B, E) and tumor grade (Figure 1C, F) (Stage: rho = -0.162, p = 0.00018; Grade: rho = -0.124, p = 0.00436). These findings indicate that KIRC tumors with high PTPN14 expression tend to present at earlier pathological stages and lower cellular grades, reflecting relatively lower malignant progression and invasiveness. Collectively, these results reveal that PTPN14 likely confers survival benefits by inhibiting KIRC progression and malignant transformation, establishing it as a promising prognostic biomarker.

2: High PTPN14 Expression Attenuates Pro-inflammatory Immune Cell Infiltration

The tumor immune microenvironment represents a central determinant of cancer progression, therapeutic response, and clinical outcomes. To further explore the underlying factors linking high PTPN14 expression to improved survival in KIRC patients, we comprehensively analyzed the correlation between PTPN14 expression and immune cell infiltration within the tumor immune microenvironment (TIM). We first evaluated associations between PTPN14 expression and six defined immune subtypes. As shown in Figure 2 [Figure 2: see original paper]A, PTPN14 expression correlated with all six subtypes, including C1 (wound healing), C2 (IFN-γ dominant), C3 (inflammatory), C4 (lymphocyte de-

pleted), C5 (immunologically quiet), and C6 (TGF-β dominant). Notably, the correlation coefficients were relatively higher in C1, C3, and C6 subtypes, suggesting that PTPN14 expression may be closely associated with wound healing, inflammatory responses, and TGF-β-related immune microenvironments.

When analyzing the relationship between PTPN14 and specific lymphocyte subset infiltration levels, we observed a noteworthy phenomenon: PTPN14 expression exhibited significant negative correlations with cytotoxic CD8+ T cells and NK cell subsets (including CD56bright and CD56dim cells). Conversely, PTPN14 expression showed significant positive correlations with various immunosuppressive or regulatory cells, including regulatory T cells (Treg), type 2 helper T cells (Th2), and memory B cells (Mem B) (Figure 2B). To seek molecular explanations, we examined correlations between PTPN14 and key immune modulators. The results demonstrated significant negative correlations between PTPN14 expression and multiple immune factors, including HLA-A, HLA-F, CD160, LAG3, PVRL2, CD274 (PD-L1), IL2LA, CCR4, CSF1R, and HLA-E (Figure 2C, 2D). Downregulation of HLA-A and HLA-F may impair tumor cell antigen presentation, potentially suppressing recognition and attack by killer immune cells (4).

3: Elevated PTPN14 Expression Inhibits Inflammatory Cytokine Secretion

Inflammatory signals recruit diverse immune cells for post-damage cleanup and repair. Known initial innate activation triggers secretion of inflammatory, regenerative, and anti-inflammatory cytokines, subsequently activating adaptive immune responses against tumors. The immunosuppressive microenvironment changes induced by PTPN14 expression are likely mediated by secreted inflammatory factors. Therefore, we further analyzed correlations between PTPN14 and inflammatory factor expression.

Analysis of PTPN14 gene correlations in KIRC using the cBioPortal database revealed significant negative correlations with the following inflammation-associated factors: CXCL12, CXCL2, CCL15, IL32, IL10RB, IL34, IL15RA, IL17RC, and IL15 (Figure 3 [Figure 3: see original paper]A). CXCL12 recruits T cells, dendritic cells, and B cells, promoting immune cell infiltration and inflammation establishment. CXCL2 chemoattracts neutrophils, participating in acute inflammatory responses and associating with various immunosuppressive molecules (5). CCL15 chemoattracts monocytes and T cells, participating in chronic inflammation and tumor-associated inflammatory responses (6). IL32 is a pro-inflammatory factor that activates NF-κB and TNF-α pathways, enhancing inflammatory responses (7). The negative correlations between PTPN14 and these factors suggest its role in suppressing pro-inflammatory signals or regulating immune activation thresholds.

4: PTPN14 Function Enriches in WNT-Mediated Cell Adhesion Regulation Pathways

To further explore the mechanism by which PTPN14 regulates inflammatory factor reduction, we analyzed the specific functions enriched in the PTPN14 transcriptome in KIRC tumors. First, analysis using the TIMER3 database revealed decreased PTPN14 expression in KIRC (Figure 4 [Figure 4: see original paper]A). Transcriptomic GO analysis demonstrated that PTPN14 function primarily enriches in epidermal growth factor response, protein dephosphorylation, and cell adhesion junctions, while KEGG analysis additionally revealed enrichment in cytoskeleton and adhesion junctions, particularly in the WNT signaling pathway (Figure 4B, C). Published literature reports that PTPN14 regulates cell adhesion junctions by dephosphorylating β-Catenin (8,9). PTPN14 shows significant positive correlation with TGFBR1 (Figure 4D), and PTPN14 can influence TGFbeta-mediated epithelial-mesenchymal transition (10). Immunohistochemistry of PTPN14 in KIRC tumor tissues revealed predominant expression near the cell membrane (Figure 4E), indicating that PTPN14 likely reshapes cytoskeleton and cell microenvironment adhesion through the Wnt signaling pathway, continuously regulating mesenchymal and epidermal growth and repair. Since PTPN14 is a tyrosine phosphatase capable of dephosphorylating β-Catenin, we hypothesize that PTPN14 blocks Wnt signaling pathway activation, thereby preventing β-Catenin nuclear translocation and affecting the transcription of related inflammatory factors.

5: PTPN14 Regulates Inflammatory Factor Expression by Inhibiting the WNT/β-catenin Signaling Pathway

To further validate the mechanism by which PTPN14 regulates inflammatory factor expression through the Wnt pathway, we first analyzed correlations between PTPN14 and key pathway factors as well as critical transcriptional regulators using TCGA transcriptomic data. As shown in Figure 5 [Figure 5: see original paper]A, PTPN14 positively correlates with CTNNB1, while β-Catenin-binding transcription factors TCF3/4 show significant positive correlations with multiple inflammatory factors and immune proteins (Figure 5B). Further confirmation using the STRING database identified CTNNB1 as a significant protein interaction partner of PTPN14 (Figure 5C).

To experimentally validate PTPN14 regulation of the Wnt signaling pathway, we suppressed PTPN14 using siRNA in KIRC cells and detected changes in β-Catenin phosphorylation. Western blot experiments showed enhanced β-Catenin phosphorylation following PTPN14 inhibition, demonstrating that PTPN14 drives β-Catenin dephosphorylation. Concurrently, immunofluorescence revealed significantly reduced nuclear localization of β-Catenin after PTPN14 inhibition, indicating that PTPN14 suppression impedes β-Catenin nuclear entry and inhibits its transcriptional activity. Through these analyses, we demonstrate that PTPN14 likely affects inflammatory factor expression by modulating the Wnt signaling pathway.

Discussion

Inflammation predisposes to cancer and promotes all stages of tumor development. Cancer cells, together with surrounding stroma and inflammatory cells, form an inflammatory tumor microenvironment (TME) through coordinated reciprocal interactions (11). Kidney renal clear cell carcinoma (KIRC) is an inflammation-associated cancer, with chronic inflammation recognized as a core driver of KIRC initiation and progression (12). Inflammation induces immune microenvironment imbalance throughout tumor evolution and serves as a potential KIRC biomarker (13).

Post-injury inflammation initially recruits immune cells capable of tumor clearance, but as it becomes chronic, it "educates" the immune system into a tumor-promoting, protective state (14). Plasticity can be manifested by different cell types at various tumor developmental stages, with inflammation-activated cancer-associated fibroblasts (CAFs) driving TME plasticity (15). CTNNB1, as the core of adhesion junctions, is fundamental for maintaining epithelial tissue integrity and polarity. Loss of CTNNB1 function dissolves cell junctions, leading to tissue disorganization and barrier failure. Cells at wound edges require rapid migration and proliferation to cover the lesion. Extensive crosstalk exists between tissue repair and inflammatory signaling. CTNNB1 maintains intercellular connections while its activated signaling pathway directly drives expression of various cell inflammation-related factors (16), recruiting immune cell infiltration to form a constantly evolving immune microenvironment.

The tissue repair process alleviates inflammatory responses and re-establishes tissue homeostasis. PTPN14 primarily localizes at intercellular junctions of the monolayer, where it not only regulates cell adhesion but also functions as a tyrosine phosphatase essential for cell integrity (17). Typically, cancer stage (Stage I, II, III, IV) represents ordinal data. Analysis revealed a weak but statistically significant negative correlation between PTPN14 expression and cancer stage (rho = -0.162, p = 0.00018). Higher PTPN14 expression is associated with lower pathological stage (tumors more localized without widespread invasion or metastasis). Although the correlation is modest (absolute rho value of only 0.162), the trend is highly significant (extremely small p-value). This perfectly aligns with survival analysis results: earlier stage correlates with better prognosis, and high PTPN14 expression associates with both earlier stage and improved outcomes. Similar to stage analysis, the negative correlation between PTPN14 expression and tumor grade in KIRC is also among the most significant (p = 10^-2.3, approximately 0.005). Again, this represents a negative correlation (rho = -0.124). Tumor grade measures cancer cell malignancy (e.g., G1, G2, G3, G4, with higher grades indicating greater malignancy). Higher PTPN14 expression correlates with lower tumor grade (better differentiation, lower malignancy). This represents another weak but significant correlation. Lower grade indicates less aggressive tumors, which again aligns with better patient survival rates.

High PTPN14 expression reconstructs cell adhesion and cytoskeleton by de-

phosphorylating the adhesion protein β-catenin. This makes dephosphorylated β-catenin unable to enter the nucleus when Wnt signals arrive, thereby suppressing its transcriptional regulation of downstream inflammatory factors. Changes in β-catenin and cell adhesion subsequently affect TGF-β, jointly shaping cell repair and immunosuppressive microenvironments (10). PTPN14 may precisely drive the phenotypic switch from an "inflammatory state" to an "immunosuppressive/tissue repair state" by synergizing with the β-catenin signaling pathway. This manifests as downregulation of inflammatory drivers such as CXCL12, CXCL2, CCL15, and IL32, while upregulating immunosuppressive molecules like CD274. The positive correlation between PTPN14 expression and CCR4 suggests that cancer cells with high PTPN14 expression recruit Treg cells. PTPN14 does not directly recruit Tregs but rather creates a microenvironment rich in Treg chemokines by modulating cancer cell behavior, thereby stabilizing tissue morphology and inflammatory regulation and improving overall survival in KIRC patients.

Materials and Methods

1. Survival, Cancer Stage, Tumor Grade, and Immune Infiltration Analysis

We obtained overall survival, cancer stage, tumor grade, and immune component abundance data for the TCGA kidney renal clear cell carcinoma (KIRC) cohort from TISIDB (http://cis.hku.hk/TISIDB/index.php).

2. PTPN14-Related Gene Correlation Analysis

Based on the 512 KIRC sample dataset from cBioPortal (https://www.cbioportal.org), we analyzed the relationship between PTPN14 expression and inflammation-related genes.

3. Protein Expression Profiling

Analysis using the Timer3 platform (https://compbio.cn/timer3) of TCGA database revealed significant differences in PTPN14 expression between tumor and adjacent normal tissues. Statistical significance was assessed using Wilcoxon rank-sum test: $p < 0.05$; $\boldsymbol{p < 0.01}$; $p < 0.001$. Immunohistochemistry images of PTPN14 expression in KIRC patient tumor tissues were obtained from the Human Protein Atlas (THPA) database (https://www.proteinatlas.org).

4. Functional Enrichment Analysis

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses of PTPN14 in KIRC were performed using LinkedOmics (http://www.linkedomics.org) and Sangerbox 3.0.

5. Cell Lines and Cell Culture

The human kidney renal clear cell carcinoma skin metastasis cell line Caki-1 was purchased from Shanghai Zhongqiao Xinzhou Biotechnology Co., Ltd. Cells were cultured in modified McCoy' s 5A medium containing 10% fetal bovine serum (FBS; Biological Industries, Israel) at 37°C in a humidified 5% CO_2 environment.

6. Patient and Public Involvement

All data in this study were derived from publicly available published patient sequencing datasets, requiring no direct patient contact or additional ethical approval.

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Data Availability Statement

All datasets analyzed in this study are publicly available online as listed in Materials and Methods. Further inquiries can be directed to the first author.

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Ethics Statement: All public databases used are open resources as indicated in Materials and Methods. No ethical approval was required as this study utilized publicly available data without direct patient involvement.

Note: Figure translations are in progress. See original paper for figures.