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Original Article

PTPN3 in cancer: unveiling its immune-mediated impact on prognosis and dysregulated signaling pathways

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Abstract: Objectives: Oncogenic processes in cancer are frequently marked by the dysregulation of critical genes, and PTPN3 (Protein Tyrosine Phosphatase, Non-Receptor Type 3) has emerged as a gene of interest due to its potential involvement in various cellular processes. This study delves into the diagnostic and prognostic implications of PTPN3 in a pan-cancer context. Methods: Leveraging comprehensive genomic datasets and experimental validation, we aimed to shed light on the role of PTPN3 in cancer. Results: Our findings revealed the pervasive up-regulation of PTPN3 across 33 cancer types, making it a ubiquitous player in tumorigenesis. Of particular note, PTPN3 up-regulation exhibited a strong association with reduced overall survival in breast cancer (BRCA) and lung adenocarcinoma (LUAD). This underscores PTPN3's potential as a valuable prognostic marker in these cancers. While genetic mutations often drive oncogenic processes, our mutational analysis demonstrated the relative stability of PTPN3 in BRCA and LUAD. Promoter methylation analysis showed that hypomethylation plays a predominant role in PTPN3 dysregulation in BRCA and LUAD. Furthermore, our study unveiled positive correlations between PTPN3 expression and CD8+ T cell infiltration, offering insights into the gene's influence on the tumor immune microenvironment. Pathway enrichment analysis highlighted the involvement of PTPN3-associated genes in crucial signaling pathways. In addition, drug prediction analysis pinpointed potential drugs capable of modulating PTPN3 expression, opening avenues for personalized treatment strategies. Conclusion: In summary, our study elucidates the multifaceted roles of PTPN3 in BRCA and LUAD, underlining its significant up-regulation, prognostic relevance, epigenetic regulation, and its impact on the tumor immune microenvironment.

Keywords: PTPN3, BRCA, LUAD, biomarker

Introduction

Cancer, one of the most formidable adversaries to human health, represents a complex interplay of genetic and environmental factors [1-4]. The diverse landscape of cancer encompasses a multitude of diseases, each exhibiting unique molecular underpinnings [5]. One of the paramount challenges in the field of oncology is the identification of robust prognostic markers that can guide patient management, inform treatment strategies, and ultimately improve clinical outcomes.

Protein Tyrosine Phosphatase Non-Receptor Type 3 (PTPN3) is a gene that has garnered significant attention from researchers due to its potential involvement in diverse cellular processes [6, 7]. PTPN3 plays a critical role in regulating signal transduction pathways through the dephosphorylation of tyrosine residues [8, 9]. While its functions are widespread, PTPN3 is

particularly noteworthy in cellular adhesion, differentiation, and the modulation of key signaling events. This gene's involvement in numerous cellular activities underscores its relevance in both normal physiology and disease, making it an intriguing subject for further study with potential clinical implications [10-12]. Our research focuses on exploring the expansive role of PTPN3 in cancer, an area where its significance remains relatively uncharted.

Bioinformatics, a burgeoning field at the intersection of biology and computational science, has revolutionized the way we analyze biological data [13-15]. It provides a vantage point to unravel intricate molecular interactions, explore gene expression patterns, and identify potential biomarkers. We leverage bioinformatics to analyze PTPN3's expression patterns, probe its associations with clinical outcomes, and identify potential links with immune infiltration. While bioinformatics offers a bird's-eye view of the genomic landscape, it is crucial to corroborate these findings through laboratory experiments. Our study integrates this computational insight with meticulous molecular experiments. We delve into the intricacies of PTPN3 through in-depth molecular analyses, including gene expression validation. These experiments allow us to transition from the realm of data to the tangible world of biology, providing a holistic understanding of PTPN3 in the context of cancer.

The outcome of our research carries profound implications for cancer prognosis and therapeutic strategies. This knowledge can inform treatment decisions, potentially leading to tailored therapies that enhance patient outcomes.

Methodology

Differential gene expression analysis of PTPN3 in pan-cancer view

UALCAN is a powerful and user-friendly database that serves as an invaluable resource for cancer researchers and clinicians [16]. It provides easy access to TCGA (The Cancer Genome Atlas) data, offering a wealth of information on gene expression and clinical data across various cancer types. UALCAN's user-friendly interface allows for straightforward data retrieval and analysis, enabling users to explore gene expression patterns and compare different genes' expression levels. With its ability to uncover critical insights into cancer biology and prognosis, UALCAN has become an essential tool in the fight against cancer, empowering researchers and healthcare professionals alike. In the current study, UALCAN was utilized for the differential gene expression analysis of PTPN3 in pan-cancer view.

Pan-cancer survival analysis of PTPN3 gene

GEPIA2 is a valuable resource for researchers delving into cancer genomics and gene expression [17]. This interactive and user-friendly platform provides access to extensive, survival, RNA sequencing data from TCGA, and the Genotype-Tissue Expression (GTEx) projects. Researchers can easily compare gene expression in normal and tumor tissues, perform survival analyses, and explore correlations between genes. GEPIA2's visualization tools allow for the generation of insightful plots and graphs, aiding in the interpretation of data. In the current study, GEPIA2 was used for the pan-cancer survival analysis of PTPN3.

PTPN3 association with different cancer stages

In the current study, we harnessed the capabilities of GEPIA2 [17] to examine the intricate association between PTPN3 and various stages of the specified cancer, allowing for a comprehensive exploration of its role in disease progression.

Promoter methylation and gene mutation analysis of PTPN3

OncoDB database: OncoDB is a specialized and indispensable database for cancer researchers and clinicians [18]. It stands out as a comprehensive repository of genomic data, aggregating information from various high-quality sources, including TCGA, International Cancer Genome Consortium (ICGC), and GTEx. OncoDB offers researchers a centralized platform for exploring genetic alterations in various cancers, including promoter methylation patterns. Users can readily access, visualize, and analyze this rich data to unveil critical insights into cancer biology, contributing to the development of novel diagnostic and therapeutic strategies. In this investigation, we utilized the platform to analyze the promoter methylation level of PTPN3 in specified cancer types.

cBioportal database: cBioPortal is an invaluable resource in the field of cancer genomics, providing a user-friendly and comprehensive platform for researchers and clinicians [19]. It offers access to a vast array of cancer genomic data from numerous projects, including TCGA and ICGC. Users can explore genetic alterations, such as mutations and copy number variations various cancer types. The platform's visualization tools enable the creation of interactive plots and networks, aiding in the interpretation of complex data. In our study, we used cBioPortal for the mutational analysis of PTPN3 gene.

TIMER2 analysis: TIMER2 is a cutting-edge resource for the exploration of tumor immune microenvironments [20]. It leverages vast datasets to provide insights into the immune cell composition of various cancer types, enabling researchers to delve into the intricate interplay between tumor and immune cells. With an intuitive interface, TIMER2 empowers users to perform in-depth analyses, including the correlation between gene expression and immune infiltration, contributing to our understanding of the immune contexture in cancer. In our study, we used TIMER2 platform to explore correlation between PTPN3 and CD+ T immune cell infiltration across specified cancers.

Protein-protein interaction and pathway analysis of PTPN3

STRING, the Search Tool for the Retrieval of Interacting Genes/Proteins, is a pivotal resource for researchers delving into molecular interactions [21]. It compiles and predicts protein-protein interactions, enabling a deeper understanding of complex biological processes and networks. We used STRING database here to construct protein-protein interaction (PPI) network of the PTPN3-enriched genes.

The Database for Annotation, Visualization, and Integrated Discovery (DAVID) tool is a vital resource for researchers in the life sciences [22]. DAVID offers a suite of bioinformatics tools designed to unravel the biological significance of large gene lists. By integrating various data sources and analytical methods, it aids in functional annotation, enrichment analysis, and the discovery of biological patterns within high-throughput data. Researchers can identify key biological themes, pathways, and potential interactions, making DAVID an essential tool for interpreting complex biological datasets. In this investigation, we used DAVID to explore PTPN3-associated pathways.

Drug prediction analysis

DrugBank is a valuable resource for cancer researchers, offering a user-friendly platform for performing drug prediction analysis [23]. In our study, DrugBank was used for the drug prediction analysis of PTPN3 gene.

In vitro validation of the PTPN3 gene expression

Cell lines: Two BRCA cell lines, including MCF-7, T-47D, as well as one normal mammary gland cell line (HMEC) were purchased from the American Type Culture Collection (ATCC, USA) and cultivated in accordance with the manufacturer's instructions.

Total RNA extraction: Total RNA extraction from BRCA and normal cell lines was done by isopycnic centrifugation as described previously [22]. The extracted RNA was then processed for DNA digestion step of incubation with RNase-free DNase I (Roche, Germany) at 37°C for 15 minutes. The quality of the extracted RNA was checked by a 2100 Bioanalyzer (Agilent Technologies, Germany).

Reverse transcription-quantitative polymerase chain reaction (RT-qPCR) analysis

The specific protocols are as follows: First, the PrimeScript™ RT reagent kit (Takara, Japan) was used for reverse transcription of the extracted RNA from cell lines into complementary DNA. Then, the RT-qPCR was carried out on an ABI ViiA 7 Real Time PCR System (Thermo Fisher, USA) with a SuperReal SYBR Green Premix Plus (Tiangen Biotech, China) as a fluorescent dye. GAPDH was chosen as the internal reference in the present study. All the experiments were in triplicate independently. All the primers of PTPN3 and GAPDH are shown as follows. The 2-ΔΔCt method was employed to evaluate the relative expression of each hub gene [24].

GAPDH-F 5'-ACCCACTCCTCCACCTTTGAC-3', GAPDH-R 5'-CTGTTGCTGTAGCCAAATTCG-3'; PTPN3-F 5'-GGACATCTCAGAACACACGCATG-3', PTPN3-R 5'-GAAGTCAGCAAATGAGCGGACAG-3'.

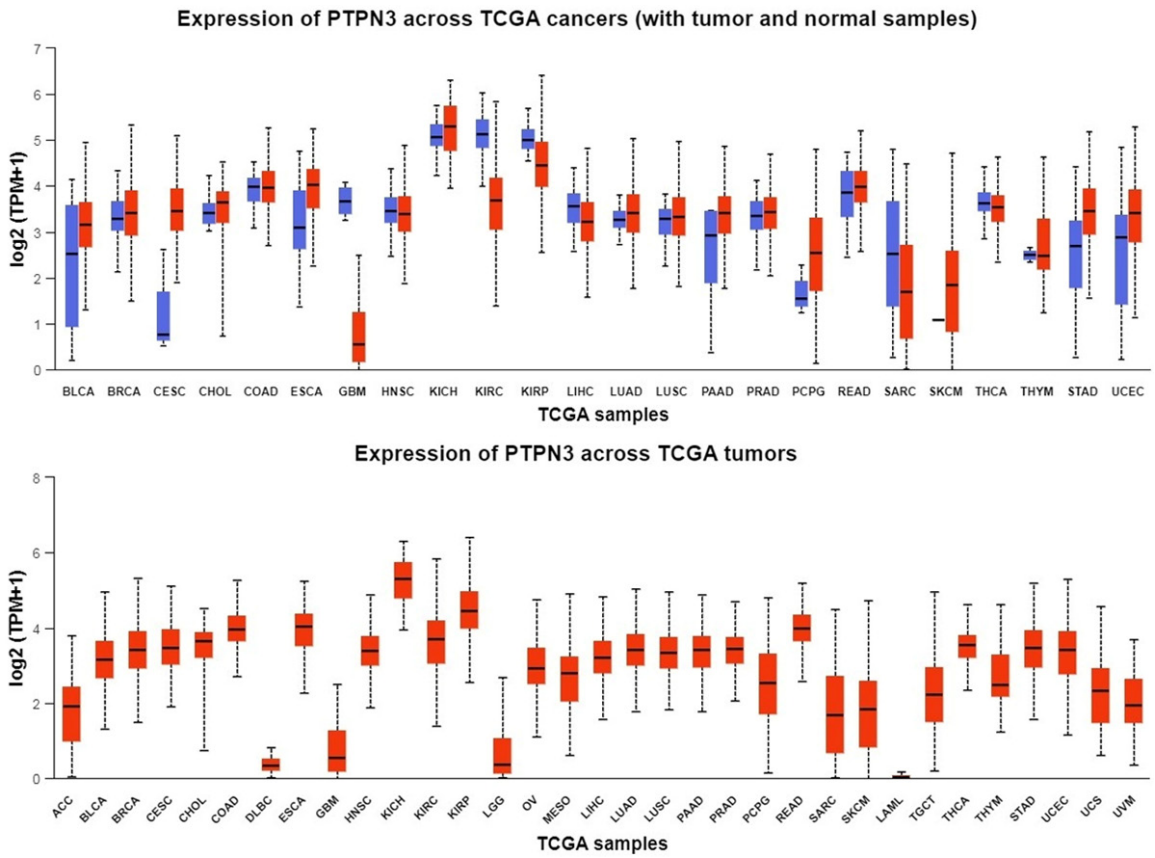

Figure 1. Detailed examination of PTPN3 gene expression across diverse cancers utilizing UALCAN. Significance was established at a *p*-value < 0.05. PTPN3 = Protein Tyrosine Phosphatase, Non-Receptor Type 3.

Receiver operating curve (ROC) analysis

Based on the RT-qPCR expression data, ROC analysis of PTPN3 gene was performed using SPSS software (Version 26).

Statistical analysis

All other analyses were performed with the use of R software (version 3.6.3). A *p*-value below 0.05 was considered statistical significance. Correlation analysis between two variables was conducted using the Spearman test.

Results

Differential gene expression analysis of PTPN3 in pan-cancer view

In our study, we utilized the pan-cancer expression analysis feature of UALCAN, which allowed us to conduct an in-depth examination of the PTPN3 gene across a comprehensive range of cancers within the TCGA cohort. The results of this extensive analysis revealed a compelling and consistent pattern: PTPN3 gene expression exhibited a notable up-regulation in all 33 types of cancers that were scrutinized (**Figure 1**). This widespread up-regulation underscores the potential significance of PTPN3 in diverse cancer types and suggests its potential role in tumorigenesis and disease progression.

Pan-cancer survival analysis of PTPN3 gene

Next, we used the powerful survival analysis feature of the GEPIA2 database to conduct a pan-cancer survival analysis of the PTPN3 gene within the TCGA cohort. The results of this extensive analysis revealed a compelling and noteworthy association between PTPN3 up-regulation and survival outcomes across the spectrum of 33 cancer types examined. Specifically, our findings indicated that PTPN3 up-regulation was significantly correlated with the worst overall survival (OS) in the context of Breast Invasive Carcinoma (BRCA) and Lung

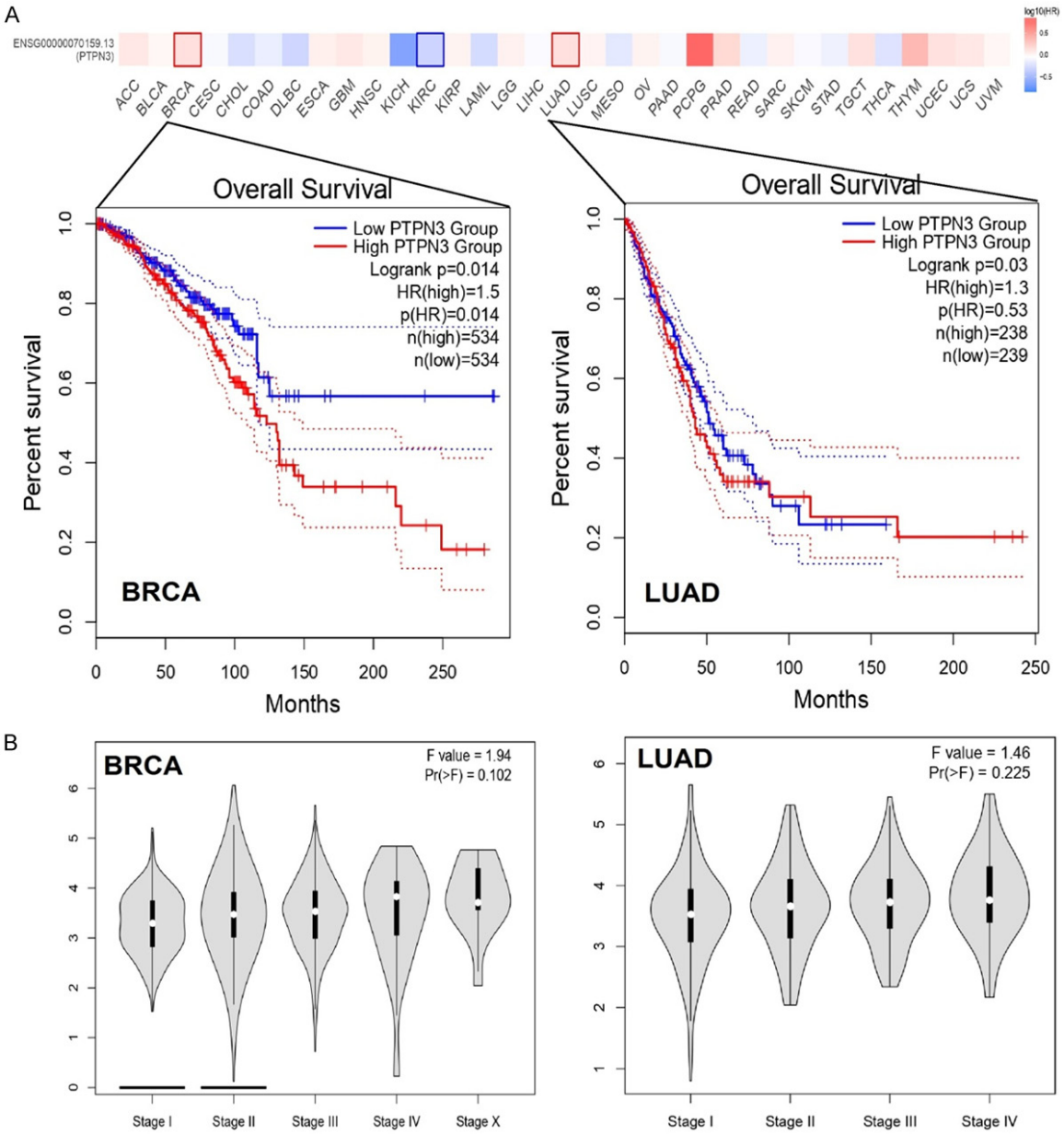

Figure 2. Pan-cancer survival analysis and expression profiling of PTPN3 across BRCA and LUAD patients of different cancer stages. (A) Depiction of survival patterns of the PTPN3 gene in various cancer types using GEPIA2, (B) Survival analysis findings centered on PTPN3 in BRCA and LUAD, and profiling of PTPN3 expression in patients with varying stages of BRCA and LUAD. A *p*-value < 0.05 was considered significant. PTPN3 = Protein Tyrosine Phosphatase, Non-Receptor Type 3, BRCA = Breast Cancer, LUAD = Lung Adenocarcinoma.

Adenocarcinoma (LUAD) among the 33 cancer types analyzed (**Figure 2A**). These results further verified that PTPN3 may play a pivotal role in the progression and prognosis of BRCA and LUAD.

PTPN3 association with different cancer stages of BRCA and LUAD

In this study, we delved further into the analysis of PTPN3 expression across distinct cancer stages within BRCA and LUAD. The results of this investigation revealed a noteworthy pattern in both cancer types. Comparing PTPN3 expression levels across cancer stages, we observed a substantial increase in expression as cancers progressed from stage I to the subsequent stages (stage II, stage III, and stage IV) in both BRCA and LUAD patients (**Figure 2B**). This escalation in PTPN3 expression emphasizes its potential significance in the aggres-

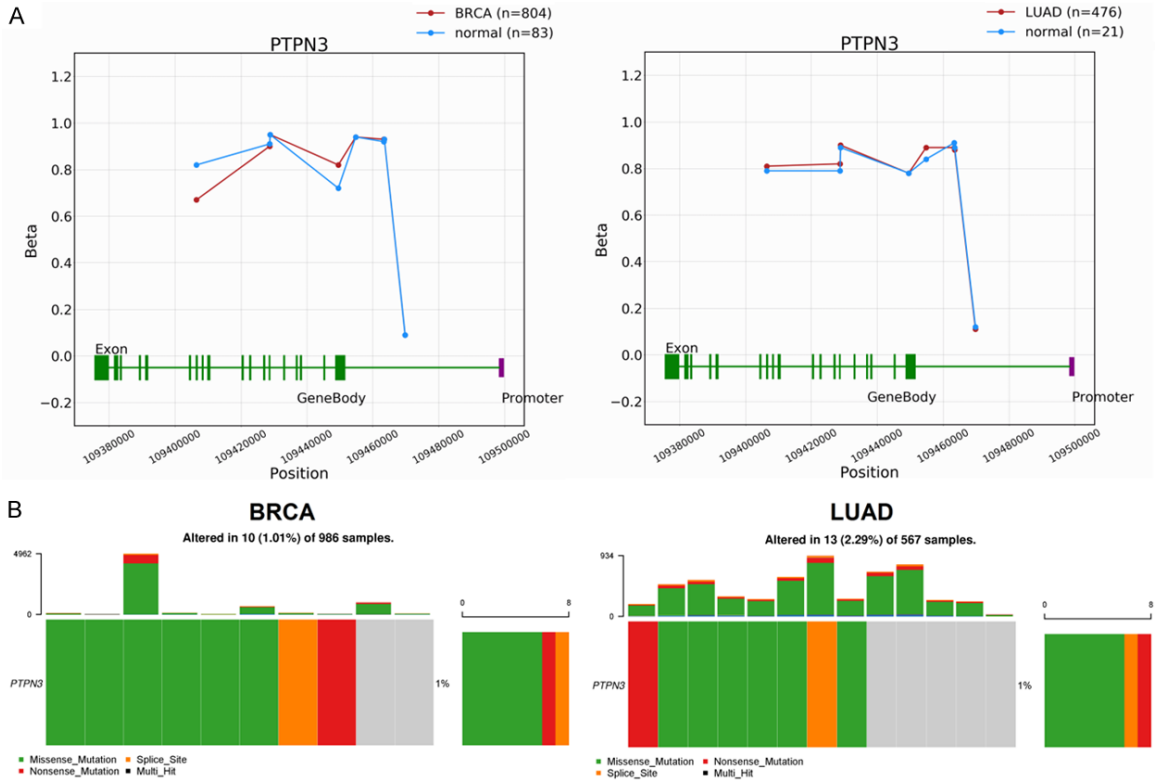

Figure 3. Exploration of PTPN3 gene promoter methylation level and mutational profile. (A) Assessment of PTPN3 promoter methylation Level in BRCA and LUAD samples paired with controls using OncoDB and (B) Examination of PTPN3 mutations in BRCA and LUAD samples using cBioPortal. A *p*-value < 0.05 was considered significant. PTPN3 = Protein Tyrosine Phosphatase, Non-Receptor Type 3, BRCA = Breast Cancer, LUAD = Lung Adenocarcinoma.

siveness of these cancers. These findings shed light on the dynamic role of PTPN3 in cancer and its potential as a disease-specific biomarker.

Promoter methylation and mutational analysis of PTPN3 gene

We conducted a comprehensive promoter methylation analysis of the PTPN3 gene using the OncoDB database. This analysis aimed to unveil potential epigenetic alterations associated with the PTPN3 gene in BRCA and LUAD. The results of our investigation revealed a statistically significant finding, with a *p*-value of less than 0.05. Specifically, we observed a pronounced hypomethylation of the PTPN3 gene in the BRCA and LUAD samples in comparison to the control samples (**Figure 3A**). This hypomethylation indicates a reduction in the methylation levels of the PTPN3 gene's promoter region in these cancer types.

Next, we undertook a thorough mutational analysis of the PTPN3 gene across BRCA and LUAD, utilizing the cBioPortal database. The results of this mutational analysis presented an intriguing finding. It was evident that the PTPN3 gene was not frequently mutated in BRCA and LUAD samples. The mutational frequencies in the analyzed TCGA BRCA and LUAD cohorts were notably low, specifically at 1% (**Figure 3B**). This low prevalence of mutations in PTPN3 suggests that genetic mutations may not be the predominant driver of gene dysregulation in these cancers. Instead, our earlier findings regarding the up-regulation of PTPN3 in BRCA and LUAD may be primarily influenced by other regulatory mechanisms, such as epigenetic modifications, as previously discussed.

Association of PTPN3 expression with the infiltration level of CD8+ T immune cell

We explored the correlation between the expression of the PTPN3 gene and the infiltration levels of CD8+ T immune cells in BRCA and LUAD using the TIMER2 database. This analysis aimed to shed light on the potential association between PTPN3 expression and the presence

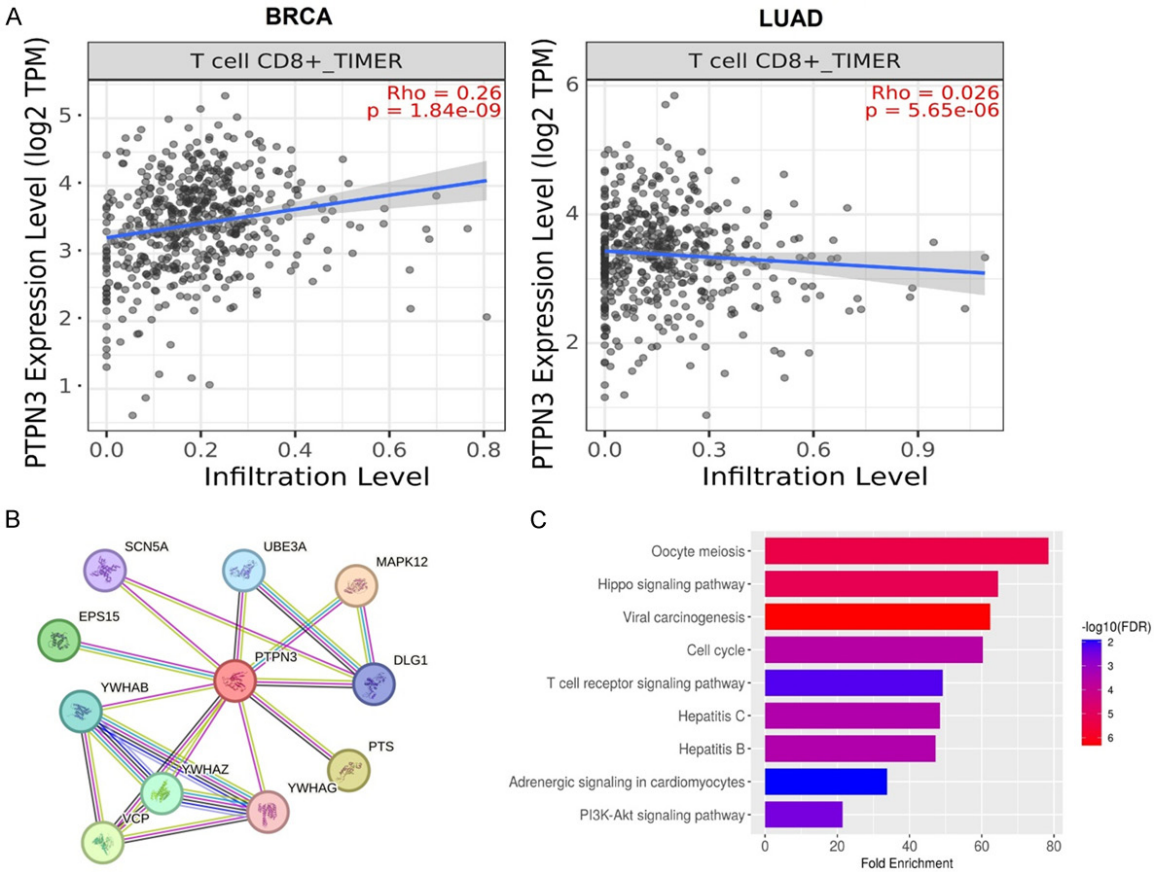

Figure 4. Spearman correlation analysis between PTPN3 and infiltration levels of CD8+ T immune cells, protein-protein interaction (PPI) network, and pathway enrichment analysis. (A) Correlation analysis results for PTPN3 and CD8+ T cell infiltration, (B) A PPI of the PTPN3-enriched genes, and (C) Pathway enrichment analysis results of the PTPN3-enriched genes. A *p*-value < 0.05 was considered significant. PTPN3 = Protein Tyrosine Phosphatase, Non-Receptor Type 3.

of CD8+ T cells, which are essential components of the tumor immune microenvironment [25]. The results of our investigation yielded a statistically significant finding, with a *p*-value of less than 0.05. We observed a significant positive correlation between PTPN3 gene expression and the infiltration levels of CD8+ T immune cells in both BRCA and LUAD (**Figure 4A**). This positive correlation suggests that as the expression of PTPN3 increases, the infiltration of CD8+ T cells also tends to increase. This finding holds particular significance, as the presence of CD8+ T cells in the tumor microenvironment is often associated with enhanced anti-tumor immune responses and improved clinical outcomes in cancer patients.

Protein-protein interaction and pathway analysis of PTPN3

We employed the STRING database to construct a PPI network centered on the PTPN3 gene, aiming to unveil the genes that interact with PTPN3. The outcome of this PPI network revealed that there are 10 genes whose encoded proteins interact with the protein encoded by PTPN3 (**Figure 4B**). These interacting partners could potentially shed light on the functional roles of PTPN3 and its involvement in various cellular processes.

Following the identification of PTPN3's binding partners, we subjected all these genes to a Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis using the DAVID tool. The KEGG analysis outcomes provided valuable insights into the pathways in which PTPN3, along with its interacting partners, is implicated. Notably, this analysis revealed that PTPN3 and its associated genes play a role in the dysregulation of diverse pathways, including "Oocyte meiosis", "Hippo signaling pathway", "Viral carcinogenesis", and "Cell cycle" etc. (**Figure 4C**). These findings suggest that

Table 1. DrugBank-based PTPN3-associated drugs

Sr. No	Hub gene	Drug name	Effect	Reference	Group
1	PTPN3	Belinostat	Decrease expression of PTPN3 mRNA	A21035	Approved
		Carmustine		A21555	
		Calcitriol		A22307	
		Polydatin		A20456	
		Tretinoin		A22307	
		Vincristine		A22706	

PTPN3 = Protein Tyrosine Phosphatase, Non-Receptor Type 3.

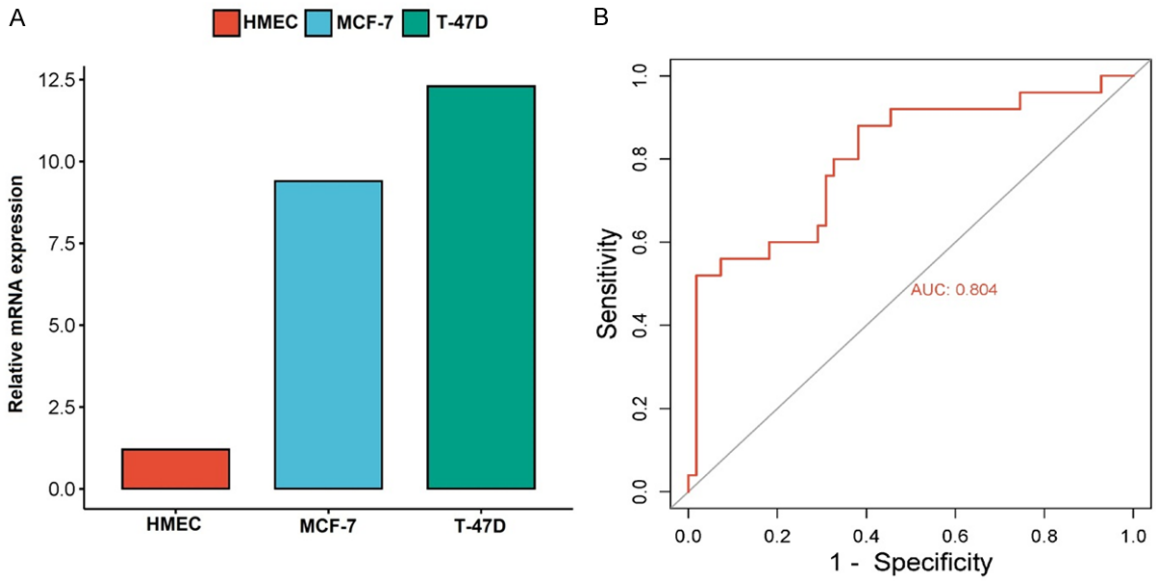

Figure 5. Expression analysis and ROC analysis of PTPN3 across BRCA cell lines. (A) Expression analysis of PTPN3 gene across BRCA cell lines paired with controls, and (B) RT-qPCR expression-based ROC curve of the PTP3 gene. A *p*-value < 0.05 was considered significant. PTPN3 = Protein Tyrosine Phosphatase, Non-Receptor Type 3, ROC = Receiver Operating Curve, BRCA = Breast Cancer.

PTPN3's functions extend beyond its individual capacity and involve intricate interactions within cellular pathways that could influence various biological processes.

Drug prediction analysis of PTPN3

Subsequently, we conducted a drug prediction analysis of the PTPN3 gene using the DrugBank database. Our results unveiled several significant drugs, as listed in **Table 1**, denoted as (Belinostat, Carmustine, Calcitriol, Polydatin, Tretinoin, and Vincristine), which possess the capability to reduce PTPN3 gene expression when administered as part of the treatment regimen for BRCA and LUAD patients. These findings open up possibilities for exploring the therapeutic potential of these drugs in modulating PTPN3 expression and potentially influencing the course of these cancers. Further investigation is necessary to validate these predictions and assess the clinical utility of these drugs in the context of BRCA and LUAD treatment.

RT-qPCR analysis

In the final step of our study, we aimed to experimentally validate the up-regulation of the PTPN3 gene in BRCA cell lines compared to control cell line. For this purpose, we utilized two BRCA cell lines, MCF-7 and T-47D, and normal control cell line, HMEC. We conducted expression analysis of PTPN3 using the robust and quantitative RT-qPCR method. The results of our experimental analysis revealed a significant and consistent up-regulation of PTPN3 in the BRCA cell lines, MCF-7 and T-47D, as compared to the control cell line, HMEC (**Figure 5A**).

Moreover, an ROC curve was constructed for PTPN3, revealing an impressive AUC of 0.804 with a *p*-value below 0.05, based on its expression level (**Figure 5B**). These ROC curves highlighted substantial diagnostic potential indicative of exceptional discriminatory capability.

Discussion

Pan-cancer analysis of PTPN3 was conducted in our study to gain a comprehensive and holistic understanding of this gene in the context of various cancer types. This approach allows us to identify common trends and variations in PTPN3 expression and its potential diagnostic and prognostic roles across a wide spectrum of cancers. PTPN3 is a member of the protein tyrosine phosphatase (PTP) family [9, 26]. PTPs are crucial regulators of signal transduction pathways, and their dysregulation has been linked to various cancers [27, 28]. As a phosphatase, PTPN3's function revolves the dephosphorylation of tyrosine residues in proteins [29]. This has wide-ranging implications for cellular processes, including proliferation, differentiation, migration, and survival [30].

Our investigation has unveiled a striking pattern of PTPN3 up-regulation across numerous cancer types. Notably, the focus of our study was directed toward BRCA and LUAD, primarily due to the compelling association we observed between PTPN3 up-regulation and poor OS in these specific cancer types. These findings are in line with previous research suggesting a role for PTPN3 in oncogenesis of different types of cancers [31-33]. However, to the best of our knowledge, we are the first to report the overexpression of the PTPN3 gene and its significant association with poor OS across BRCA and LUAD in pan-cancer view.

The integration of promoter methylation and mutational analysis into our study highlights the multifaceted nature of gene dysregulation in BRCA and LUAD. The interaction between genetic and epigenetic factors is a complex and dynamic process that can have a profound impact on gene expression [34, 35]. Prior research has underscored that genetic mutations and aberrant promoter methylation levels are pivotal factors contributing to the disruption of gene expression [36-43]. In our study, while PTPN3 is not frequently mutated, the hypomethylation of its promoter is a key contributor to its overexpression in BRCA and LUAD. These findings emphasize that a comprehensive understanding of gene dysregulation in cancer requires an exploration of both genetic and epigenetic alterations.

The immune system plays a pivotal role in the development of cancer [44, 45], and understanding how PTPN3 influences immune responses is of paramount importance. Our results reveal a positive correlation between PTPN3 expression and CD8+ T cell infiltration. This suggests that PTPN3 may play a role in shaping the tumor immune microenvironment. The presence of CD8+ T cells is associated with an anti-tumor immune response, and their infiltration is indicative of a more favorable prognosis in some cancer types [46, 47]. The positive correlation with PTPN3 could indicate an immunosuppressive environment, potentially fostering immune evasion. Further research is needed to elucidate the exact mechanisms by which PTPN3 influences immune cell infiltration and function.

Furthermore, the pathway analysis results highlighted the potential involvement of PTPN3 in diverse signaling pathways such as "Oocyte meiosis", "Hippo signaling pathway", "Viral carcinogenesis", and "Cell cycle" etc. Notably, earlier research has suggested a strong correlation between elevated PTPN3 expression and the perturbation of these signaling pathways [26, 48-52].

Our study opens the door to several clinical implications. The up-regulation of PTPN3 across a wide spectrum of cancer types, its potential as a therapeutic target, and its influence on the immune microenvironment collectively point to its clinical relevance. PTPN3 could serve as a diagnostic biomarker, aiding in the early detection and classification of cancer. Additionally, its role in modulating immune responses may have implications for immunotherapeutic strategies. To comprehensively understand the role of PTPN3 in cancer, it is essential to investigate its specific molecular interactions, signaling pathways, and regulatory mechanisms. This includes examining how PTPN3 may influence cancer cell behavior, proliferation, and survival. Furthermore, detailed mechanistic studies are needed to explore the relationship between PTPN3 and immune responses, which could potentially guide the

development of immunotherapeutic strategies.

Conclusion

In conclusion, our study on PTPN3 highlights its potential as a pivotal player, diagnostic, and prognostic biomarker in BRCA and LUAD development. Its consistent up-regulation, potential as a therapeutic target, and influence on the immune microenvironment present exciting avenues for future research and clinical applications. PTPN3's significance in the pan-cancer context underscores its importance in the field of oncology and warrants further investigation.

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Disclosure of conflict of interest

None.

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