

Comprehensive Biological Information Analysis of PTEN Gene in Pan-Cancer

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ABSTRACT

Background: PTEN was a multifunctional tumor suppressor gene mutating at high frequency in a variety of cancers. However, its expression in pan-cancer, correlated genes, survival prognosis, and regulatory pathways were not completely described. Here, we aimed to conduct a comprehensive analysis from the above perspectives in order to provide reference for clinical application.

Methods: We studied the expression levels in cancers by using data from TCGA and GTEx database. Obtain expression box plot from UALCAN database, performed mutation analysis on the cBioportal website, obtained correlation genes on the GEPIA website, constructed protein network and perform KEGG and GO enrichment analysis on the STRING database and conducted prognostic analysis on the Kaplan-Meier Plotter website. We also performed transcription factor prediction on the PROMO database and RNA-RNA association/RNA-protein interaction on the RNAup Web server and RPISeq. The gene 3D structure, protein sequence and conserved domain were obtained from NCBI.

Results: PTEN was underexpressed in all cancers we studied. It was closely related to the clinical stage of tumors, suggesting PTEN may involve in cancer development and progression. The mutations of PTEN were present in a variety of cancers, most of which were truncation mutations and missense mutations. Among cancers (KIRC, LUAD, THYM, UCEC, gastric cancer, liver cancer, lung cancer, breast cancer), patients with low expression of PTEN had a shorter OS time and poorer OS prognosis. The low expression of PTEN can cause the deterioration of RFS in certain cancers (TGCT, UCEC, LIHC, LUAD, THCA), suggesting that the expression of PTEN was related to the clinical prognosis. Our study identified genes correlated with PTEN and performed GO enrichment analysis on 100 PTEN-related genes obtained from the GEPIA website.

Conclusion: The understanding of PTEN gene and the in-depth exploration of its related regulatory pathways may provide insight for the discovery of tumor-specific biomarkers and clinical potential therapeutic targets.

Keywords: PTEN; Correlated genes; TCGA; GEPIA; UALCAN; GTEx; Expression; Cancer

INTRODUCTION

PTEN (Phosphatase and Tensin Homolog) was a classical tumor suppressor gene located on chromosome 10 in region 10q23. Encoding 403 amino acids, it was a multifunctional protein that was often absent in tumors [1-3]. Loss of heterozygosity often occurred in this area in various types of cancers [4].

The protein encoded by this gene was phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase. It contained a catalytic domain and a tensin like domain which was similar to the bispecific protein tyrosine phosphatase. PTEN acted as a classical tumor suppressor and was primarily involved in the homeostasis maintenance of the phosphatidylinositol 3 kinase (PI3K)/Akt cascade.

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In most human cancers, the function of PTEN was typically lost through somatic mutation, gene silencing or epigenetic mechanisms. Tumor-associated mutations may occur in all PTEN domains, suggesting that each different protein region may be pathologically involved in the development and progression of cancer. Thus, partial loss of PTEN function was sufficient to promote the growth of some human malignancies [5]. Studies have shown that somatic cells without PTEN were present in a variety of tumor diseases, including melanoma, glioblastoma, colon and endometrial cancers [6,7]. Studies have also shown that low expression of PTEN often led to a worse prognosis in cancer (bladder cancer [8], gastric cancer [9], prostate cancer [10], epithelioid malignant peritoneal mesothelioma [11], etc).

In this study, we used data from The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) to assess PTEN expression levels in 17 different cancers, and evaluated PTEN expression in different histological subtypes, molecular subtypes, patient status and individual pathological cancer stage. The clinical correlation with patient prognosis was also assessed. In addition, in order to further analyze the role of PTEN in the occurrence and development of diseases, our study analyzed the mutation conditions of PTEN in tumors, studied the relationship between PTEN levels and prognosis in different tumors, identified a variety of genes in the protein regulatory network of PTEN and performed KEGG enrichment analysis. This will provide information and direction for subsequent clinical and basic researches.

METHODS

In the current research, our research was conducted by using different bioinformatics tools and databases, including GEPIA [46] (GEPIA: a web server for cancer and normal gene expression profiling and interactive analyses, <http://gepia.cancer-pku.cn/>), UALCAN [47] (an interactive web portal for the in-depth analysis of TCGA gene expression data, <http://ualcan.path.uab.edu>) and STRING database [48] (protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets, <https://string-db.org/>).

In this research, we conducted the following research investigations: expression of PTEN in 17 kinds of cancers and their subtypes, analysis of gene expression in different pathological stages, mutation analysis of PTEN in cancer, correlation between PTEN expression and cancer prognosis, Overall Survival (OS) analysis, Relapse Free Survival (RFS) analysis and investigation on genes correlated to PTEN expression. In addition, we constructed PTEN protein network, searched for the related and involved pathways among these proteins, and we carried out KEGG pathway enrichment analysis and GO enrichment analysis. The RNA-RNA interaction and RNA protein interaction between YY1 and PTEN were also analyzed. Finally, we analyzed the basic structure of PTEN and found the conserved domain of PTEN protein in different species.

We obtained the basic information of PTEN from GenCards website. To investigate the expression of PTEN in 17 human tumor types compared with normal samples, we used GEPIA webserver (accessed on March 15, 2021). One advantage of

GEPIA is that it also uses normal data in the GTEx project to provide a comparison baseline. Because normal tissue is sampled from the area adjacent to the tumor in most of the cancer researches, but they may be precancerous tissues rather than true normal healthy tissues. PTEN expression between tumors, their matched normal, and data from the GTEx database in 17 tumor types were compared. These tumors include ACC, BLCA, BRCA, COAD, DLBC, KICH, KIRP, LUAD, LUSC, OV, PRAD, SKCM, TGCT, THCA, THYM, UCEC and UCS. About parameter options, we used the ANOVA statistical method for differential gene expression analysis, selected $\log_2(\text{TPM} + 1)$ transformed expression data for plotting, TCGA tumors compared to TCGA normal and GTEx normal for matched normal data in plotting, $|\log_2\text{FC}|$ cutoff of 1, and a q-value cutoff of 0.01. In addition, for cancers with different subtypes and stages, we used UALCAN webserver to analyze them (accessed on March 16, 2021).

In order to provide PTEN expression box plots based on the pathological stages of patients with TCGA cancer types (I, II, III, IV and V groups), we used the UALCAN webserver to obtain data from TCGA (accessed on March 18, 2021).

In order to provide mutation analysis of PTEN, we conducted the corresponding analysis on the cBioportal website (<http://www.cbioportal.org/>) (accessed on March 18, 2021). In addition, we also performed overall survival (OS) and Relapse Free Survival (RFS) analysis based on PTEN gene expression by using Kaplan-Meier Plotter (<http://kmplot.com/analysis/index.php?p=background#>) (accessed on March 19, 2021). Correlation analysis between PTEN and other genes was performed by pair-wise gene expression correlation analysis with the expression data of TCGA and GTEx, using the method of the Pearson correlation coefficient. First, we searched for the expression correlation of PTEN and other genes in all 17 cancers on average (the Pearson correlation coefficient between 0.4 and 1). Then, we investigated the correlation of PTEN expression of each gene in each cancer to understand the exact correlation. We considered the following correlation coefficients: 0.00-0.009 is almost no correlation, 0.10-0.19 is very weak, 0.20-0.39 is weak, 0.40-0.49 is moderate and 0.50-1.00 is strong.

In order to provide the PTEN protein network, we used the STRING database (accessed on March 21, 2021). We analyzed some genes correlated to PTEN (extracted from TCGA cancer types by using GEPIA), some genes closely related to PTEN, and YY1 (transcription factor). In addition, we extracted relevant information about KEGG pathway enrichment analysis and GO enrichment analysis on the STRING database (accessed on March 21, 2021). In addition, we performed PTEN transcription factor prediction in the PROMO database (accessed on March 22, 2021) (http://algggen.lsi.upc.es/cgi-bin/promo_v3/promo/promoinit.cgi?dirDB=TF_8.3), and we used the Venn Diagram to find the intersection between the obtained genes and the genes similar to PTEN (obtained from GEPIA), from which the YY1 gene is obtained. To predict the RNA-RNA association and RNA-protein interaction between YY1 and PTEN, we used RNAup Webserver (<http://rna.tbi.univie.ac.at/cgi-bin/RNAWebSuite/RNAup.cgi>) and RPISeq (<http://pridb.gdcb.iastate.edu/RPISeq/>) (accessed on March 24, 2021).

Tumor	Histological Subtypes	Molecular Subtypes	Tumor Grade	Other Patient Conditions
BLCA	N-vs-Papillary tumors: $p < 10^{-2}$ N-vs-NonPapillary tumors: $p < 10^{-2}$	N-vs-Neuronal: $p < 10^{-2}$ N-vs-Basal squamous: $p < 10^{-2}$ N-vs-Luminal: $p < 10^{-4}$ N-vs-Luminal_Papillary: $p < 10^{-4}$		N-vs-Non smoker: $p < 10^{-2}$ N-vs-Smoker: $p < 10^{-2}$ N-vs-Reformed smoker1: $p < 10^{-3}$ N-vs-Reformed smoker2: $p < 10^{-2}$
KIRP	N-VS-Type1 PRCC: $p < 10^{-2}$ N-VS-Type2 PRCC: $p < 10^{-4}$			
PRAD		N-vs-ERG fusion: $p < 10^{-4}$ N-vs-ETV1 fusion: $p < 10^{-4}$ N-vs-FOXA1 mutation: $p < 10^{-3}$ N-vs-SPOP mutation: $p = 0.011$		N-vs-Gleason score 6: $p < 10^{-4}$ N-vs-Gleason score 7: $p < 10^{-4}$ N-vs-Gleason score 8: $p < 10^{-4}$ N-vs-Gleason score 9: $p < 10^{-6}$
BRCA	N-vs-IDC: $p < 10^{-11}$ N-vs-ILC: $p < 10^{-12}$ N-vs-Mixed: $p < 10^{-2}$ N-vs-Other: $p < 10^{-11}$ N-vs-Mucinous: $p < 10^{-2}$ N-vs-Metaplastic: $p < 10^{-6}$ N-vs-Medullary: $p < 10^{-4}$	N-vs-Luminal: $p < 10^{-11}$ N-vs-HER2Pos: $p < 10^{-10}$ N-vs-TNBC-BL1: $p < 10^{-6}$ N-vs-TNBC-BL2: $p < 10^{-6}$ N-vs-TNBC-IM: $p < 10^{-9}$ N-vs-TNBC-LAR: $p < 10^{-4}$ N-vs-TNBC-MSL: $p < 10^{-5}$ N-vs-TNBC-M: $p < 10^{-15}$ N-vs-TNBC-UNS: $p < 10^{-10}$		N-vs-Pre-Menopause: $p < 10^{-11}$ N-vs-Peri-Menopause: $p < 10^{-6}$ N-vs-Post-Menopause: $p < 10^{-12}$
COAD	N-vs-Adenocarcinoma: $p < 10^{-14}$ N-vs-Mucinous-adenocarcinoma: $p < 10^{-3}$			
PAAD			N-vs-Grade 2: $p = 0.023$ N-vs-Grade 3: $p = 0.033$	N-vs-Non Drinker: $p = 0.035$ N-vs-Daily Drinker: $p = 0.011$ N-vs-Diabetic: $p = 0.047$ N-vs-Pancreatitis: $p < 10^{-2}$
LUSC	N-vs-NOS: $p < 10^{-8}$ N-vs-Basaloid: $p < 10^{-3}$			N-vs-Smoker: $p < 10^{-9}$ N-vs-Reformed smoker1: $p < 10^{-2}$ N-vs-Reformed smoker2: $p < 10^{-8}$
THYM	N-VS-Type A: $p < 10^{-3}$ N-VS-Type C: $p < 10^{-2}$ N-VS-Type AB: $p = 0.028$			

	N-VS-Type B3:p=0.014 N-VS-Type B2 B3:p<10 ⁻²			
THCA	Classical-VS-N:p<10 ⁻⁸ Tall-VS-N:p<10 ⁻⁶ Follicular-VS-N:p<10 ⁻⁴ Other-VS-N:p<10 ⁻²			
UCEC	N-vs-Endometrioid:p<10 ⁻¹¹ N-vs-Serous :p<10 ⁻¹¹ N-vs-Mixed serous and endometrioid:p<10 ⁻⁹			N-vs-Pre-Menopause:p<10 ⁻⁵ N-vs-Peri-Menopause:p<10 ⁻⁶ N-vs-Post-Menopause:p<10 ⁻¹¹

Finally, we obtained PTEN structural features, basic information and 3D structure of PTEN in the NCBI gene database (accessed on March 28, 2021). In addition, we obtained the comparison of PTEN protein sequences and homology domains in different species by using NCBI HomoloGene database.

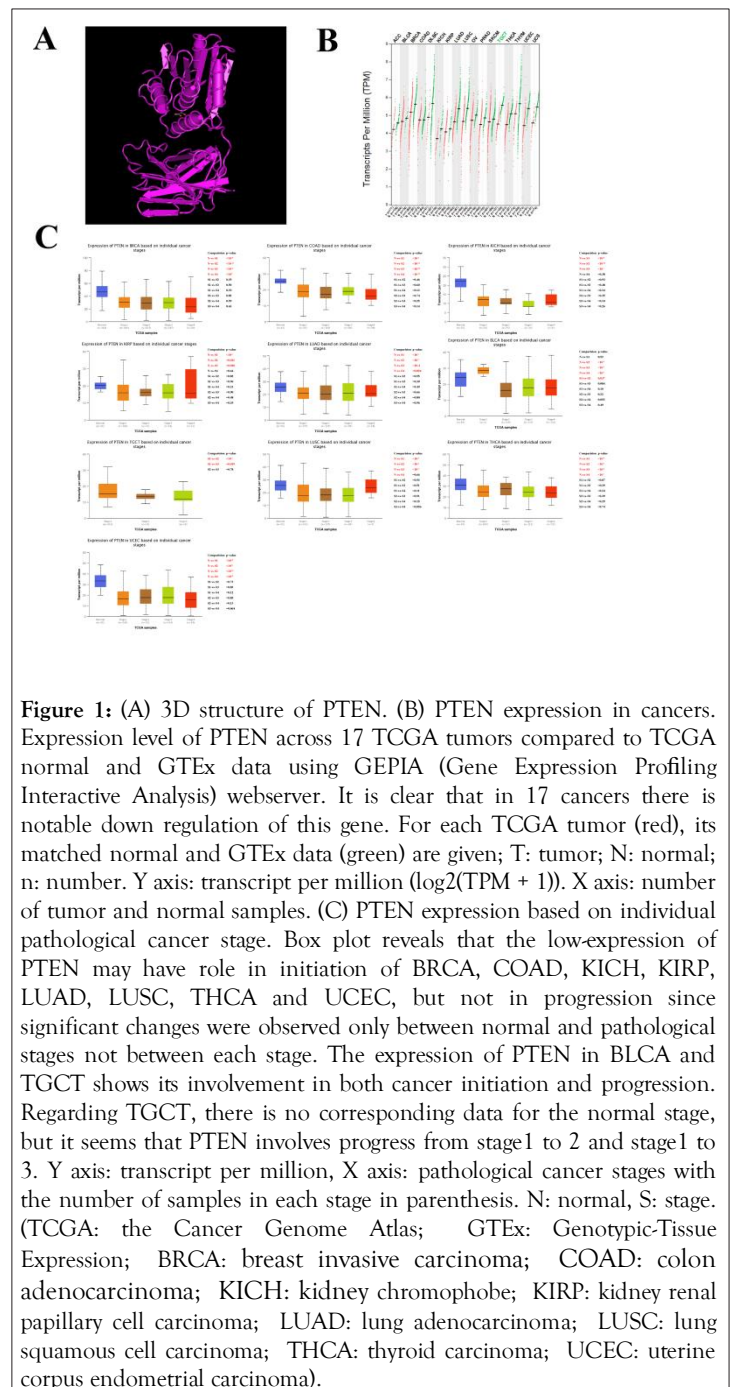
RESULTS

Low expression of PTEN in tumors, their pathological stages and subtypes

Data extracted from the TCGA showed that PTEN expression was lower in 17 tumors (ACC BLCA, BRCA, COAD, DLBC, KICH, KIRP, LUAD, LUSC OV, PRAD, SKCM, TGCT, THCA, THCA, THYM, UCEC UCS) compared with matched TCGA normal tissue and GTEx data (Figure 1B). Then, we assessed the expression of PTEN in normal tissue by using RNA-sequencing data available from GTEx data. In particular, we compared expression levels of PTEN between tumors with respect to normal matches, and GTEx data. We found that in terms of its expression in normal tissues, PTEN showed lower levels in these 17 cancers, and the differences between these cancers and normal samples were shown in boxplot form in Figure S1.

Next, we evaluated PTEN expression levels with respect to tumor molecular and histological subtypes of tumors, tumor grades, and other patient conditions based on data obtained from UALCAN.

In urologic cancer, we found that the expression of the histological subtypes of BLCA was decreased in both papilloma and non-papilloma compared with normal people (Table 1 and Data S1 Panel 1A). Regarding its molecular subtypes, the PTEN expression level in neuronal, basal squamous, luminal and luminal_papillary decreased significantly compared to normal (Table 1 and Data S1 panel 1B). While luminal and luminal_papillary decreased most significantly, followed by neuronal and basal squamous. In KIRP tumors, the expression of PTEN was significantly decreased in both Type1 PRCC and Type2 PRCC (Table 1 and Data S1 panel 1D), and the decrease was more significant in Type2 PRCC. In PRAD tumors, the expression of PTEN was decreased in Gleason score 9, Gleason score 6, Gleason score 7 and Gleason score 8. In their molecular subtypes, the expression of PTEN was also decreased significantly in ERG fusion, ETV1 fusion, FOXA1 mutation and SPOP mutation (Table 1 and Data S1 Panel 1E).



Compared to normal tissue in BRCA tumors, the expression of PTEN was lower in all different molecular subtypes, including

triple negative breast cancer (TNBC), HER2-amplification and luminal subtype. (Table 1 and Data S1 Panel 2D). In terms of TNBC type in BRCA, the statistically significant changes were seen in TNBC-mesenchymal (TNBC-M), followed by TNbC-UNS, TNBC-immunomodulatory (TNBC-IM), TNbC-basal like2 (BL2) and TNBC-basal like1(BL1). (Table 1 and Data S1 Panel 2A). PTEN expression level was decreased in pre-menopausal, peri-menopausal, and post-menopausal patients having BRCA compared with normal. However, only the difference between pre-menopausal and post-menopausal was statistically significant (Table 1 and Data S1 Panel 2C). In addition, the expression of PTEN in BRCA was low in all histologic subtypes, most notably in Invasive Lobular Carcinoma (ILC) and Invasive Ductal Carcinoma (IDC) (Table 1 and Data S1 Panel 2B). The expression of amplified MYC proto-oncogene (MYC), cyclin D1 (CnD1) and ERB-B2 receptor tyrosine kinase 2 (ERBB2) in metastatic breast cancer compared to conditions without amplification indicated no significant correlation with PTEN expression (Table 1 and Data S1 panel 2E).

About digestive system tumors, COAD tumor showed increased PTEN levels in adenocarcinoma and mucinous-adenocarcinoma (Table 1 and Data S1 panel 3A). In PAAD tumor, the reduction of PTEN expression level was statistically significant in non-drinkers and daily drinkers (Table 1 and Data S1 panel 3E). In addition, compared with normal people, in patients with acute pancreatitis, their PTEN level decreased more significantly than patients with acute pancreatitis, but the comparison between them and patients without pancreatitis was not statistically significant (Table 1 and Data S1 panel 3C). The reduction of PTEN in patients with diabetes was also more significant than that in normal patients (Table 1 and Data S1 Panel 3B). In terms of tumor grade, PTEN reduction was more significant in Grade 2 and Grade 3 than in normal subjects (Table 1 and Data S1 Panel 3D).

Regarding the expression of PTEN in LUSC tumors, we found that for LUSC patients based on smoking habits, the PTEN expression of all cancer types was decreased compared with normal people, and was more significant in smoker, reformed smoker1 and reformed smoker2 (Table 1 and Data S1 Panel 4A). The reduction of PTEN was more obvious in LUSC NOS in terms of the histological subtypes of LUSC, followed by Lusc Mixed, Lusc Solid Pattern Predominant and LUSC papillary (Table 1 and Data S1 panel 4B).

For THYM tumor, the expression level of PTEN in THYM Type A, THYM Type B2|B3, THYM Type C, THYM Type AB and THYM Type B3 was all significantly reduced (Table 1 and Data S1 panel 5A). In THCA tumor, the decrease of PTEN expression was most obvious in THCA Classical based on the histological subtype of THCA, followed by THCA tall and THCA follicular (Table 1 and Data S1 panel 5B). For UCEC tumors, the expression level of PTEN decreased in UCEC endometrioid, UCEC serous and UCEC Mixed serous and endometrioid, which was statistically significant. Among them, the most significantly decrease was occurred in UCEC endometrioid. Based on the menopausal stage of UCEC patients, the expression of PTEN was significantly decreased in pre-menopausal, peri-menopausal and post-menopausal patients, which was most significant in post-menopausal patients, followed by peri-menopausal and pre-menopausal patients. However, there was no significant difference in the expression

level of PTEN among pre-menopausal, peri-menopausal and post-menopausal patients.

Next, we investigated PTEN expression based on patients' pathological stage in TCGA cancer types. We found that the expression level of PTEN in BRCA, COAD, KICH, KIRP, LUAD, LUSC, THCA and UCEC was significantly lower at the early stage (Figure 1C, $p < 0.05$), suggesting that PTEN may be involved in the onset of cancers. In addition, compared with the early stage, the expression level of PTEN in BLCA and TGCT was lower at advanced cancer, suggesting that PTEN may play a role in cancer progression and cancer invasion (Figure 1C, cancer without and/or small numbers of normal matches (when there is only one sample in each stage) were excluded from this analysis).

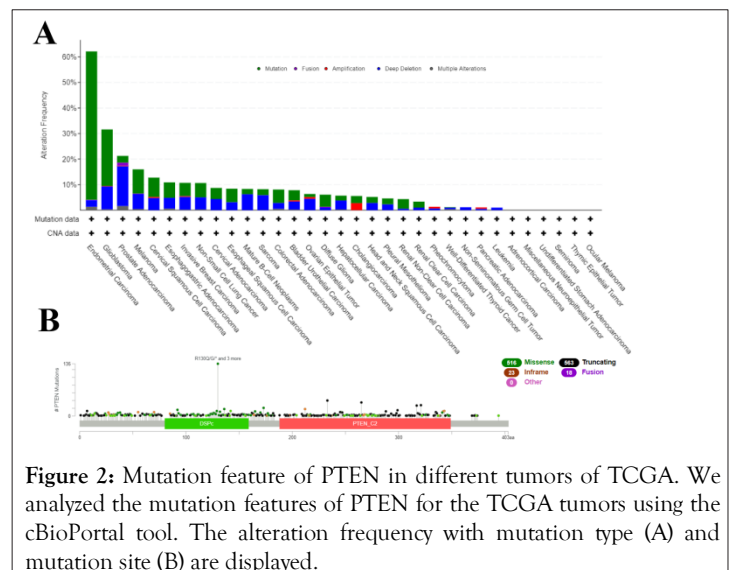


Figure 2: Mutation feature of PTEN in different tumors of TCGA. We analyzed the mutation features of PTEN for the TCGA tumors using the cBioPortal tool. The alteration frequency with mutation type (A) and mutation site (B) are displayed.

Genetic variation analysis of PTEN

We observed the genetic alteration condition of PTEN in different tumors of TCGA. As shown in Figure 2A, Endometrial cancer (in which mutation is the main change type) showed the highest mutation frequency (>60%). The frequency of PTEN changes in prostate cancer was about 20% and deep deletion was the main type of PTEN changes. It is worth noting that in these cancers, there are almost no Fusion and Multiple Alterations among the types of PTEN gene alterations.

Figure 2B shows the type, location and the number of cases of PTEN gene change. In the 1203 group of mutation cases (including samples of single patient with double mutations), we found that the truncation mutation of PTEN was the main type of genetic changes (563 cases), followed by missense mutation (516 cases) while the number of cases with inframe mutation and fusion mutation was relatively small. In addition, the R130Q/G/*L/P/QFS *4 mutation in DSPc domain can induce the development of a variety of cancers (uterine cancers account for the vast majority).

Role of PTEN low expression in cancer prognosis

In the Kaplan-Meier Plotter database, we compared the OS time between tumor patients with high PTEN expression level and tumor patients with low PTEN expression level, and the data showed that patients with low PTEN expression levels had a shorter OS time and worse prognosis compared with patients having high PTEN expression levels in the following cancers: KIRC, LUAD, Gastric Cancer, Liver Cancer, Lung Cancer,

Breast Cancer, THYM and UCEC (Figure 3A).

About RFS time, compared with the high PTEN expression level of the following tumor patients, the low expression level of PTEN in these tumor patients can lead to a worse prognosis (Figure 3B). These tumors are: Liver Cancer, TGCT, UCEC, LIHC, LUAD and THCA.

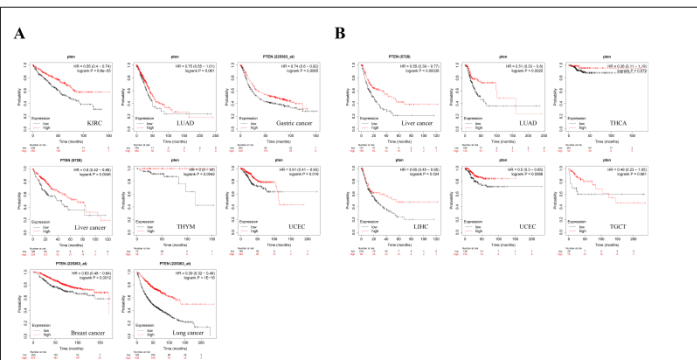


Figure 3: (A) OS time between PTEN high-expression-level and PTEN low-expression-level tumors in some tumor types with shorter overall time and worse OS prognosis. Red line shows the cases with highly expressed PTEN and black line is indicated for the cases with lowly expressed PTEN. (B) RFS time between PTEN higher-expression-level and PTEN lower-expression-level tumors in some tumor types with worse prognosis. Red lines shows the cases with highly expressed PTEN and black lines is indicated for the cases with lowly expressed PTEN (OS: overall survival; RFS: Relapses Free Survival).

In summary, the data proved that in the tumors mentioned above, lower-expressed PTEN level can lead to a worse clinical consequence.

Correlation between gene expression of PTEN and other genes in cancer

Our research showed that the expression of PTEN has a moderate to strong positive correlation with these genes in 17 cancers (Table S1, which provides all information on coefficient correlations and p-value, using different colors to distinguish correlations as follows: Strong positive correlation in green; medium positive correlation in black; weak positive correlation in red; very weak correlation in violet and almost no correlation is indicated in light blue). As seen in Table S1 and Table 2. Among 12 or more cancers, the following genes have a strong positive correlation with PTEN expression (R between 0.5 and 1, p -value <0.05): Phosphatase And Tensin Homolog Pseudogene 1 (PTENP1), ATPase family AAA domain containing 1 (ATAD1), wings apart-like homolog (WAPAL), tankyrase 2 (TNKS2), membrane-associated ring finger 5 (MARCH5), coiled-coil serine rich protein 2 (CCSER2), component of inhibitor of nuclear factor kappa B kinase complex (CHUK) and eukaryotic translation initiation factor 3 subunit A (EIF3A). In addition, the following genes showed a strong positive correlation with PTEN among 10 to 12 cancer types: hypoxia inducible factor 1 subunit alpha inhibitor (HIF1AN), survival motor neuron domain containing 1 (SMNDC), chromosome 10 open reading frame (C10orf12), Sp3 transcription factor (SP3), chondroitin sulfate N-acetylgalactosaminyltransferase 2 (CSGALNACT2), structural maintenance of chromosomes 3 (SMC3), NOC3 like DNA replication regulator (NOC3L), family with sequence similarity 35 member A (FAM35A), STE20 like kinase (SLK) and golgi

brefeldin A resistant Guanine Nucleotide Exchange Factor 1 (GBF1). In addition, some genes showed strong positive associations with PTEN in several cancers among 17 studied cancers as indicated in the Table S1 and Table 2. For the UCEC cancer mentioned in Table S1 (shown in light blue) and Table 2, the expression of PTEN in this cancer has almost no correlation with the following genes ($R<0.1$): DEAD-box helicase 46(DDX46), family with sequence similarity 160, member B1(FAM160B1), ubiquitin specific peptidase 37(USP37), nuclear receptor binding SET domain protein 1(NSD1), RIC1 homolog, RAB6A GEF complex partner 1(RIC1), golgi brefeldin A resistant guanine nucleotide exchange factor 1(GBF1), ubiquitin specific peptidase 9 X-linked(USP9X), RP11-244H3.4 and atlastin GTPase 3(ATL3).

In addition, we searched for genes with protein products that have transcription factor binding sites in the PTEN promoter region. Intersection analysis of these genes and the PTEN-related genes obtained from the GEPIA database is performed by using Venn diagram, which led to the discovery of YY1 transcription factor (YY1), and we found that among the 17 cancers we studied, YY1 has a strong positive correlation with DLBC, KIRP, THCA, THYM, ACC, KICH and BRCA (ranked from high to low).

It can be seen from Table S1 that the genes most closely correlated to PTEN are phosphatase and tensin homolog pseudogene 1 (PTENP1), tankyrase 2 (TNKS2), membrane-associated ring finger 5 (MARCH5), ATPase family AAA domain containing 1 (ATAD1), wings apart-like homolog (WAPAL), coiled-coil serine rich protein 2 (CCSER2), component of inhibitor of nuclear factor kappa B kinase complex (CHUK) and eukaryotic translation initiation factor 3 subunit A (EIF3A). It is worth noting that PTENP1 has a strong positive correlation with PTEN in all 17 cancers. In UCEC tumor, we observed that TNKS2, MARCH5, ATAD1 and CHUK all had a weak positive correlation with PTEN ($0.2<R<0.4$). Besides, WAPAL, CCSER2 and EIF3A had a very weak correlation with PTEN ($0.1<R<0.2$). In addition, we found that MARCH5, CHUK and EIF3A all had a weak correlation in LUSC tumor. In UCS tumor, WAPAL and CHUK had a weak correlation with EIF3A. In THYM tumor, ATAD1 had a weak correlation (Table S1 and Table 2). The above data was shown in Table 2. Notably, among the genes positively correlated with PTEN, some genes can be considered as targets for several types of cancers. Such as: The lncRNA of Phosphatase And Tensin Homolog Pseudogene 1 (PTENP1) can inhibit the progression of cervical cancer by inhibiting mir-106b [12]. In addition, studies have pointed out that the overexpression of lncRNA PTENP1 has been observed *in vitro* to successfully inhibit the proliferation and metastasis of glioma cells [13]. In gastric cancer, PTENP1 can inhibit the progression of gastric cancer by regulating the expression of PTEN protein [14]. In bladder cancer [15], breast cancer [16] and clear-cell renal cell carcinoma [17], PTENP1 also has a tumor suppressor effect. cAMP responsive element binding protein 1 (CREB1) can be used as a potential target for the treatment of hepatocellular carcinoma [18], colorectal cancer [19], gastric cancer [20] and bladder cancer [21]. Polybromo 1 (PBRM1) has clinical application value in kidney cancer [22], breast cancer [23] and cholangiocarcinoma [24]. Heterogeneous nuclear ribonucleoprotein K (HNRNPK) can be used as a potential therapeutic target for gastric cancer [25].

Genes with Strong Positive PTEN Expression Correlations in 12 or more Cancers	Genes with Strong Positive PTEN Expression Correlations in 10 to 12 Cancers	Genes with Strong Positive PTEN Expression Correlations in Several Cancers, but Moderate in Few Cancers	Genes with almost no Correlation with PTEN Expression in UCEC Cancer
PTENP1, ATAD1, WAPAL, TNKS2, MARCH5, CCSER2, CHUK and EIF3A	HIF1AN, SMNDC1, C10orf12, SP3, CSGALNACT2, SMC3, NOC3L, FAM35A, SLK and GBF1	CACUL1, CEP350, BCLAF1, IDE, FAM175B, VTI1A, SHOC2, ZFP91, LCOR and RBM12	DDX46, FAM160B1, USP37, NSD1, RIC1, GBF1, USP9X, RP11-244H3.4 and ATL3
Gene with almost no correlation with PTEN expression in different cancers			Positive expression correlation between PTEN and gene having TF binding site on promoter regions of PTEN in different cancers
<p><u>RFX7</u> in UCS</p> <p><u>DDX46</u> in UCEC</p> <p><u>FAM160B1</u> in UCEC</p> <p><u>USP37</u> in UCEC</p> <p><u>BMPR2</u> in THYM, UCS</p> <p><u>NSD1</u> in UCEC</p> <p><u>RIC1</u> in UCEC</p> <p><u>GBF1</u> in UCEC</p> <p><u>USP9X</u> in UCEC</p> <p><u>RP11-244H3.4</u> in UCEC</p> <p><u>ATL3</u> in UCEC</p>			<p>ACC (YY1: R=0.58)</p> <p>BRCA (YY1: R=0.5)</p> <p>DLBC (YY1: R=0.72)</p> <p>KICH (YY1: R=0.51)</p> <p>KIRP (YY1: R=0.7)</p> <p>THCA (YY1: R=0.65)</p> <p>THYM (YY1: R=0.61)</p>
Genes with the strongest correlation with PTEN in cancers			
<p><u>PTENP1</u>: Strong(ACC, BLCA, BRCA, COAD, DLBC, KICH, KIRP, LUAD, LUSC, OV, PRAD, SKCM, TGCT, THCA, THYM, UCEC, UCS)</p> <p><u>TNKS2</u>: Strong(ACC, BLCA, BRCA, COAD, DLBC, KICH, KIRP, LUAD, LUSC, OV, PRAD, TGCT, THCA); Moderate(SKCM, THYM, UCS); Weak(UCEC)</p> <p><u>MARCH5</u>: Strong(ACC, BRCA, COAD, DLBC, KICH, KIRP, LUAD, OV, SKCM, TGCT, THCA, THYM, UCS); Moderate(BLCA, PRAD); Weak(LUSC, UCEC)</p> <p><u>ATAD1</u>: Strong(ACC, BLCA, BRCA, COAD, DLBC, KICH, KIRP, LUAD, LUSC, OV, PRAD, SKCM, THCA); Moderate(TGCT, UCS); Weak(THYM, UCEC)</p> <p><u>WAPAL</u>: Strong(ACC, BLCA, BRCA, COAD, DLBC, KICH, KIRP, LUAD, OV, PRAD, TGCT, THCA, THYM);</p>			

Moderate(LUSC, SKCM); Weak(UCS); Very Weak(UCEC)
<u>CCSER2</u> : Strong(ACC, BLCA, DLBC, KICH, KIRP, LUSC, OV, PRAD, SKCM, TGCT, THCA, THYM);
Moderate(BRCA, COAD, LUAD, UCS); Very Weak(UCEC)
<u>CHUK</u> : Strong(ACC, BLCA, BRCA, COAD, DLBC, KICH, KIRP, LUAD, OV, TGCT, THCA, THYM);
Moderate(PRAD, SKCM); Weak(LUSC, UCEC, UCS)
<u>EIF3A</u> : Strong(ACC, BLCA, BRCA, COAD, DLBC, KICH, KIRP, LUAD, OV, PRAD, TGCT, THCA);
Moderate(SKCM, THYM); Weak(LUSC, UCS); Very Weak(UCEC)

Table 2: Expression correlation between PTEN and various genes.

Genes	Cancers with low expression of Proposed Cancer Target Genes (Normal-vs-Primary)	OS (Lower Expression Levels vs. Higher Expression Levels)
PTENP1	BRCA(p<10 ⁻¹⁶); Metastatic breast cancer(MYC-amplification(+) vs MYC-amplification(-) p<10 ⁻¹² , CCND1-amplification(+) vs CCND1-amplification(-) <10 ⁻¹² , ERBB2-amplification(+) vs ERBB2-amplification(-) <10 ⁻¹²); COAD(p<10 ⁻³); ESCA(p=0.044); GBM(p=0.013); HNSC(p<10 ⁻⁸); KICH(p<10 ⁻⁶); KIRP(p<10 ⁻³); LIHC(p<10 ⁻⁶); PRAD(p<10 ⁻⁶); Metastatic prostate cancer(ERG-fusion(+) vs ERG-fusion(-) p<10 ⁻¹² , AR-amplification(+) vs AR-amplification(-) p<10 ⁻¹²); STAD(p<10 ⁻⁶); THYM(p=0.033); Thyroid carcinoma(p<10 ⁻⁶);	KIRC(p<10 ⁻⁴) Gastric cancer(p=0.00022) Liver cancer(p=0.0056) Lung cancer(p<10 ⁻⁴)
CREB1	BRCA(p<10 ⁻⁴); KICH(p<10 ⁻¹³); KIRC(p<10 ⁻²); KIRP(p<10 ⁻³); PRAD(p<10 ⁻²); Thyroid carcinoma(p<10 ⁻¹¹); UCEC(p<10 ⁻²)	Esophageal Squamous Cell Carcinoma(p=0.05) KIRC(p<10 ⁻⁴) READ(p=0.0048) THYM(p=0.0082) Lung cancer(p<10 ⁻¹⁵) Breast cancer(p=0.0024)
PBRM1	BLCA(p=0.023); BRCA(p<10 ⁻¹⁰); KICH(p=0.038); KIRC(p<10 ⁻¹⁰); KIRP(p<10 ⁻³); LUAD(p<10 ⁻²); LUSC(p<10 ⁻⁶); PRAD(p=0.031); Metastatic prostate cancer(ERG-fusion(+) vs ERG-fusion(-) p=0.039);	Esophageal Squamous Cell Carcinoma(p=0.026) HNSC(p=0.014) KIRC(p=0.00036) KIRP(p=0.026)

	READ(p=0.011); THYM(p=0.044); Thyroid carcinoma(p<10 ⁻⁸); UCEC(p<10 ⁻⁵);	READ(p=0.018) THYM(p<10 ⁻³) Gastric Cancer(p<10 ⁻⁴) Lung Cancer(p=9.9e ⁻¹⁴)
HNRNPK	KICH(p<10 ⁻¹²); KIRC(p<10 ⁻³); KIRP(p<10 ⁻³); Thyroid carcinoma(p<10 ⁻⁷); UCEC(p=0.013)	BRCA(p=0.049) Esophageal Squamous Cell Carcinoma(p=0.0064) KIRC(p<10 ⁻⁸) READ(p=0.047) STAD(p=0.0023) THYM(p=0.0055) UCEC(p=0.0084) Gastric Cancer(p=3.9e ⁻¹⁴) Lung Cancer(p<10 ⁻⁶)
FBXW2	BLCA(p=0.047); BRCA(p=0.048); KIRC(p<10 ⁻⁶); KIRP(p<10 ⁻²); LUAD(p<10 ⁻⁹); LUSC(p<10 ⁻⁶); PAAD(p=0.049); THYM(p=0.024); Thyroid carcinoma(p<10 ⁻⁸); UCEC(p<10 ⁻¹¹);	Esophageal Squamous Cell Carcinoma(p= 0.0055) KIRC(p<10 ⁻⁵) THYM(p=0.0014) Liver Cancer(p=0.045) Gastric Cancer(p=0.039) Lung Cancer(p<10 ⁻⁶)
APC	BLCA(p<10 ⁻²); BRCA(p<10 ⁻¹³); COAD(p<10 ⁻¹⁴); GBM(p<10 ⁻⁴); KICH(p<10 ⁻²); KIRC(p=0.043); KIRP(p<10 ⁻⁵); LUAD(p<10 ⁻¹⁰); LUSC(p<10 ⁻¹⁰); PRAD(p=0.013); READ(p<10 ⁻⁷); Thyroid carcinoma(p<10 ⁻¹¹); UCEC(p<10 ⁻⁸)	HNSC(p=0.0071) KIRC(p<10 ⁻⁶) LUSC(p=0.048) Gastric Cancer(p=0.0072) Lung Cancer(p<10 ⁻¹³)

Table 3: Statistically significant down-expression of different proposed target genes in most common cancers.

F-box and WD repeat domain containing 2 (FBXW2) can be used as a tumor suppressor in lung cancer to inhibit the growth of cancer cells [26]. Mutations in APC regulator of WNT signaling pathway (APC) can promote the occurrence and development of colorectal cancer [27] and bladder cancer [28]. The genes mentioned above show obvious low expression in some cancers, have abnormal expression in different pathological cancer stages and poor OS prognosis is occurred in several cancers in Table 3 and Table S2.

PTEN Protein Network

We analyzed some genes, including genes that have strongly positive correlation with PTEN, genes that are closely related to PTEN and positively correlated with PTEN found in the STRING database (Analysis using Venn diagram, Figure 4A) (Table 2 and Table S1), and genes which have protein products that have transcription factor binding sites on the promoter regions of PTEN.

KEGG Number	Cellular Process	Protein Gene
hsa05165	Human papillomavirus infection	UBE3A,APC,PPP2R5E,CHUK,PTEN,CREB1
hsa05200	Pathways in cancer	APC,SP1,CHUK,PTEN,MAPK8,ROCK1,CUL2
hsa04071	Sphingolipid signaling pathway	PPP2R5E,PTEN,MAPK8,ROCK1
hsa05161	Hepatitis B	CHUK,PTEN,MAPK8,CREB1
hsa05131	Shigellosis	CHUK,MAPK8,ROCK1
hsa05166	HTLV-I infection	APC,CHUK,MAPK8,CREB1
hsa05215	Prostate cancer	CHUK,PTEN,CREB1
hsa04668	TNF signaling pathway	CHUK,MAPK8,CREB1
hsa04931	Insulin resistance	PTEN,MAPK8,CREB1
hsa04068	FoxO signaling pathway	CHUK,PTEN,MAPK8
hsa04120	Ubiquitin mediated proteolysis	UBE3A,HERC4,CUL2
hsa04380	Osteoclast differentiation	CHUK,MAPK8,CREB1
hsa04728	Dopaminergic synapse	PPP2R5E,MAPK8,CREB1
hsa04151	PI3K-Akt signaling pathway	PPP2R5E,CHUK,PTEN,CREB1
hsa04934	Cushing's syndrome	APC,SP1,CREB1
hsa05206	MicroRNAs in cancer	APC,PTEN,ROCK1
hsa05224	Breast cancer	APC,SP1,PTEN
hsa05225	Hepatocellular carcinoma	APC,PTEN,PBRM1
hsa05167	Kaposi's sarcoma-associated herpesvirus infection	CHUK,MAPK8,CREB1
hsa04024	cAMP signaling pathway	MAPK8,ROCK1,CREB1
hsa04510	Focal adhesion	PTEN,MAPK8,ROCK1
hsa05213	Endometrial cancer	APC,PTEN
hsa04137	Mitophagy - animal	SP1,MAPK8
hsa04927	Cortisol synthesis and secretion	SP1,CREB1
hsa05120	Epithelial cell signaling in Helicobacter pylori infection	CHUK,MAPK8
hsa04622	RIG-I-like receptor signaling pathway	CHUK,MAPK8
hsa04920	Adipocytokine signaling pathway	CHUK,MAPK8
hsa05212	Pancreatic cancer	CHUK,MAPK8
hsa04350	TGF-beta signaling pathway	SP1,ROCK1
hsa05132	Salmonella infection	MAPK8,ROCK1
hsa05210	Colorectal cancer	APC,MAPK8
hsa04658	Th1 and Th2 cell differentiation	CHUK,MAPK8

hsa04657	IL-17 signaling pathway	CHUK,MAPK8
hsa05222	Small cell lung cancer	CHUK,PTEN
hsa01522	Endocrine resistance	SP1,MAPK8
hsa05231	Choline metabolism in cancer	SP1,MAPK8
hsa04620	Toll-like receptor signaling pathway	CHUK,MAPK8
hsa04659	Th17 cell differentiation	CHUK,MAPK8
hsa05142	Chagas disease (American trypanosomiasis)	CHUK,MAPK8
hsa05145	Toxoplasmosis	CHUK,MAPK8
hsa04114	Oocyte meiosis	PPP2R5E,SMC3
hsa04152	AMPK signaling pathway	PPP2R5E,CREB1
hsa04110	Cell cycle	SMC3,STAG1
hsa04140	Autophagy - animal	PTEN,MAPK8
hsa04210	Apoptosis	CHUK,MAPK8
hsa04915	Estrogen signaling pathway	SP1,CREB1
hsa04926	Relaxin signaling pathway	MAPK8,CREB1
hsa05160	Hepatitis C	CHUK,MAPK8
hsa05418	Fluid shear stress and atherosclerosis	CHUK,MAPK8
hsa04261	Adrenergic signaling in cardiomyocytes	PPP2R5E,CREB1
hsa04310	Wnt signaling pathway	APC,MAPK8
hsa04150	mTOR signaling pathway	CHUK,PTEN
hsa04022	cGMP-PKG signaling pathway	ROCK1,CREB1
hsa04530	Tight junction	MAPK8,ROCK1
hsa04621	NOD-like receptor signaling pathway	CHUK,MAPK8
hsa05152	Tuberculosis	MAPK8,CREB1
hsa04062	Chemokine signaling pathway	CHUK,ROCK1
hsa05168	Herpes simplex infection	CHUK,MAPK8
hsa05203	Viral carcinogenesis	UBE3A,CREB1
hsa05016	Huntington's disease	SP1,CREB1
hsa05169	Epstein-Barr virus infection	CHUK,MAPK8
hsa04810	Regulation of actin cytoskeleton	APC,ROCK1

Table 4: Biological pathways related to proteins involved in PTEN network.

Data from the STRING database showed that these proteins are in the same protein network (Figure 4B, Some genes that have strongly positive correlation with PTEN, some genes that are closely related to PTEN, and genes that express PTEN transcription factor binding site proteins are shown).

The proteins in this network participated in different pathways, including human papillomavirus infection, pathways in cancer, sphingolipid signaling pathway, hepatitis B, shigellosis, HTLV-1 infection, prostate cancer, TNF signaling pathway, insulin resistance, FoxO signaling pathway, ubiquitin mediated

proteolysis, osteoclast differentiation, dopaminergic synapse, PI3K-Akt signaling pathway, Cushing's syndrome, MicroRNAs in cancer, Breast cancer, hepatocellular carcinoma and so on (Table 4 and Table S2). All the pathways that PTEN is mainly involved in were indicated in red (Table S2). The protein (YY1) with transcription factor binding site in the promoter region of PTEN also participated in the PTEN protein network. As shown in Table S2, this protein was also involved in most pathways with the participation of PTEN (Table S2). In addition, we used the RNAup webserver to analyze the RNA-RNA interaction and RNA-protein interaction between YY1 and PTEN, which indicated that they had close correlations (Figure 4C and Figure 4D).

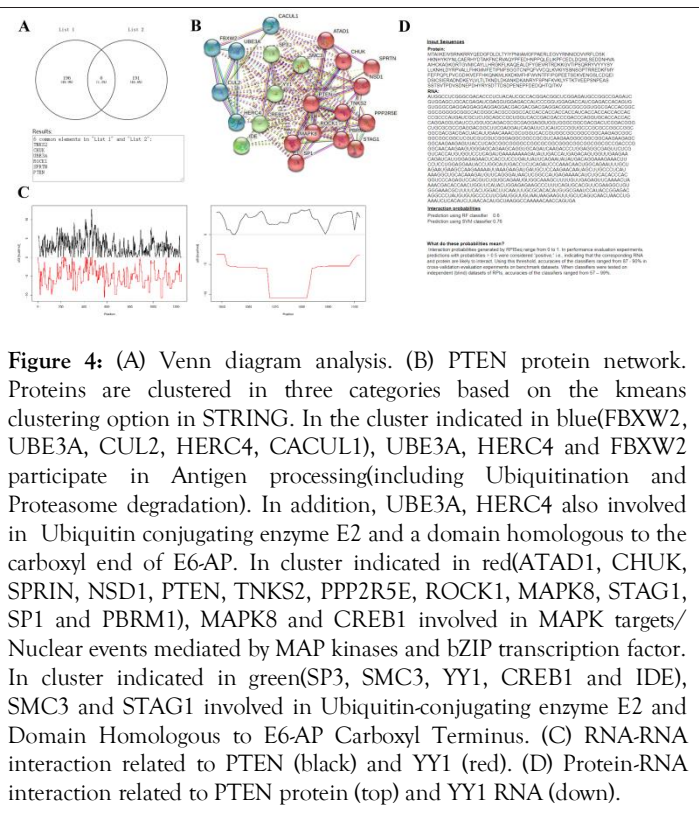


Figure 4: (A) Venn diagram analysis. (B) PTEN protein network. Proteins are clustered in three categories based on the kmeans clustering option in STRING. In the cluster indicated in blue(FBXW2, UBE3A, CUL2, HERC4, CACUL1), UBE3A, HERC4 and FBXW2 participate in Antigen processing(including Ubiquitination and Proteasome degradation). In addition, UBE3A, HERC4 also involved in Ubiquitin conjugating enzyme E2 and a domain homologous to the carboxyl end of E6-AP. In cluster indicated in red(ATAD1, CHUK, SPRIN, NSD1, PTEN, TNKS2, PPP2R5E, ROCK1, MAPK8, STAG1, SP1 and PBRM1), MAPK8 and CREB1 involved in MAPK targets/ Nuclear events mediated by MAP kinases and bZIP transcription factor. In cluster indicated in green(SP3, SMC3, YY1, CREB1 and IDE), SMC3 and STAG1 involved in Ubiquitin-conjugating enzyme E2 and Domain Homologous to E6-AP Carboxyl Terminus. (C) RNA-RNA interaction related to PTEN (black) and YY1 (red). (D) Protein-RNA interaction related to PTEN protein (top) and YY1 RNA (down).

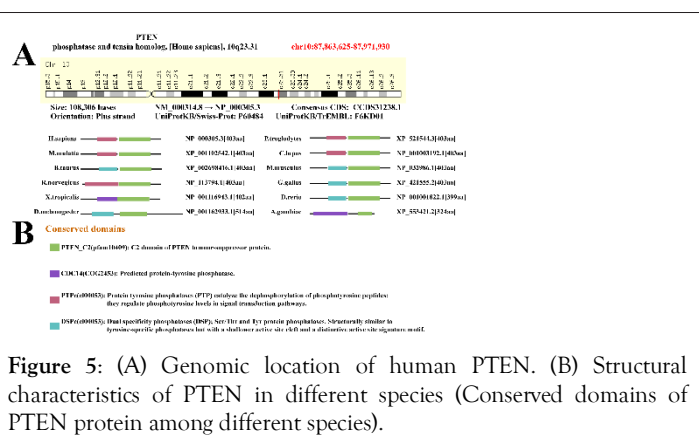


Figure 5: (A) Genomic location of human PTEN. (B) Structural characteristics of PTEN in different species (Conserved domains of PTEN protein among different species).

Analysis of PTEN Structural Features

We analyzed the basic structure of PTEN (NM_000314.8 for mRNA and NP_000305.3 for protein) (Figure 5A), and the conserved domains of PTEN among different species. As shown in Figure 5B, PTEN has conserved protein structures in different species (eg. H.sapiens, P.troglodytes, M.mulatta, C.lupus, etc) and all of these contain the PTEN_C2 domain (Figure 5B).

DISCUSSION

PTEN acts as a dual-specific protein phosphatase dephosphorylating tyrosine, serine and threonine in proteins, and it can also act as a lipid phosphatase, which is essential for its tumor suppressor effect. Therefore, the occurrence of PTEN mutations and the abnormally low expression of PTEN may lead to uncontrolled cell proliferation, which may be one of the main characteristics of cancer.

Our study firstly conducted a comprehensive analysis of the expression of PTEN in a variety of tumors. Our results showed that PTEN was down-regulated in all 17 different cancers studied, which is in agreement with earlier reports about PTEN showing decreased somatic expression of PTEN in various tumor types. In fact, low expression of PTEN has been reported in gastric cancer [29], prostate cancer [30], liver cancer [31], colorectal cancer [32], etc. This was also confirmed in our data. For example, a study by Monica Prasad Hayes et al showed that PTEN mutations often occur in endometrioid carcinoma [33], and our study also showed that PTEN expression is significantly absent in UCEC Endometrioid tissue subtype (Table 1). More importantly, our research showed that the low expression of PTEN was a common feature in the 17 human cancers analyzed in this study, which indicated that it is a tumor suppressor gene. Moreover, the current study revealed the significant PTEN low-expression across the histological and molecular subtypes of different tumors mentioned in the results and possible associations between PTEN expression and different patient conditions. For example, smoking and drinking habits in LUSC and PAAD. In addition, the expression of PTEN, based on the pathological stage of the patient, indicated that the low expression of PTEN may be related to tumor occurrence, progression and invasion. Also, we found that PTEN mutations existed in a variety of cancers, most of which are truncation mutations and missense mutations.

We showed that patients with low PTEN expression had a shorter overall survival time and poorer prognosis. Moreover, the low expression level of PTEN also lead to poor prognosis of relapse free survival in many cancers, thus confirming that low expression of PTEN can lead to poor clinical prognosis of many tumors. For example, a report by J P Fan et al showed that lower levels of PTEN can lead to worse prognosis of gastric cancer, and our data also confirmed this point (Figure 3A).

Our research had identified some genes related to the PTEN protein network, these genes were involved in multiple pathways among the tumors we studied, including Pathways in cancer (APC, SP1, CHUK, PTEN, MAPK8, ROCK1, CUL2), Cell cycle (SMC3 STAG1) and Apoptosis (CHUK, MAPK8), etc. Among the genes involved in the pathway of cancer, lncRNA activated by APC can inhibit the occurrence of colorectal cancer by reducing the production of exosomes [34]; LINC01638 activated by SP1 can promote the proliferation and migration of gastric cancer cells by regulating epithelial-mesenchymal transition [35]; as a target of miR-379, CHUK inhibition induced by miR-379 can prevent the growth of NSCLC tumors [36]; abnormality in the Fas signaling pathway involved by MAPK8 can increase the risk of gastric cancer [37]; activated Rho/ROCK1 signaling pathway can worsen breast cancer [38]. Among the genes involved in the cell cycle, the RAD21 protein complex composed of genes such as SMC and SMC1A participates in the aggregation of sister chromatids [39]. Similarly, STAG1/STAG2 is also part of the adhesion protein complex, which participates in the adhesion of

sister chromatids(40). Among the genes involved in apoptosis, the overexpression of CHUK can promote the proliferation of Mantle cell lymphoma cells and inhibit its apoptosis pathway [41]. MAPK8 can inhibit tumor cell apoptosis through the MAPK signaling pathway [42]. Among the genes involved in oocyte meiosis, SMC3 can enhance chromosome cohesion to ensure accurate chromosome separation [43]. Among the genes involved in the AMPK signaling pathway, CREB1 can upregulate GLUT3 to enhance the efficacy of colorectal cancer therapy [44]. Our data emphasizes that the PTEN network is one of the main protein networks involved in cancer, and further research on it in tumors may provide inspiration for new treatment strategies for cancer.

We analyzed the gene transcription factor YY1 which was co-expressed by PTEN. It has a binding site in the PTEN promoter region and can affect the expression of PTEN to regulate tumor development. This is consistent with previous studies [45]. In addition, we also analyzed the RNA interaction and RNA-protein interaction between YY1 and PTEN, indicating that YY1 and PTEN were closely related (Figure 4C and Figure 4D).

In addition, we searched for several PTEN-correlated genes (PTENP1, CREB1, PBRM1, HNRNPK, FBXW2, APC) that may be closely related to cancer treatment. Moreover, their expression levels in some tumors were significantly reduced, and these low-expressed genes had a worse OS prognosis (Table 3), which indicated that they may be potential targets for cancer treatment.

Finally, we analyzed the structural characteristics of PTEN and the structural diagrams of PTEN protein in different species, from which we obtained the conserved domains of PTEN in different species. Moreover, the conserved protein structures of PTEN in different species all contain the PTEN_C2 domain (Figure 5).

CONCLUSION

All in all, the current research showed that PTEN can be regarded as a tumor marker and research on its related pathways can help discover common therapeutic targets for cancer. However, further functional studies are needed to clarify the relevant role of PTEN in cancer.

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the GEPIA repository, [<http://gepia.cancer-pku.cn/>];

The datasets generated and/or analysed during the current study are available in the UALCAN database, [<http://ualcan.path.uab.edu/>];

The datasets generated and/or analysed during the current study are available in the STRING database, [<https://string-db.org/>];

The datasets generated and/or analysed during the current study

are available in the cBioportal website, [<http://www.cbioportal.org/>];

The datasets generated and/or analysed during the current study are available in the Kaplan-Meier Plotter, [<http://kmplot.com/analysis/index.php?p=background#>];

The datasets generated and/or analysed during the current study are available in the PROMO database, [http://algen.lsi.upc.es/cgi-bin/promo_v3/promo/promoinit.cgi?dirDB=TF_8.3];

The datasets generated and/or analysed during the current study are available in the RNAup Webserver, [<http://rna.tbi.univie.ac.at/cgi-bin/RNAWebSuite/RNAup.cgi>] and RPISeq, [<http://pridb.gdcdb.iastate.edu/RPISeq/>].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CSY offered main direction and significant guidance of this review. ZH and ZWH drafted the manuscript. YXY, WSZ, ZBC, FJL and CBZ revised the manuscript. All authors read and approved the final manuscript.

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None.

ABBREVIATIONS

TCGA: the Cancer Genome Atlas; GTEX: Genotypic-Tissue Expression; PTEN: Phosphatase and tensin homolog; OS: overall survival; RFS: Relapses Free Survival; PI3K: phosphatidylinositol 3 kinase; PRCC: papillary renal cell carcinoma; TNBC: triple negative breast cancer; M: mesenchymal; IM: immunomodulatory; BL2: basal like2; BL1: basal like1; ILC: invasive lobular carcinoma; IDC: invasive ductal carcinoma; MYC: MYC proto-oncogene; CnD1: cyclin D1; ERBB2: ERB-B2 receptor tyrosine kinase 2; PTENP1: phosphatase and tensin homolog pseudogene 1; ATAD1: ATPase family AAA domain containing 1; WAPAL: wings apart-like homolog; TNKS2: tankyrase 2; MARCH5: membrane-associated ring finger 5; CCSER2: coiled-coil serine rich protein 2; CHUK: component of inhibitor of nuclear factor kappa B kinase complex; EIF3A: eukaryotic translation initiation factor 3 subunit A; HIF1AN: hypoxia inducible factor 1 subunit alpha inhibitor; SMNDC: survival motor neuron domain containing 1; C10orf12: chromosome 10 open reading frame; SP3: Sp3 transcription factor; CSGALNACT2: chondroitin sulfate N-acetylgalactosaminyltransferase 2; SMC3: structural maintenance of chromosomes 3; NOC3L: NOC3 like DNA replication regulator; FAM35A: family with sequence similarity 35 member A; SLK: STE20 like kinase; GBF1: golgi brefeldin A resistant guanine nucleotide exchange factor 1; DDX46: DEAD-box helicase 46; FAM160B1: family with sequence similarity 160,

member B1; USP37: ubiquitin specific peptidase 37; NSD1: nuclear receptor binding SET domain protein 1; RIC1: RIC1 homolog, RAB6A GEF complex partner 1; GBF1: golgi brefeldin A resistant guanine nucleotide exchange factor 1; USP9X: ubiquitin specific peptidase 9 X-linked; ATL3: atlastin GTPase 3; PBRM1: Polybromo 1; HNRNPK: Heterogeneous nuclear ribonucleoprotein K; FBXW2: F-box and WD repeat domain containing 2; ACC: adrenocortical carcinoma; BLCA: bladder urothelial carcinoma; BRCA: breast invasive carcinoma; COAD: colon adenocarcinoma; DLBC: lymphoid neoplasm diffuse large B-cell lymphoma; KICH: kidney chromophobe; KIRP: kidney renal papillary cell carcinoma; LUAD: lung adenocarcinoma; LUSC: lung squamous cell carcinoma; OV: ovarian serous cystadenocarcinoma; PRAD: prostate adenocarcinoma; SKCM: skin cutaneous melanoma; TGCT: testicular germ cell tumors; THCA: thyroid carcinoma; THYM: thymoma; UCEC: uterine corpus endometrial carcinoma; UCS: uterine carcinosarcoma

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