Overexpressing PTTG Family Genes Predict Poor Prognosis in KIRC

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Research

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Abstract

Background: Pituitary tumor transforming genes (PTTG1, PTTG2 and PTTG3P) play a key role in the pathogenesis and development of human cancers. Studies show that overexpression of the PTTG genes is associated with tumor progression and migration. However, little is known about the function of the PTTG genes in the prognostic value of renal clear cell carcinoma (KIRC).

Methods: the expression and survival data for KIRC patients were mined from ONCOMINE, UALCAN, Human Protein Atlas, TCGAportal, GEPIA2, MetascapecBioPortal databases and STRING.

Results: PTTG1, 2, and 3P mRNA and protein expression was upregulated in KIRC patients compared to normal tissues, and higher expression levels of PTTG family genes were associated with shorter overall survival (OS). what's more, overexpression of the PTTG family genes has been found to correlate with individual cancer stages and pathological tumor grades. In addition, 18% of mutations in the PTTG family genes were associated with short-term survival in patients with KIRC

Conclusions: we found that a single PTTG genes or PTTG family genes as a whole may be a potential prognostic biomarker for KIRC.

Background

Renal cell carcinoma (RCC) is one of the most common malignancies in the world, accounting for 4.2% of all new cancer cases, with an estimated 73,820 new case in the United States in 2019, The incidence and mortality of kidney cancer have been steadily increasing, especially with clear cell carcinoma of the kidney (KIRC) accounting for 75% of all kidney cancers [1, 2]. Because the kidney is located deep in the body and protected by surrounding tissues and organs, it can be difficult to identify lesions that appear on it. As a result, the clinical symptoms of KIRC disease are often difficult to diagnose until advanced stage or distant metastasis, which results in a 3-year survival rate of less than 5% in the KIRC population [3]. Although efforts have been made to study the mechanism of the occurrence, development and metastasis of KIRC disease. However, the molecular characterization of KIRC remains unknown. Therefore, in order to improve prognosis, reliable biomarkers must be found to identify high-risk patients who require treatment and intervention. PTTG was originally separated from the tumor of the pituitary tumor, a multi-function protein, involved in cell cycle, cell proliferation, angiogenesis, and metastasis [4]. PTTG consistins of two genes with protein products PTTG1 and PTTG2, and a processed pseudogene PTTG3P, has been described in the context of carcinogenesis [5]. Overexpression of PTTG was reported in many cancers including lung, gastric, kidney, pancreatic, breast cholangiocarcinoma, psoriasis, Adrenocortical Carcinomacarcinoma, hepatocellular carcinoma, glioblastoma, esophageal squamous cell carcinoma, and prostate cancer [6–15]. Therefore, the PTTG family genes could not only act as prognostic signatures but also become druggable targets for cancer therapy. Even though there have been extensive researches have investigated the role of on PTTG family genes in human malignant tumors, the utility of the PTTG family genes however for the KIRC diagnosis and prognosistic role of

PTTG deletion in KIRC remains unclear. In present study, we investigated the association between PTTG expression and its diagnostic as well as prognostic value in KIRC. In addition, we explored potential molecular pathways for KIRC through analyzed the gene interaction network analysisby obtaining similar genes to further explore the potential molecular pathway in KIRC.

Methods

ONCOMINE

ONCOMINE database (www.oncomine.org) is an integrated online cancer microarray database used for DNA or RNA sequence analysis and to facilitate gene expression analysis for discovery [16]. In our study, transcriptional expressions of PTTG members between different cancer tissues and their corresponding adjacent normal control samples were got from ONCOMINE database. Difference of transcriptional expression was compared by students' t-test. We set 0.05 as p-value cutoff and 1.5 as fold change to generate a p-value. The Cut-off values for p-value and fold change are as follows: p value: 0.01, fold change: 1.5, gene rank:10%, data type: mRNA.

UALCAN

UALCAN (http://ualcan.path.uab.edu) is an interactive web resource based on level 3 RNA sequences and clinical data from 31 cancers in the TCGA database. It is mainly used to analyze the relative transcriptional expression of a gene between tumor and normal samples, and the correlation between transcriptional expression and related clinicopathological parameters [17]. In this study, UALCAN was used to analyze the mRNA expressions of PTTG family members in KIRC tissues and their association with clinicopathologic parameters and tumor grades and individual cancer stages. the cutoff of p-value was set as 0.01 in the Student's t-test.

Human Protein Atlas

The Human Protein Atlas (https://www.proteinatlas.org) is a nearly 20 kinds of immunohistochemical expression data of common types of cancer, each tumor types including 12 individual tumors site [18]. Users can identify proteins that are differentially expressed in a particular tumor type, In this study. We compare the protein expression of different members of the PTTG family in normal tissues and in KIRC tissues.

cBioPortal

cBioPortal (http://www.cbioportal.org) has been used as an online access database to explore cancer genomic data from multiple perspectives [19]. Our current study obtained gene mutation and survival data from 510 KIRC samples in the TCGA database in cBioPortal. We set ± 1.8 as the z-score threshold of mRNA Expression (RNASeq V2 RSEM) were also applied to explore the relationship among the genetic

alterations in PTTG family members and the overall survival (OS) of KIRC patients. p value as 0.05 was accepted.

TCGAportal

TCGAportal (www.tcgaportal.org) is an online portal allows parallel comparisons of multiple tumors and detailed analysis of individual tumors, which we use to view survival information in the PTTG family and cross-verify with other sites.

GEPIA2

GEPIA2 (http://gepia2.cancer-pku.cn/#index) Is an open access dataset used to analyze RNA sequencing expression data from 9,736 tumors and 8,587 normal samples of TCGA. In our study, We looked for the top 30 genes that are similar to the PTTG family in KIRC by using the similar gene detection module. After removing the repeated genes, 90 genes were reserved to further analysis. The cutoff of p-value was set as 0.05 in Student's t-test.

Metascape

Metascape (http://metascape.org/gp/index.html#/main/ step1) is a database that uses data from more than 40 independent knowledge bases combined with rich features, interaction analysis, gene annotation, and member search. In addition, it facilitates the comparative analysis of multiple independent and orthogonal experiments across data sets by the portal [20]. The GO module can analyze the functional roles of genes related to PTTG family members in biological processes (BP), cellular components (CC), and molecular functions (MF). And KEGG pathways of the PTTG family members.

STRING

STRING (http://string-db.org) is a database that collects, aggregates, and scores publicly available data to explore potential protein interaction networks. Members of the PTTG family genes and their similar genes were generated PPI network by STRING.

Result

The mRNA and protein of the PTTG family gene is overexpressed in patients with KIRC disease

To explore distinct prognostic and potential therapeutic value of different PTTGs in KIRC patients, mRNA expression and protein expression were analyzed by ONCOMINE database, UALCAN, and Human Protein Atlas. As shown in Fig. 1and Fig. 2, mRNA expressions of PTTGs family members in 20 types of cancers were first measured and compared to normal tissues by ONCOMINE database. As were shown in Fig. 1, mRNA expression of PTTGs family members in 20 types of cancers were measured and compared to normal tissues by ONCOMINE database. and in Fig. 1 Significant changes in *PTTG1* and *PTTG2* transcriptional levels between KIRC and normal tissues were observed in different datasets, In Beroukhim Renal Statistics, *PTTG1* over-expression was found in Non-Hereditary Clear Cell Renal Cell Carcinoma

tissues compared with normal tissues with a fold change of 5.231 (p = 7.53E-10), and Hereditary Clear Cell Renal Cell Carcinoma was a fold change of 4.026 (p = 7.66E-10) and in Lenburg Renal Statistics, they found 1.683 fold change in *PTTG1* mRNA expression in KIRC tissues (p = 9.18E-4). In Gumz Renal Statistics, they found 1.922fold change in *PTTG1* mRNA expression in KIRC tissues (p = 9.38E-5) when in Jones Renal Statistics, 1.676fold change (p = 1.08E-8) has been found. Significant up-regulation of *PTTG2* was also found in KIRC tissues compared to normal tissues. The result from Lenburg Renal Statistics showed that there were 1.060fold change (p = 0.039) increase in *PTTG2* mRNA expression in KIRC tissues, respectively. We further examined the mRNA expression profiles of PTTGs family members using UALCAN, which, unlike oncomine, was sourced from clinical data on 31 cancer types in the Level 3 RNA-seq and TCGA databases. As was shown in Fig. 2, mRNA expression of PTTGs members were all found to be significantly up-regulated in KIRC tissues compared to normal samples (all $p < 0.05$). Then we tried to explore the protein expression patterns of PTTGs in KIRC by the Human Protein Atlas, *PTTG3P* protein were not expressed in normal renal tissues and in KIRC tissues. however, low protein expressions of *PTTG1, PTTG2* were expressed in normal renal tissues, while high protein expressions of them were observed in KIRC tissues (Fig. 2). Taken together, our results showed that transcriptional and proteinic expressions of PTTGs were over-expressed in patients with KIRC.

Relationship between mRNA expression of genes of different PTTG family members and clinical pathological in KIRC patients

After mRNA expression and protein expressions were found to be over-expressed in KIRC patients, we next analyzed the relationship between mRNA expression of different PTTGs family members with clinicopathological parameters of KIRC patients by UALCAN, including individual cancer stages and tumor grades. As was shown in Fig. 3, The mRNA expression of PTTGs family members was correlated with individual cancer stage, indicating that patients with more advanced cancer stages tended to have higher PTTGs mRNA expression. Similarly, mRNA expressions of PTTGs family members were significantly related to tumor grades, and as tumor grade increased, the mRNA expression of PTTGs have a tendency to increase. the results above suggested that mRNA expressions of PTTGs family members were significantly associated with clinicopathological parameters in KIRC patients.

Prognostic value of mRNA and protein expression of PTTGs in KIRC patients

We used UALCAN to analyze the prognostic values of the mRNA expression of PTTGs in KIRC patients. As was shown in Fig. 4, mRNA expression in members of the PTTG family was significantly associated with prognosis in patients with KIRC disease. First, The relationship between mRNA expression of different family members and prognosis of patients with KIRC disease was analyzed, higher mRNA expression of PTTGs were significantly associated with shorter OS of KIRC patients, then we used Human Protein Atlas to analyze the prognostic values of the protein expression of PTTGs in KIRC patients, The results showed that the expression level of PTTGs was significantly correlated with prognosis in KIRC. finally, we used TCGAportal to analyze the prognostic values of the mRNA expression of PTTGs in KIRC patients, The results also showed a correlation with prognosis, These results indicate that PTTGs mRNA

and protein expression are significantly associated with prognosis in patients with KIRC and can be used as a biomarker to predict survival in patients with KIRC.

The correlations between genetic mutations in PTTGs family numbers and OS of KIRC patients

We used cBioPortal to analyze the genetic mutations of differentially expressed PTTG family members in KIRC patients. Based on Fig. 5, the mutation rate of *PTTG1, PTTG2, PTTG3P* genes was 14%, 4% and 5% in 510 samples. What's more, the association between genetic mutations and the prognosis of KIRC patients was explored. And a statistically significant correlation was found between genetic mutations of PTTG family numbers and OS (p = 9.838 E-3) in KIRC patients.

Networks Analyses and Functional Enrichment Analysis of PTTG family genes and their Neighboring Genes in KIRC patients

After confirmed the correlation between genetic mutations in PTTG family numbers and prognose values. Then, similar genes of the PTTG family (90 in total) obtained from GEPIA2 and Metascape were used for GO enrichment to explore the interaction between similar genes. Based on 90 adjacent genes, the online tools of Metascape and STRING were used for functional and pathway enrichment analysis, and a PPI interaction network was established to explore the biological classification of PTTG. The functions of PTTG family members neighboring genes were predicted by analyzing GO and KEGG in Metascape. The GO enrichment items were classified into four functional groups:,KEGG pathway, biological process group, molecular function group, and cellular component group (Figs. 6). The PTTG family members and their similar genes was Enriched in the following information, cell division, microtubule cytoskeleton organization involved in mitosis, regulation of chromosome segregation, positive regulation of ubiquitin protein ligase activity, chromosome condensation, kinetochore organization in biologic processes (BP); and spindle, midbody, platelet alpha granule lumen, mitochondrial outer membrane in cellular components (CC); and HTLV-I infection in KEGG pathway. The PPI network interaction of PTTG family genes and similar genes was conducted by String to seek possible downstream targets and mechanism research, and it was found that *CENPW, CENPA, HMMR, CDC20* and other genes could be used as the target genes for further research and analysis.

Discussion

As mentioned earlier, the PTTG family is widely expressed in a variety of tumors. Although PTTG has been shown to play a role in the occurrence and prognosis of many cancers, The role of PTTG in KIRC still requires further bioinformatics analysis, We hope that our study will provide new insights into the clinical diagnosis, therapeutic targets and tumor development mechanisms of KIRC. Our results indicate that overexpression of the PTTG gene is found in KIRC, and that PTTG is significantly associated with individual cancer stage and tumor grade in KIRC patients. mRNA expressions of PTTGs were significantly associated with shorter OS in KIRC patients. *PTTG1* and *PTTG2* protein over-expressions also associated with shorter OS, Moreover, The mutation rate (18%) of PTTGs was observed in KIRC patients and the genetic alteration in PTTGs was associated with shorter OS. Finally The PTTG family members and their

similar genes was Enriched in cell division, microtubule cytoskeleton organization involved in mitosis, regulation of chromosome segregation, positive regulation of ubiquitin protein ligase activity, chromosome condensation, kinetochore organization in biologic processes (BP); and spindle, midbody, platelet alpha granule lumen, mitochondrial outer membrane in cellular components (CC); and HTLV-I infection in KEGG pathway. *PTTG1* has the ability to promote tumorigenesis in human embryonic kidney cells at least in part by regulating the expression or secretion of bFGF, VEGF and IL-8 [21]. *PTTG1* expression was significantly correlated with lymph node metastasis, clinical stage and degree of tumor differentiation in patients with laryngeal cancer [22]. *PTTG1* is overexpressed in KIRC, and the higher the grade of tumor cells, the higher the expression is, and it is associated with poor prognosis [23]. In our present study, Consistent with previous studies, *PTTG1* mRNA and protein expression was found to be significantly higher in KIRC tissues compared to normal tissues, and *PTTG1* mRNA expression was significantly associated with individual cancer stage and tumor grade in patients. In addition, high *PTTG1* expression was also significantly associated with shorter survival in patients with KIRC, suggesting that *PTTG1* is involved in the development of KIRC tumors. It has been reported that *PTTG2* is involved in the regulation of epidermal cell survival and migration, induces epithelial-mesenchymal transformation by regulating the expression of vimentin and E-cadherin, and is a potential therapeutic target for psoriasis [9]. It has been found that *PTTG2* leads to the down-regulation of E-cadherin and the increase of vimentin level, which is involved in the occurrence and development of tumors [24]. In addition, *PTTG2* overexpression also inhibits apoptosis in glioblastoma by affecting caspase-3-dependent signaling pathways [25]. In our study, significantly higher mRNA and protein expression of *PTTG2* were found in KIRC tissues, and mRNA expression of *PTTG2* was remarkably correlated with patients' individual cancer stages and tumor grades. Moreover, higher mRNA expression of *PTTG2* was also significantly related with poorer OS of KIRC patients and was an independent prognostic factor for shorter OS of KIRC patients, playing an oncogenic role of *PTTG2* in KIRC. Overexpression of *PTTG3P* has been shown to promote tumorigenesis by upregulating *PTTG1* and activating *PI3K/ Akt* signaling and downstream signaling, including genes related to cell cycle progression, apoptosis, and epithelial mesenchymal transformation (EMT) [26]. Previous studies have also reported high expression of *PTTG3P* in breast cancer and found that *PTTG3P* expression is inversely correlated with estrogen receptor (ER) and progesterone receptor (PR) status, and high expression of *PTTG3P* has also been found to be associated with poor prognosis of breast cancer [27]. In addition, some studies have shown that enhanced *PTTG3P* expression stimulates the migration and invasion of ESCC cells, thus promoting the expression levels of *PTTG1* and *PTTG2* in vitro, and realizing its carcinogenic function by positively regulating its parent genes *PTTG1* and *PTTG2* [28]. In our study, significantly higher *PTTG3P* expression was found in the KIRC tissues, and *PTTG3P* expression was significantly correlated with individual cancer stage and tumor grade of the patients. High expression of *PTTG3P* was also significantly associated with adverse OS in patients with KIRC and was an independent prognostic factor for shorter OS in patients with KIRC, suggesting that *PTTG3P* is involved in the oncogenesis of KIRC.

Conclusion

The PTTG family genes plays an important role in KIRC. High expression of PTTG family genes may be a diagnostic and prognostic indicator in patients with KIRC. In addition, The relationship between genes related to cell division and KIRC disease and the relationship between genes such as *CENPW, CENPA, HMMR, CDC20* and KIRC are also worthy of further study.

Abbreviations

KIRC：Kidney renal clear cell carcinoma

Declarations

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Authors' contributions

Yonghui Gui is responsible for writing and submitting the papers; Xueni Liu are responsible for data analysis and collation; Chao Wang are responsible for the production of pictures; PengYang are responsible for the manuscript fees and ideas guidance. The authors read and approved the final manuscript.

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Availability of data and materials

The data used to support the findings of this study are included within the article.

Ethics approval and consent to participate

There were no cell, tissue, or animal studies. No ethical requirements are involved.

Consent for publication

All authors agree to publish the paper.

Competing interests

The authors declare that they have no competing interests.

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