GPR137 is a promising novel bio-marker for the prognosis of bladder cancer patients

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Abstract

Objective: G protein-coupled receptor 137 (GPR137) was reported to be associated with several cancers, but its role in bladder cancer has not been reported. The purpose of this study was to evaluate clinical significance of GPR137 in bladder cancer.

Methods: The expressions of GPR137 in pathological tissues and corresponding normal tissues from bladder cancer patients were detected via quantitative real time polymerase chain reaction (qRT-PCR). Western blot was performed to detect GPR137 expression in bladder cancer tissues and adjacent normal tissues. Chi-Squared test analyzed the relationship between GPR137 expression and clinical features of bladder cancer patients. Additionally, Kaplan–Meier method was adopted in estimating overall survival of bladder cancer patients. Prognostic value of GPR137 was evaluated through Cox regression analysis.

Results: The expression of GPR137 mRNA and protein in pathological tissues was significantly higher than that in adjacent normal tissues ($P<.001$). Moreover, similar result was found for bladder cancer patients and healthy controls ($P<.001$). And GPR137 expression was associated with tumor size ($P=.006$) and TNM stage ($P=.012$). The results of Kaplan–Meier analysis suggested that patients with high expression of GPR137 had shorter overall survival time than those with low expression (Log rank test, $P=.001$). Cox regression analysis indicated that GPR137 could act as an independent biomarker for bladder cancer prognosis ($HR=1.850$, 95\% CI = 1.272–2.689, $P=.001$).

Conclusion: Abnormal expression of GPR137 is associated with bladder cancer and GPR137 is a potential biomarker for the therapy and prognosis of bladder cancer.

Abbreviations: cDNA = complementary DNA, CNS = central nervous system, GPCRs = G-protein-coupled receptors, GPR137 = G protein-coupled receptor 137, MIBC = muscle invasive bladder cancer, oGPCRs = orphan GPCRs, qRT-PCR = quantitative real-time polymerase chain reaction.

Keywords: biomarker, bladder cancer, G protein-coupled receptor 137

1. Introduction

Bladder cancer is one of the most common genitourinary malignancies with frequent recurrence and high mortality.\cite{1,2} Currently, main diagnostic and surveillance strategies for bladder cancer depend on cystoscopy and urine cytology.\cite{3} However, these techniques have some limitations and could not provide satisfactory outcomes.\cite{4} Thus, exploiting novel biomarkers related to genetic alterations during tumorigenesis may greatly help to improve clinical outcomes of bladder cancer patients. G-protein-coupled receptors (GPCRs) are the largest family of membrane proteins for signal transduction on cell surface.\cite{5} There are approximately over 800 GPCRs in human genome, most of which share 7 homology transmembrane domains.\cite{6,7} In order to activate specific heterotrimeric G proteins, GPCRs change the conformation of specific ligands via combining with the ligands. Then signal network will be activated, causing various cellular responses.\cite{8} At the present, corresponding specific ligands for most GPCRs are known, but there are still over 100 GPCRs called orphan GPCRs (oGPCRs) whose ligands are unknown.\cite{9} G protein-coupled receptor 137 (GPR137) is an oGPCR encoding gene, generally expressing in central nervous system (CNS), endocrine gland, thymus and lung.\cite{10} It has been reported that GPCRs play crucial roles in tumor progression and metastasis.\cite{11} Moreover, GPR137 was found to be associated with different cancers including gastric cancer,\cite{12} pancreatic cancer,\cite{13} colon cancer,\cite{14} and malignant glioma.\cite{15} GPR137 was highly expressed in clinical ovarian cancer tissues, and it played pro-oncogenic roles in the disease via regulating PI3K/AKT pathway.\cite{16} But its function in bladder cancer has not been reported in previous studies.

In this study, we aimed to detect relative expression of GPR137 in pathological tissues and corresponding normal tissues from bladder cancer patients. In addition, the associations between the levels of GPR137 and clinical features were analyzed to estimate...
the impact of GPR137 on bladder cancer progression. We also expected to evaluate overall survival between patients showing different GPR137 levels and to assess prognostic value of GPR137 adopting Cox regression analysis.

2. Materials and methods

2.1. Patients and specimens

One hundred ten patients confirmed with bladder cancer through pathological and clinical diagnoses in First People’s Hospital, Jining were included in this study. Pathological specimens and adjacent normal tissues were collected and stored in liquid nitrogen until application. None of the patients had received chemotherapy or radiotherapy before tissue samples were collected. 62 healthy controls were from physical examination center of the hospital. The study was approved by Ethics Committee of the hospital and all of the patients had signed written informed consents in advance. Bladder cancer tissues and adjacent normal tissues were obtained and immediately snap-frozen in liquid nitrogen and stored at −80°C. 2 ml peripheral venous blood from each of bladder cancer patients and healthy controls were put into blood collection tube with EDTA, centrifugated for supernate (serum), stored at 2°C for 40 minutes. RNA extraction was conducted in a short time, stored at −80°C for quantitative analysis. The sampling was completed about 1 and a half years.

Follow-up investigation lasted about 5 years and all patients participated in the investigation. Follow-up data and clinical features were collected in a database. Overall survival was used for estimating clinical influence of GPR137 on bladder cancer.

2.2. RNA extraction and qRT-PCR

Total RNA was separately extracted from pathological tissues, corresponding normal tissues and serum samples using Trizol reagent (Invitrogen, Carlsbad, CA) according to the manufacturer’s instruction. Residual DNA in total RNA was dealt with residual DNA removal reagent (Invitrogen, Carlsbad, CA) according to the manufacturer’s instruction. Residual DNA in total RNA was dealt with. UV absorbance was used to detect the concentration of total RNA (A260/A280). The quality of total RNA was tested adopting 1% agarose gel electrophoresis. The concentration and purity of extracted RNA were detected through ultraviolet spectrophotometer, and extracted RNA samples were stored in −80°C refrigerator.

2.3. Immunohistochemistry

Paraffin-embedded tissue sections (formalin fixed) was cut into 4-μm and put into 65°C oven for deparaffinization, antigen retrieval for 60 minutes. It was blocked by goat serum and sections were incubated overnight with primary antibody (1:100 dilution) at 4°C. After treatment with antigen retrieval, antibody, antibody complex was detected employing avidin-biotin-peroxidase complex solution and visualized using DAB, hematoxylin stain.

The staining of tissue sections were observed and recorded by 2 pathologists. Staining ranges contained: <5%, 0 point; 5% to 25%, 1 point; 26% to 50%, 2 points; 51% to 75%, 3 points; >75%, 4 points. Staining intensities were as follows: non-staining, 0 point; light yellow, 1 point; brownish yellow, 2 points and brown, 3 points. Final scores were the sum of scores for staining range and staining intensity. And scores ≤3 stood for low expression while those >3 for high expression.

2.4. Western blot analysis

Total protein from tissues was isolated using RIPA lysis buffer (Beyotime, Nantong, China) and quantified using a BCA assay kit (Pierce, Rockford, IL, USA). A total of 200 μg of protein was separated by SDS-PAGE and transferred onto PVDF membranes (Schleicher & Schuell GmbH, Dassel, Germany). After incubating with 5% skim milk at room temperature, the membranes were incubated with primary antibodies overnight at 4°C. Then, the membranes were incubated with corresponding secondary antibodies at room temperature for 1 hour. Protein expression levels were normalized by β-actin. The intensity of protein expression was quantified with ImageJ software (National Institutes of Health, Bethesda, MD, USA).

2.5. Statistical analysis

The comparison of GPR137 expression between pathological samples and normal tissue samples were operated through Student t test and the results were shown as mean ± SD. The relationship between GPR137 expression and clinical features in bladder cancer patients was estimated by Chi-Squared test. Chi-Squared test is the degree of deviation between the actual observation value and the theoretical inference value of statistical samples. The deviation between the actual observation value and the theoretical inference value determines the size of the Chi-Squared value. If the Chi-Squared value is larger, the deviation between the 2 values is smaller; conversely, the deviation between the 2 values is larger. If the 2 values are completely equal, the Chi-Squared value is 0. Indicating that the theoretical value is completely consistent. Kaplan–Meier method, also known as product-limit estimate, is one of the most commonly used survival analysis methods. It is mainly suitable for estimating survival rate and drawing survival curve for non-grouped survival data. Kaplan–Meier method was applied in overall survival analysis and prognostic significance of GPR137 was evaluated by Cox regression analysis. All statistical analyses were performed in SPSS 18.0 software and SigmaPlot software was used for drawing. P < .05 was considered as significant level.

Table 1

The sequences of the primers used in this study.

| Name     | Sequences                      |
|----------|--------------------------------|
| GPR137   | Forward 5’-GCTGGGAAACAAAGGCTAC-3’ |
|          | Reverse 5’-TAATCCCGAAGGGGAACAC-3’ |
| GAPDH    | Forward 5’-GAAGTGAACCTCAGAATC-3’ |
|          | Reverse 5’-GAAGATGGTACAGTGGATTCC-3’ |
3. Results

3.1. Relative expression of GPR137 in bladder cancer patients

Total RNA extracted through 1.1% agarose gel electrophoresis (Fig. 1A) showed that the 28S rRNA and 18S rRNA bands were clear and brightness ratio was close to 2:1, indicating that RNA was not degraded and relatively intact. QRT-PCR was used to detect relative expression of GPR137 in pathological tissues and normal tissues from the bladder cancer patients as well as for serum from the patients and healthy controls. Relative expression level in pathological tissues was 1.83 ± 0.33, while the figure for corresponding normal tissues was 1 ± 0.09 (Fig. 1B), showing significant difference between them (P < .001). Similarly, the expression of serum GPR137 in bladder cancer patients was also significantly higher than that in healthy controls (P < .001, Fig. 1C). We also analyzed the expression of GPR137 in patients at different stages, and found that the expression of GPR137 at stages I-II and III-IV was significantly increased compared with that in adjacent normal tissues (P < .001), but there was no significant difference in the expression of GPR137 between stages I-II and III-IV (P > .5, Fig. 1D). Besides, Western blotting was used to detect the expression of GPR137 in bladder cancer tissues and adjacent normal tissues. Compared with adjacent normal tissues, bladder cancer tissues showed significantly increased GPR137 expression (P < .001, Fig. 2).

IHC results showed that in bladder cancer tissue sections, GPR137 expression was significantly strong and the percentage of positive staining cells was as high as 80.9% (89/110). But GPR137 expression in normal tissues was weak and the proportion of positive staining cells was only 30.9% (34/110). The difference was significant between bladder cancer tissues and normal tissues (P < .05).

3.2. Relationship between GPR137 expression and clinical features

The clinical features of bladder cancer patients were showed in Table 2. A total of 142 bladder cancer patients were divided into 2 groups: low- and high-expression groups according to the median of GPR137 expression so as to describe the association between GPR137 expression and clinical features. Chi-square method was used to analyze the relationship and the results showed that the expression of GPR137 was associated with tumor size (P = .006) and TNM stage (P = .012), but not with gender, age, multiplicity, histological grade, or lymph node metastasis (P > .05). Moreover, based on gender and age, we carefully analyzed expression differences of GPR137 among bladder cancer patients and found that the expression of GPR137 in male patients was significantly higher than that in female ones (P = .023, Fig. 3), but no significance dissimilarity in the levels was observed after stratification analysis by age (P = .810).
3.3. Overall survival analysis and prognostic value of GPR137

All participants were followed up for 5 years and Kaplan–Meier method was performed to analyze overall survival of bladder cancer patients with different levels of GPR137. Patients in low expression group had the relatively longer overall survival time than that in high expression group and there was a remarkable difference between the 2 groups (Log rank test: $P = .001$, Fig. 4). Cox regression analysis was used to estimate the prognostic value of GPR137 and the results were shown in Table 3. Accordingly, GPR137 over-expression was significantly associated with poor prognosis of bladder cancer patients ($P = .001$) and GPR137 could act as an independent biomarker for bladder cancer prognosis (HR = 1.850, 95% CI = 1.272–2.689, $P = .001$).

### Table 2
The association between GPR137 expression and clinical features of bladder cancer patients.

| Characteristics          | Total number (n) | GPR137 expression | $\chi^2$ | $P$ value |
|--------------------------|------------------|-------------------|---------|-----------|
|                         | High (n) | Low (n) |       |           |           |
| Gender                   |          |        |       |           |           |
| Male                     | 64       | 33     | 31    | 0.549     | .459      |
| Female                   | 46       | 27     | 19    |           |           |
| Age                      |          |        |       |           |           |
| >55                      | 46       | 23     | 23    | 0.659     | .417      |
| ≤55                      | 64       | 37     | 27    |           |           |
| Tumor size               |          |        |       |           |           |
| >3 cm                    | 46       | 18     | 28    | 7.577     | .006      |
| ≤3 cm                    | 64       | 42     | 22    |           |           |
| Multiplicity             |          |        |       |           |           |
| Single                   | 58       | 29     | 29    | 1.022     | .312      |
| Multiple                 | 52       | 31     | 21    |           |           |
| Histological grade       |          |        |       |           |           |
| G1                       | 59       | 30     | 29    | 0.702     | .402      |
| G2+G3                    | 51       | 30     | 21    |           |           |
| TNM stage                |          |        |       |           |           |
| I–II                     | 65       | 29     | 36    | 6.319     | .012      |
| III–IV                   | 45       | 31     | 14    |           |           |
| Lymph node metastasis    |          |        |       |           |           |
| Yes                      | 55       | 27     | 28    | 1.320     | .251      |
| No                       | 55       | 33     | 22    |           |           |

Figure 2. The expression of GPR137 in patients with bladder cancer was significantly higher than that in adjacent normal tissues at protein level. **$P < .001$** represented significant difference between the compared 2 groups.

Figure 3. The expression of GPR137 among bladder cancer patients stratified by gender and age. The results showed that GPR137 expression in male patients was significantly higher than that in female patients ($P = .023$).
cells’ proliferation, thus providing a plausible therapeutic target for the malignancy treatment. Smith et al found that GPR30 was preferentially expressed in high risk epithelial ovarian cancer, relating to low survival rates of the patients. Moreover, over expression of GPR161 was detected in breast cancer and a previous study indicated that the gene was an important regulator and a potential drug target in triple-negative breast cancer. Therefore, investigating the mechanism and function of GPCRs in tumorigenesis might provide an opportunity for cancer prevention and treatment.

In order to investigate clinical effects of GPR137 on bladder cancer, we detected its levels in pathological tissues and corresponding normal tissues from bladder cancer patients. The results suggested that the expression of GPR137 was different between pathological tissues and normal tissues. A further study indicated that the expression of GPR137 was associated with tumor size and TNM stage. We also found that GPR137 expression in bladder cancer patients at stages I-II and III-IV was significantly increased compared with adjacent normal tissues. Moreover, GPR137 expression was also significantly higher in patients at stage III-IV than those at stage I-II. The results suggested that GPR137 might influence the progression of bladder cancer. These findings suggested that GPR137 might be an oncogene in bladder cancer. Du et al indicated that GPR137 was associated with the proliferation of bladder cancer cells in vitro. Knockdown of GPR137 in pancreatic cancer cells could inhibit cancer cell growth and induce apoptosis. In medulloblastoma, GPR137 also acted as an oncogene and its knockdown could disturb cell cycle progression.

In this study, overall survival and Cox regression analyses were used to estimate prognostic value of GPR137 in bladder cancer. The patients with high expression of GPR137 had lower survival rate than those with low expression. And the results of Cox regression analysis suggested that GPR137 might be an independent biomarker for bladder cancer prognosis. Therefore, we inferred that the function of oGPCRs and their regulatory mechanism in human cancer may improve the outcomes of cancer patients. For example, GPR37, 1 of oGPCRs, was proved to act as a tumor-suppressor in bladder cancer and might be a novel indicator for its prognosis.

GPCRs have been reported to take part in cell proliferation, survival and motility, and their functions in tumor growth, angiogenesis, and metastasis also attract increasing attentions. GPCR48 was reported to promote prostate cancer progression, thus providing a plausible therapeutic target for the malignancy treatment. Smith et al found that GPR30 was preferentially expressed in high risk epithelial ovarian cancer, relating to low survival rates of the patients. Moreover, over expression of GPR161 was detected in breast cancer and a previous study indicated that the gene was an important regulator and a potential drug target in triple-negative breast cancer. Therefore, investigating the mechanism and function of GPCRs in tumorigenesis might provide an opportunity for cancer prevention and treatment.

In conclusion, the expression of GPR137 in patients with bladder cancer was significantly higher than that in adjacent

### Table 3

| Features                              | Univariate analysis | Multivariate analysis |
|---------------------------------------|---------------------|-----------------------|
|                                       | HR                  | 95% CI                | P         | HR                  | 95% CI                | P         |
| GPR137 (high vs low)                  | 1.837               | 1.267–2.664           | .001      | 1.850               | 1.272–2.689           | .001      |
| Gender (male vs female)               | 0.996               | 0.698–1.420           | .981      | 0.980               | 0.682–1.408           | .914      |
| Age (≥55 vs <55)                      | 0.986               | 0.691–1.407           | .938      | 1.018               | 0.710–1.460           | .921      |
| Tumor size (>3cm vs <3cm)             | 1.083               | 0.760–1.546           | .658      | 1.121               | 0.777–1.619           | .541      |
| Multiplicity (single vs multiplicity) | 1.313               | 0.916–1.881           | .139      | 1.385               | 0.957–2.003           | .084      |
| Histological grade (G1 vs G2 vs G3)   | 1.025               | 0.719–1.463           | .890      | 1.043               | 0.724–1.502           | .823      |
| TNM stage (I-II vs III-IV)            | 1.180               | 0.826–1.684           | .363      | 1.172               | 0.816–1.684           | .390      |
| Lymph node metastasis (yes vs no)     | 1.083               | 0.750–1.546           | .659      | 1.114               | 0.776–1.600           | .559      |

95%CI = 95% confidence interval, HR = hazard ratio.
normal tissues at both mRNA and protein levels. The expression of GPR137 was associated with tumor size. In addition, bladder cancer patients with different GPR137 expressions experienced varied clinical outcomes, specifically, high expression was associated with low survival rate. GPR137 may be a valuable indicator for bladder cancer prognosis and a potential therapeutic target for the disease.

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