Correlation of pituitary tumor transforming gene 1 with proliferation and invasion genes in prostate cancer

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ABSTRACT

Objective: To study the change of pituitary tumor transforming gene 1 (PTTG1) expression in prostate cancer and its correlation with proliferation and invasion genes. Methods: Patients with prostate cancer who underwent radical operation in our hospital between March 2015 and January 2018 were selected as the malignant group of the research, and the prostate cancer lesions were collected; patients who underwent transurethral resection of the prostate due to benign prostatic hyperplasia in our hospital during the same period were selected as the benign group of the research, and the benign prostate lesions were collected. The mRNA expression levels of PTTG1, proliferation genes and invasion genes in the lesions were determined. Results: PTTG1, Survivin, Bcl-2, CyclinD1, GPRC6A, ZEB1, CatB, CatD and PAR-1 mRNA expression in prostate cancer lesions of malignant group were significantly higher than those of benign group whereas CDKN2, p21 and TFPI2 mRNA expression were significantly lower than those of benign group; Survivin, Bcl-2, CyclinD1, GPRC6A, ZEB1, CatB, CatD and PAR-1 mRNA expression in prostate cancer lesions with high PTTG1 were significantly higher than those in prostate cancer lesions with low PTTG1 whereas CDKN2, p21 and TFPI2 mRNA expression were significantly lower than those in prostate cancer lesions with low PTTG1. Conclusion: The PTTG1 gene is highly expressed in prostate cancer lesions and it is closely related to the changes of proliferation and invasion gene expression.

1. Introduction

Prostate cancer is the most common male urogenital system malignancy, surgical resection, endocrine castration and chemoradiotherapy are the main therapies[1], but it is still short of effective targeted therapy drugs, and the key molecular mechanisms associated with the disease development have also not been clarified. Pituitary tumor transforming gene 1 (PTTG1) is a newly discovered malignant tumor-related gene in recent years, and several studies have confirmed that high expression of PTTG1 is the common pathological link in the occurrence and development of colon cancer, esophageal cancer and other malignant tumors[2,3]. In vitro cell research of domestic CAO Xi-liang has shown that inhibiting the expression of PTTG1 in prostate cancer cells can make cancer cell proliferation and invasion process blocked[4], which indicates that PTTG1 may be involved in the occurrence and development of prostate cancer. In the following study, in order to define the specific role of PTTG1 in the occurrence and development of prostate cancer, we analyzed the change of PTTG1 expression in prostate cancer lesions and its correlation with proliferation and invasion genes.

2. Clinical information and research methods

2.1 Clinical case information

The patients with prostate cancer who underwent radical operation in our hospital between March 2015 and January 2018 were chosen as the malignant group of the research, all patients were diagnosed with prostate cancer by postoperative pathological examination, there were a total of 82 cases, and they were 48-69 years old, (171.3±19.4) cm in height and (68.3±8.4) kg in weight. The patients who underwent transurethral resection of the prostate
due to benign prostatic hyperplasia in our hospital during the same period were chosen as the benign group of the research, all patients were diagnosed with benign prostatic hyperplasia by postoperative pathologic examination, there were a total of 114 cases, and they were 50-71 years old, (179.6±18.4) cm in height and (67.5±9.1) kg in weight. There was no significant difference in the general data between the two groups (P>0.05).

2.2 Research methods

2.2.1 Lesion tissue collection

After surgical resection, right amount of prostate cancer lesion was collected from malignant group, right amount of prostatic hyperplasia lesion was collected from benign group, and the lesions were washed with saline, put on filter paper to remove the moisture, placed in cryopreserved tubes and cryopreserved in liquid nitrogen; the tissues were used for subsequent detection after their properties were confirmed by pathology.

2.2.2 Gene mRNA expression detection

Right amount of prostate cancer lesion of malignant group and right amount of prostatic hyperplasia lesion of benign group were taken, joined by Trizol lysate and fully ground to get tissue grinding fluid, the RNA extraction kit manual was referred to separate RNA from the tissue, then RT-PCT kit manual was followed to configure the reaction system for amplification reaction, and the reaction curves were referred to calculate the mRNA expression levels of PTTG1, Survivin, Bcl-2, CyclinD1, CDKN2, p21, GPRC6A, TFPI2, ZEB1, CatB, CatD and PAR-1.

2.3 Statistical methods

Software SPSS 22.0 was used to input data, the measurement data between groups were analyzed by t test and P<0.05 indicated statistical significance in the differences.

3. Results

3.1 PTTG1 expression

PTTG1 mRNA expression in prostate cancer lesions of malignant group was (2.31±0.36) and PTTG1 mRNA expression in prostatic hyperplasia lesion of benign group was (1.03±0.15). The t test analysis of the difference in PTTG1 expression in prostate cancer lesions of malignant group and prostatic hyperplasia lesion of benign group showed that PTTG1 mRNA expression in prostate cancer lesions of malignant group was significantly higher than that of benign group (P<0.05).

3.2 Proliferation gene expression and its correlation with PTTG1

Analysis of proliferation genes Survivin, Bcl-2, CyclinD1, CDKN2 and p21 expression in prostate cancer lesions of malignant group and prostatic hyperplasia lesion of benign group was as follows: Survivin, Bcl-2 and CyclinD1 mRNA expression in prostate cancer lesions of malignant group were significantly higher than those of benign group (P<0.05) whereas CDKN2 and p21 mRNA expression were significantly lower than those of benign group (P<0.05).

Analysis of proliferation genes Survivin, Bcl-2, CyclinD1, CDKN2 and p21 expression in prostate cancer lesions of malignant group with different PTTG1 expression was as follows: Survivin, Bcl-2 and CyclinD1 mRNA expression in prostate cancer lesions with high PTTG1 were significantly higher than those in prostate cancer lesions with low PTTG1 (P<0.05) whereas CDKN2 and p21 mRNA expression were significantly lower than those in prostate cancer lesions with low PTTG1 (P<0.05).

3.3 Invasion gene expression and its correlation with PTTG1

Analysis of invasion genes GPRC6A, TFPI2, ZEB1, CatB, CatD and PAR-1 expression in prostate cancer lesions of malignant group and prostatic hyperplasia lesion of benign group was as follows: GPRC6A, ZEB1, CatB, CatD and PAR-1 mRNA expression in prostate cancer lesions of malignant group were significantly

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Survivin</th>
<th>Bcl-2</th>
<th>CyclinD1</th>
<th>CDKN2</th>
<th>p21</th>
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<tbody>
<tr>
<td>Malignant group</td>
<td>82</td>
<td>2.44±0.37</td>
<td>2.09±0.34</td>
<td>3.18±0.47</td>
<td>0.42±0.06</td>
<td>0.38±0.06</td>
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<td>Benign group</td>
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<td>1.04±0.15</td>
<td>1.01±0.13</td>
<td>0.99±0.14</td>
<td>1.05±0.16</td>
<td>1.02±0.13</td>
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<td>t</td>
<td>27.698</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
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<th>Bcl-2</th>
<th>CyclinD1</th>
<th>CDKN2</th>
<th>p21</th>
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<tbody>
<tr>
<td>PTTG1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>High expression</td>
<td>41</td>
<td>3.20±0.51</td>
<td>2.75±0.41</td>
<td>4.75±0.62</td>
<td>0.25±0.04</td>
<td>0.21±0.04</td>
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<tr>
<td>Low expression</td>
<td>41</td>
<td>1.69±0.25</td>
<td>1.46±0.22</td>
<td>1.71±0.23</td>
<td>0.61±0.08</td>
<td>0.55±0.07</td>
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<tr>
<td>t</td>
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<td>&lt;0.05</td>
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<tr>
<td>P</td>
<td>15.676</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
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</table>

Table 1. Comparison of proliferation gene expression between malignant group and benign group.

Table 2. Correlation between proliferation genes and PTTG1 in malignant group.
Correlation between invasion genes and PTTG1 in malignant group.

Table 4.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>GPRC6A</th>
<th>TFPI2</th>
<th>ZEB1</th>
<th>CatB</th>
<th>CatD</th>
<th>PAR-1</th>
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<tbody>
<tr>
<td>Malignant group</td>
<td>82</td>
<td>2.33±0.35</td>
<td>0.56±0.08</td>
<td>1.87±0.24</td>
<td>1.96±0.25</td>
<td>2.55±0.46</td>
<td>2.71±0.41</td>
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<tr>
<td>Benign group</td>
<td>114</td>
<td>1.04±0.15</td>
<td>1.02±0.13</td>
<td>0.97±0.12</td>
<td>0.99±0.14</td>
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<td>1.01±0.15</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
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<td>&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

higher than those of benign group (P<0.05) whereas TFPI2 mRNA expression was significantly lower than that of benign group (P<0.05).

Analysis of invasion genes GPRC6A, TFPI2, ZEB1, CatB, CatD and PAR-1 expression in prostate cancer lesions of malignant group with different PTTG1 expression was as follows: GPRC6A, ZEB1, CatB, CatD and PAR-1 mRNA expression in prostate cancer lesions with high PTTG1 were significantly higher than those in prostate cancer lesions with low PTTG1 (P<0.05) whereas TFPI2 mRNA expression was significantly lower than that in prostate cancer lesions with low PTTG1 (P<0.05).

4. Discussion

The incidence of prostate cancer has been rising year by year, the malignant cell proliferation and invasion within the lesions are the biological behaviors closely related to disease development, but the related molecular mechanisms that regulate the above biological behaviors have not been clarified. PTTG1 is involved in the occurrence and development of esophageal cancer, colorectal cancer and other malignant tumors, and the in vitro cell experiment results of domestic scholars have shown that inhibiting the expression of PTTG1 in prostate cancer cells can inhibit the activation of PI3K/AKT/mTOR pathway and the RAF/MEK/ERK pathway so as to impede the proliferation and invasion process of cancer cells[4], which indicates that PTTG1 may be involved in the occurrence and development of prostate cancer. In the study, in order to define the direct role of PTTG1 in the occurrence and development of prostate cancer, the change of PTTG1 expression in prostate cancer lesions was analyzed, and the results showed that PTTG1 mRNA expression in prostate cancer lesions of malignant group was significantly higher than that of benign group. This means that the high PTTG1 expression in local lesion is closely related to the occurrence of prostate cancer, and it is speculated based on the in vitro biological effect of PTTG1 gene that the highly expressed PTTG1 can promote the proliferation and invasion of cells within the lesion through PI3K/AKT/mTOR pathway and RAF/MEK/ERK pathway so as to cause the occurrence and development of prostate cancer.

The excessive proliferation of prostate cancer cells is an important biological behavior that causes the growth of the lesion, and various proliferation-related genes are involved in the regulation of this behavior. Survivin and Bcl-2 are anti-apoptotic genes that inhibit apoptosis to create favorable conditions for cell proliferation, the former can directly antagonize the activity of various caspase family members and inhibit the cascade activation of apoptosis response[5], and the latter can block the release of cytochrome C in the mitochondria and the mitochondrial pathway apoptosis mediated by it[6,7]; CyclinD1 is a key gene involved in cell cycle regulation, and it can form complexes with CDK4 and CDK6 to cause Rb phosphorylation and promote the E2F to be dissociated, enter into the nucleus, launch the transcription of a variety of DNA synthesis-related enzymes, accelerate the process of cell cycle and promote cell proliferation[8]. CDKN2 and p21 negatively regulate the cell cycle, the former can block the E2F dissociation mediated by Rb, the latter can block the activation of CDKs family members, and they work together to hinder cell cycle development and inhibit cell proliferation[9]. Analysis of the change of above proliferation gene expression in prostate cancer lesions showed that Survivin, Bcl-2 and CyclinD1 mRNA expression in prostate cancer lesions of malignant group significantly increased whereas CDKN2 and p21 mRNA expression significantly decreased. It means that the up-regulation of pro-proliferation gene expression and the down-regulation of anti-proliferation gene expression are related to the occurrence of prostate cancer. Further analysis of the relationship between high PTTG1 gene expression and above proliferation gene expression within the prostate cancer lesions showed that Survivin, Bcl-2 and CyclinD1 mRNA expression in prostate cancer lesions with high PTTG1 significantly increased whereas CDKN2 and p21 mRNA expression significantly decreased. This indicates that the up-regulation of PTTG1 gene expression in prostate cancer lesions can affect the expression of multiple proliferation genes to promote the proliferation of cancer cells.

Prostate cancer is characterized by invasive growth, and the biological behaviors associated with this feature include not only excessive cell proliferation, but also excessive cell invasion. Cellular epithelial mesenchymal transition is the first stage of cell invasion, and its characteristics are the transition from epithelial phenotype
of cells to mesenchymal phenotype, the weakening of intercellular polarity and the enhancement of movement performance[10,11]; GPRC6A is the G-protein-coupled receptor that regulates epithelial mesenchymal transition, and it can activate transcription factor ZEB1 through the downstream signal transduction, and the promote the epithelial mesenchymal transition of the cells through the hindering effect of ZEB1 on epithelial marker gene E-cadherin expression[12,13]. After the cells gain movement performance, they need to degrade extracellular matrix and basement membrane; PAR-1 can enhance the activity of protease and promote cell invasion. TFPI2 can reduce the activity of protease and inhibit cell invasion[14,15]. Analysis of the change of above invasion gene expression in prostate cancer lesions showed that GPRC6A, ZEB1, CatB, CatD and PAR-1 mRNA expression in prostate cancer lesions of malignant group significantly increased whereas TFPI2 mRNA expression significantly decreased. This indicates that the up-regulation of pro-invasion gene expression and the down-regulation of anti-invasion gene expression are related to the occurrence of prostate cancer. Further analysis of the relationship between high PTTG1 gene expression and above invasion gene expression within the prostate cancer lesions showed that GPRC6A, ZEB1, CatB, CatD and PAR-1 mRNA expression in prostate cancer lesions with high PTTG1 significantly increased whereas TFPI2 mRNA expression significantly decreased. This indicates that the up-regulation of PTTG1 gene expression in prostate cancer lesions can affect the expression of multiple invasion genes to promote the invasion of cancer cells.

The analysis of the above gene expression can be concluded as follows: the expression of PTTG1 gene significantly increases in prostate cancer lesions; the highly expressed PTTG1 is closely related to the changes in the expression of various proliferation and invasion genes, and can promote the proliferation and invasion of cancer cells.

References