Correlation of S100A13 and FOXA1 expression with cell cycle and cell invasion in fine needle aspiration thyroid carcinoma tissue

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ABSTRACT

Objective: To study the correlation of S100A13 and FOXA1 expression with cell cycle and cell invasion in fine needle aspiration thyroid carcinoma tissue. Methods: Patients who received ultrasound-guided thyroid nodule fine needle aspiration in Haiyang People’s Hospital between April 2015 and February 2017 were selected, and the tissues were divided into malignant thyroid tissue and benign thyroid nodules according to the pathological results after biopsy. The expression of S100A13, FOXA1, cell cycle molecules and cell invasion molecules were measured. Results: S100A13, FOXA1, CDK2, CyclinD1, MCM2, MCM7, SKP2, CLOCK, STAT3, STAT5, N-cadherin, MT1-MMP and ADAM17 mRNA expression in thyroid carcinoma tissue were significantly higher than those in benign thyroid nodule; CDK2, CyclinD1, MCM2, MCM7, SKP2 and CLOCK mRNA expression in thyroid carcinoma tissue with high FOXA1 expression were significantly higher than those in thyroid carcinoma tissue with low FOXA1 expression; STAT3, STAT5, N-cadherin, MT1-MMP and ADAM17 mRNA expression in thyroid carcinoma tissue with high S100A13 expression were significantly higher than those in thyroid cancer tissue with low S100A13 expression. Conclusions: High expression of S100A13 and FOXA1 in thyroid carcinoma can promote cell invasion and cell cycle progression.

1. Introduction

The incidence rate and detection rate of malignant thyroid tumor are rising year by year, the development of thyroid ultrasonography can provide the basis for preliminary screening for thyroid nodules, and then the ultrasound-guided fine needle aspiration can accurately determine the tissue nature. The proliferation and invasion of cancer cells are the critical malignant biological behaviors in the pathogenesis of thyroid malignancy, but the specific regulatory mechanism is still unclear[1−3]. S100A13 is a new member of the S100 protein family that can mediate transmembrane signal transport of multiple bioactive peptides; FOXA1 is a member of the FOXA1 transcription factor family that can enter the nucleus and regulate the expression of multiple genes. Relevant cell studies in vitro have confirmed that S100A13 could promote the invasion of thyroid cancer cells and FOXA1 could promote the development of thyroid cancer cell cycle[4,5]. At present, it is still unclear about the expression and specific biological functions of S100A13 and FOXA1 in thyroid cancer tissue. In the following studies, we specifically analyzed the correlation of S100A13 and FOXA1 expression with cell cycle and cell invasion in fine needle aspiration thyroid carcinoma tissue.

2. Materials and methods

2.1. General case information

Patients who received ultrasound-guided thyroid nodule fine needle aspiration in Haiyang People’s Hospital between April 2015 and February 2017 were selected, all patients were with thyroid
nodule detected by ultrasound and in accordance with the indications for thyroid fine needle aspiration, and there were a total of 105 cases. The tissues were divided into malignant thyroid tissue and benign thyroid nodules according to the pathological results after biopsy. There were 46 cases of malignant thyroid tissues, which were from 27 male patients and 19 female patients who were 39-61 years old; there were 58 cases of benign thyroid nodules, which were from 32 male patients and 26 female patients who were 36-58 years old. There was no statistically significant difference in general information between the two groups of patients ($P$>0.05).

2.2. Sample collection

The thyroid lesion location was confirmed by ultrasonic location, fine needle aspiration guided by ultrasound was done after the local anesthesia, the thyroid lesion tissue was obtained and then divided into two parts, one was sent for pathologic examination in order to make clear the tissue nature, and the other was frozen with liquid nitrogen and then stored in -70°C cryogenic refrigerator.

2.3. Gene expression detection

RNAiso lysate was used to extract the RNA in malignant thyroid tissue and benign thyroid nodules, the kits were used to synthesize the obtained RNA into cDNA by reverse transcription, then PCR reaction was done, the adopted primers were specifically for S100A13, FOXA1, CDK2, CyclinD1, MCM2, MCM7, SKP2, CLOCK, STAT3, STAT5, N-cadherin, MT1-MMP and ADAM17, and the mRNA expression was calculated according to the PCR curve.

2.4. Statistical methods

SPSS 19.0 software was used to input and analyze data, measurement data analysis between two groups was by $t$ test and $P$<0.05 meant that the differences were statistically significant.

3. Results

3.1. S100A13 and FOXA1 expression in thyroid carcinoma tissue

S100A13 and FOXA1 mRNA expression in malignant thyroid tissue were (2.75±0.36) and (3.11±0.52), respectively; S100A13 and FOXA1 mRNA expression in benign thyroid nodule were (1.04±0.18) and (1.02±0.15), respectively. After $t$ test, S100A13 and FOXA1 mRNA expression in thyroid carcinoma tissue were significantly higher than those in benign thyroid nodule ($P$<0.05).

3.2. Cell cycle molecule expression in thyroid carcinoma tissue and their correlation with FOXA1

CDK2, CyclinD1, MCM2, MCM7, SKP2 and CLOCK mRNA expression in thyroid carcinoma tissue were significantly higher in malignant thyroid tissue than those in benign thyroid nodule ($P$<0.05) (Table 1).

Table 1. Cell cycle molecule expression in malignant thyroid tissue and benign thyroid nodule.

<table>
<thead>
<tr>
<th>Tissue nature</th>
<th>n</th>
<th>CDK2</th>
<th>CyclinD1</th>
<th>MCM2</th>
<th>MCM7</th>
<th>SKP2</th>
<th>CLOCK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant tissue</td>
<td>46</td>
<td>2.98±0.45</td>
<td>3.41±0.48</td>
<td>2.33±0.39</td>
<td>2.73±0.41</td>
<td>3.55±0.52</td>
<td>3.12±0.52</td>
</tr>
<tr>
<td>Benign nodule</td>
<td>58</td>
<td>1.03±0.18</td>
<td>0.98±0.14</td>
<td>1.01±0.15</td>
<td>1.04±0.17</td>
<td>0.96±0.15</td>
<td>0.99±0.11</td>
</tr>
<tr>
<td>$P$</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>
<td>&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

3.3. Cell invasion molecule expression in thyroid carcinoma tissue and their correlation with S100A13

STAT3, STAT5, N-cadherin, MT1-MMP and ADAM17 mRNA expression in thyroid carcinoma tissue were significantly higher than those in benign thyroid nodule ($P$<0.05) (Table 3).

Table 2. Cell cycle molecule expression in thyroid carcinoma tissue with different FOXA1 expression.

<table>
<thead>
<tr>
<th>FOXA1</th>
<th>n</th>
<th>CDK2</th>
<th>CyclinD1</th>
<th>MCM2</th>
<th>MCM7</th>
<th>SKP2</th>
<th>CLOCK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low expression</td>
<td>23</td>
<td>2.02±0.30</td>
<td>2.23±0.33</td>
<td>1.58±0.23</td>
<td>1.62±0.24</td>
<td>2.14±0.38</td>
<td>1.41±0.18</td>
</tr>
<tr>
<td>High expression</td>
<td>23</td>
<td>3.88±0.51</td>
<td>4.65±0.62</td>
<td>3.20±0.51</td>
<td>3.89±0.58</td>
<td>4.77±0.69</td>
<td>4.92±0.72</td>
</tr>
<tr>
<td>$P$</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>
<td>&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>
of thyroid cancer cells and the process of cell cycle respectively. The over-expression of S100A13 and FOXA1 can promote the invasion of malignant thyroid tissue and benign thyroid nodule. Cellular experimental studies in vitro have shown that the cell proliferation by influencing the expression of cell cycle molecules in the cell cycle are regulated by FOXA1, which promotes release and promote the corresponding gene transcription; multiple and dimethylated H3 lysine to make the sensitized chromatin region family, which can enter the nucleus and then replace histone H1 and FGF-2. FOXA1 is a member of the FOXA transcription factor family, which can enter the nucleus and then replace histone H1 and dimethylated H3 lysine to make the sensitized chromatin region release and promote the corresponding gene transcription; multiple molecules in the cell cycle are regulated by FOXA1, which promotes cell proliferation by influencing the expression of cell cycle molecules. Cellular experimental studies in vitro have shown that the over-expression of S100A13 and FOXA1 can promote the invasion of thyroid cancer cells and the process of cell cycle respectively[6,7].

In order to define the roles that S100A13 and FOXA1 played in the thyroid cell invasion and cell cycle development respectively to be involved in the occurrence and development of thyroid carcinoma. FOXA1 is a molecule that participates in the regulation of the cell cycle process, and multiple molecules that positively regulate the cycle are highly expressed in the cell cycle process of thyroid cancer cells. CDK2 is a kinase involved in cell cycle regulation, which can form complexes with CyclinD1 to cause Rb phosphorylation, enable cells to cross through the checkpoints in G1/S and G2/M phase, quickly enter into the next cell cycle and accelerate cell proliferation[8]. MCM2 and MCM7 are the MCM family members involved in DNA replication and cell cycle regulation, which can accelerate the cell cycle of thyroid cancer cells; SKP2 is a key control factor for cell cycle from G1 phase to S phase, which can make use of ubiquitin proteasome pathway to degrade P27 and other molecules that negatively regulate cell cycle, weaken their blocking effect on cell cycle and promote the cell cycle development[9,10]. CLOCK is a kind of rhythm gene, which can regulate the cell rhythm and ensure the smooth progress of the cell cycle[10]. Analysis of the above cell cycle molecule expression in thyroid carcinoma tissue showed that CDK2, CyclinD1, MCM2, MCM7, SKP2 and CLOCK mRNA expression in thyroid carcinoma tissue were significantly higher than those in benign thyroid nodule. This indicates that the high expression of molecules that positively regulate cell cycle is closely related to the occurrence of thyroid cancer. Further analysis of the correlation between FOXA1 and cell cycle molecules in thyroid carcinoma tissue showed that CDK2, CyclinD1, MCM2, MCM7, SKP2 and CLOCK mRNA expression in thyroid carcinoma tissue with high FOXA1 expression were significantly higher than those in thyroid carcinoma tissue with low FOXA1 expression. This indicates that the high expression of FOXA1 in thyroid cancer tissue can promote the expression of various molecules that positively regulate cell cycle to accelerate cell cycle and promote cell proliferation.

S100A13 is a molecule involved in cell invasion regulation. The invasion of thyroid cancer cells involves the epithelial-mesenchymal transition and extracellular matrix degradation[11]. STAT3 and STAT5 are the key signal molecules regulating the epithelial-mesenchymal transition of thyroid cancer cells, which are activated by upstream JAK and then transfer into the nucleus and increase the expression of mesenchymal phenotype marker gene N-cadherin[12]; the high expression of N-cadherin can make the epithelial phenotype transit into mesenchymal phenotype, then reduce the intercellular polarity and adhesion, and promote cell migration and movement[13]. MT1-
MMP is a hydrolase that can hydrolyze laminin, type I and type III collagen and vitronectin, and it promotes cell invasion by degrading the various components of extracellular matrix[14]. ADAM17 can hydrolyze and release EGFR and then mediate the invasion of cells by identifying multiple ligands[15]. Analysis of the above cell invasion molecules in thyroid carcinoma tissue showed that STAT3, STAT5, N-cadherin, MT1-MMP and ADAM17 mRNA expression in thyroid carcinoma tissue were significantly higher than those in benign thyroid nodule. This indicates that the high expression of cell invasion molecules is closely related to the occurrence of thyroid cancer. Further analysis of the correlation between S100A13 and cell invasion molecules in thyroid carcinoma tissue showed that STAT3, STAT5, N-cadherin, MT1-MMP and ADAM17 mRNA expression in thyroid carcinoma tissue with high S100A13 expression were significantly higher than those in thyroid carcinoma tissue with low S100A13 expression. It indicates that the high expression of S100A13 in thyroid cancer tissue can promote the expression of multiple cell invasion molecules and thus promote cell invasion.

S100A13 and FOXA1 are highly expressed in thyroid carcinoma; the highly expressed S100A13 can promote the epithelial-mesenchymal transition and invasion of cells, and the highly expressed FOXA1 can accelerate cell cycle progression and promote cell invasion.

References


