Effects of anti-HPV bioprotein dressing combined with interferon α-2b therapy on the malignant molecule expression in patients with CIN III complicated by high-risk HPV positive

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ABSTRACT

Objective: To study the effects of anti-HPV bioprotein dressing combined with interferon α-2b therapy on the malignant molecule expression in patients with cervical intraepithelial neoplasia (CIN) III complicated by high-risk HPV positive. Methods: Patients who were diagnosed with CINIII and high-risk HPV positive and underwent conization in the 3201 Hospital Affiliated to Xi'an Jiaotong University between June 2014 and February 2017 were selected and randomly divided into the observation group who received preoperative anti-HPV bioprotein dressing combined with interferon α-2b therapy and the control group who received no special treatment. CIN lesion was collected to determine the expression of pro-proliferation molecules, pro-apoptosis molecules and epithelial-mesenchymal transition molecules. Results: Rsf1, Piwil2, TOPK, p38MAPK, ERK, Snail, Twist, N-cadherin and Vimentin mRNA expression in cervical intraepithelial neoplasia lesions of observation group were greatly lower than those of control group whereas LRIG3, SARI, IEX-1, FHIT and E-cadherin mRNA expression were greatly higher than those of control group. Conclusion: Anti-HPV bioprotein dressing combined with interferon α-2b therapy can inhibit the proliferation and invasive growth of tumor cells in patients with CINIII complicated by high-risk HPV positive.

1. Introduction

Cervical intraepithelial neoplasia (CIN) is a group of continuous lesions closely related to the incidence of cervical cancer, the risk of CIN stage I and II progression to cervical cancer is low, but the incidence of CIN stage III progression to cervical cancer has reached 15%(1). Cervical conization is a common clinical method to treat the CIN III stage, which can effectively remove the cervical lesion and prevent further development of the disease. High-risk human papilloma virus (HPV) infection has played a vital role in the occurrence and progression of CIN, the surgical resection of HPV lesions alone cannot completely eliminate HPV, and the residual HPV can be hidden sources of infection and cause CIN recurrence(2). Therefore, it is necessary to combine surgical resection and drug therapy to kill and eliminate HPV(3). Anti-HPV bioprotein dressings can use the principle of interaction between positive and negative charges to change the HPV protein conformation, and then kill HPV; interferon α-2b is the cytokine with antiviral activity, and human recombinant interferon α-2b can enter into the body, enhance immune cell activity and activate antiviral immune response to prompt the HPV to be cleared. In the following study, we specifically analyzed the effects of anti-HPV bioprotein dressings combined with interferon α-2b therapy on the malignant molecule expression in patients with CINIII complicated by high-risk HPV positive.

2. Research subjects and methods

2.1 Clinical information of research subjects

Patients who were diagnosed with CINIII and high-risk HPV positive in the 3201 Hospital Affiliated to Xi'an Jiaotong University between June 2014 and February 2017 were selected, and all patients were diagnosed with CIN and high-risk HPV positive by
biopsy, conformed to the indications for conization, and were without surgical contraindications. A total of 86 patients were enrolled and divided into two groups by random number table method, each with 43 cases. Observation group were 29-42 years old, the gravidity was 0-4 times, and the parity was 0-2 times; control group was aged between 31 and 44 years, the gravidity was 0-3 times, and the parity was 0-3 times. There was no statistically significant difference in general information between the two groups ($P>0.05$).

2.2 Therapy

Observation group of patients received anti-HPV bioprotein dressing combined with interferon $\alpha$-2b therapy, which was as follows: transvaginal administration of anti-HPV bioprotein dressing, 1 each time, 1 time/every other day, before sleep, for 14 d in a row; recombinant human interferon $\alpha$-2b gel, local administration, 1 g/time, 1 time per day, for 14 d in a row. Control group of patients received no special treatment.

2.3 Molecule expression detection

Right amount of surgical removed cervical intraepithelial neoplasia lesion tissue was collected and added in Trizol lysate to isolate the RNA, it was synthesized into cDNA by reverse transcription, then fluorescence quantitative PCR amplification was done, and the Rsf1, Piwil2, TOPK, p38MAPK, ERK, LRIG3, SARI, IEX-1, FHIT, Snail, Twist, N-cadherin, Vimentin and E-cadherin mRNA expression were calculated according to the amplification curve.

2.4 Statistical methods

SPSS 20.0 software was used to input data, the measurement data between two groups were by t test and $P<0.05$ meant that the differences in test results were statistically significant.

3. Results

3.1 Pro-proliferation molecule expression

Analysis of pro-proliferation molecules Rsf1, Piwil2, TOPK, p38MAPK and ERK expression in surgically removed cervical intraepithelial neoplasia lesions between the two groups of patients was as follows: Rsf1, Piwil2, TOPK, p38MAPK and ERK mRNA expression in cervical intraepithelial neoplasia lesions of observation group were greatly lower than those of control group. Differences in Rsf1, Piwil2, TOPK, p38MAPK and ERK expression in cervical intraepithelial neoplasia lesions were statistically significant between the two groups of patients ($P<0.05$).

3.2 Pro-apoptosis molecule expression

Analysis of pro-apoptosis molecules LRIG3, SARI, IEX-1 and FHIT expression in surgically removed cervical intraepithelial neoplasia lesions between the two groups of patients was as follows: LRIG3, SARI, IEX-1 and FHIT mRNA expression in cervical intraepithelial neoplasia lesions of observation group were greatly higher than those of control group. Differences in LRIG3, SARI, IEX-1 and FHIT expression in cervical intraepithelial neoplasia lesions were statistically significant between the two groups of patients ($P<0.05$).

3.3 Epithelial-mesenchymal transition molecule expression

Analysis of epithelial-mesenchymal transition molecules Snail, Twist, N-cadherin, Vimentin and E-cadherin expression in surgically removed cervical intraepithelial neoplasia lesions between the two groups of patients was as follows: Snail, Twist, N-cadherin and Vimentin mRNA expression in cervical intraepithelial neoplasia lesions of observation group were greatly lower than those of control group whereas E-cadherin mRNA expression was greatly higher than that of control group. Differences in Snail, Twist, N-cadherin, Vimentin and E-cadherin expression in surgically removed cervical intraepithelial neoplasia lesions were statistically significant between the two groups of patients ($P<0.05$).

Table 1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Rsf1</th>
<th>Piwil2</th>
<th>TOPK</th>
<th>p38MAPK</th>
<th>ERK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>43</td>
<td>0.31±0.08</td>
<td>0.24±0.06</td>
<td>0.42±0.09</td>
<td>0.38±0.07</td>
<td>0.48±0.06</td>
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<tr>
<td>Control group</td>
<td>43</td>
<td>1.05±0.18</td>
<td>1.01±0.15</td>
<td>0.99±0.14</td>
<td>1.04±0.18</td>
<td>0.97±0.15</td>
</tr>
<tr>
<td>P</td>
<td></td>
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<td>$&lt;0.05$</td>
<td>$&lt;0.05$</td>
<td>$&lt;0.05$</td>
<td>$&lt;0.05$</td>
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</tbody>
</table>

Table 2.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>LRIG3</th>
<th>SARI</th>
<th>IEX-1</th>
<th>FHIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>43</td>
<td>2.77±0.41</td>
<td>2.33±0.38</td>
<td>3.09±0.55</td>
<td>2.62±0.42</td>
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<tr>
<td>Control group</td>
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<td>1.07±0.18</td>
<td>1.02±0.15</td>
<td>0.98±0.11</td>
<td>1.05±0.18</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>15.321</td>
<td>12.348</td>
<td>21.393</td>
<td>16.409</td>
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<tr>
<td>P</td>
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<td>$&lt;0.05$</td>
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</tbody>
</table>
tumor cells by maintaining the stem cell characteristics, and it guarantees the proliferation of tumor stem cell characteristics, and it guarantees the proliferation of proliferation and DNA uncoiling so as to promote gene replication and cell proliferation. Rsf1 is a kind of chromatin remodeling element that can cooperate with histone to adjust ATPase activity, and promote the nucleosome movement so as to control the expression of multiple pro-proliferation molecules. The abnormal proliferation of tumor cells in CIN lesions is not only related to the high expression of pro-proliferation molecules, but also related to the expression deletion of pro-apoptosis molecules, and increasing the expression of pro-apoptosis molecules in lesion can significantly inhibit cell proliferation and induce cell apoptosis to hinder the development of the disease. Lrig3 is a newly discovered member of the LRIG family, which is similar to LRIG1 in structure and function, and can antagonize the biological effects mediated by EGFR receptor and hinder cell growth[11]. SARI is an inducer of apoptosis, which can cooperate with c-jun to induce downstream apoptosis gene expression and promote apoptosis[12]. IEX-1 is a member of the immediate early response gene family, which can act on the downstream p53, RB, PP2A and other molecules, inhibit cell proliferation and hinder the disease progress in the course of CIN; FHIT is a molecule that participates in the regulation of gene methylation, and it causes the proliferation gene methylation to hinder cell proliferation.

Vimentin and E-cadherin expression in cervical intraepithelial neoplasia lesions were statistically significant between the two groups of patients (P < 0.05).

### 4. Discussion

Cervical intraepithelial neoplasia (CIN) is a precancerous lesion of cervical carcinoma, and the risk of CIN progression to cervical cancer increases gradually as the disease progresses. When the disease progresses to CIN III, the chances of natural reversal of the disease are smaller, while the incidence of progression to cervical cancer reaches 15%. Persistent high-risk HPV infection is the most important pathological factor in the occurrence and development of CIN, and the viral DNA integration into the genomic DNA of cervical epithelial cells can change the expression of various genes in host cells, thus resulting in abnormal cell proliferation and invasion[4,5]. At present, the main clinical method for treating CIN III disease is surgical resection, but surgery alone cannot eliminate HPV completely, and the remaining HPV will increase the risk of postoperative CIN recurrence and cervical cancer. Anti-HPV bioprotein dressings and recombinant human interferon α-2b are the drugs for HPV treatment in recent years. The former is mainly composed of JB protein and carbomer, JB protein can damage the HPV protein conformation and HPV inactivation by the principle of interaction between positive and negative charge, and carbomer can wrap the deactivated HPV and excrete it, and can also promote the wound repair[6]; the latter is synthetic interferon α-2b, which enhances the immune response of host cells and removes HPV through antiviral immunity[7].

In this study, anti-HPV bioprotein dressings combined with recombinant human interferon α-2b was adopted to treat CIN III lesions, and the cell proliferation within the lesions was analyzed in order to define its therapeutic value. The abnormal proliferation of diseased cells in CIN lesions is closely related to the high expression of multiple pro-proliferation molecules. Rsf1 is a kind of chromatin remodeling element that can cooperate with histone to adjust ATPase and helicase activity, and promote the nucleosome movement and DNA uncoiling so as to promote gene replication and cell proliferation[8]; Piwil2 is a molecule involved in the maintenance of tumor stem cell characteristics, and it guarantees the proliferation of tumor cells by maintaining the stem cell characteristics[6,9]; TOPK is the MAPKK family member that can promote the phosphorylation of downstream p38MAPK, ERK and other signaling molecules, and the phosphorylated p38MAPK and ERK can conduct signal transduction and increase the expression of multiple downstream pro-proliferation molecules to promote cell proliferation[10]. The analysis of the expression of these pro-proliferation molecules in lesions after treatment showed that Rsf1, Piwil2, TOPK, p38MAPK and ERK mRNA expression in cervical intraepithelial neoplasia lesions of observation group were significantly lower than those of control group. This indicates that the anti-HPV bioprotein dressings combined with recombinant human interferon α-2b can reduce the expression of pro-proliferation molecules in the CIN lesions to inhibit cell proliferation.

The abnormal proliferation of tumor cells in CIN lesions is not only related to the high expression of pro-proliferation molecules, but also related to the expression deletion of pro-apoptosis molecules, and increasing the expression of pro-apoptosis molecules in lesion can significantly inhibit cell proliferation and induce cell apoptosis to hinder the development of the disease. The infiltrative growth of tumor cells in the course of CIN is an important link in the development of the disease, and the epithelial-mesenchymal transition is the key factor to promote the infiltrative growth of tumor cell[14,15]. Snail and Twist are the transcription factors that are currently known to be able to modulate the epithelial-
mesenchymal transition processes[14]. Snail is a transcription factor with zinc finger structure, which can specifically bind the E-cadherin gene promoter region and block the initiation of gene transcription to reduce the expression of E-cadherin; Twist is a transcription factor with basic helix-loop-helix structure, which can not only inhibit the expression of E-cadherin, but also inhibit apoptosis[16]. The expression of E-cadherin reduces under the function of Snail and Twist, which results in the weakening of epithelial phenotype, and the decline of intercellular polarity and adhesion; at the same time, the phenotype transits to mesenchymal phenotype, the expression of E-cadherin, Vimentin and other mesenchymal markers increases, and the ability of cells to move and invade towards the surrounding tissues is enhanced[16]. The analysis of the expression of above epithelial mesenchymal transition molecules in lesions after treatment showed that Snail, Twist, N-cadherin and Vimentin mRNA expression in cervical intraepithelial neoplasia lesions of observation group were significantly lower than those of control group whereas E-cadherin mRNA expression was significantly higher than that of control group. This means that the anti-HPV bioprotein dressings combined with recombinant human interferon α-2b can inhibit the epithelial mesenchymal transition in CIN lesions to inhibit the invasive growth of the cells.

Anti-HPV bioprotein dressing combined with interferon α-2b can decrease the expression of pro-proliferation molecules and mesenchymal phenotype marker molecules, and increase the expression of pro-apoptosis molecules and epithelial phenotype marker molecules in the lesions of patients with CINIII complicated by high-risk HPV positive so as to inhibit the proliferation and invasive growth of tumor cells.

References


