PRODUCTION OF GROWTH FACTORS IN PAPILLARY THYROID CANCER

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INTRODUCTION

Growth factors are regulatory and informative molecules produced by many types of cells. They have presently local effects (autocrine and paracrine). A lot of them are products of oncogenes. IGF-1 (Insulin Like Growth Factor I), HGF (Hepatocyte Growth Factor), TGFß1 (Transforming Growth Factor ß 1), bFGF (basic Fibroblast Growth Factor) and VEGF (vascular Endothelial Growth Factor) are growth factors, that take part in the thyroid gland tumors origin and growth.

It was proved, that all of these growth factors (except of IGF) have a de-differentiating effect on follicular thyroid cells and that all of them (except of TGFß1 and VEGF) are potential mitogens of follicular cells. The expansion of thyroid tissue is accompanied by the expansion of vessels, neo-vascularisation. These two processes limit each other to a certain extent. bFGF and VEGF play an important role in the process of angiogenesis.

The aim of this study was to describe the production of these growth factors by papillary thyroid cancer (PTC) and to compare it with their production by thyroid gland adenoma and normal thyroid tissue. We also tried to find the suitable peripheral marker of thyroid papillary cancer.

MATERIALS AND METHODS

We measured levels of IGF-1, HGF, TGFß1, bFGF and VEGF in serum from 28 patients (23 women and 5 men) with thyroid gland tumor. A benign thyroid adenoma was found in 14 persons (12 women, 2 men) and papillary cancer was found in other 14 subjects (11 women, 3 men). 20 ml of peripheral blood were obtained from every patient before the operation and centrifuged for 10 minutes at 2600 rpm. This serum was frozen in liquid nitrogen and stored in a closed plastic tube at -80°C. Growth factors concentrations were detected by the ELISA method. Results were statistically evaluated by one-way analysis of variance (IGF-I, TGFß1) and by Kruskal-Wallis test (HGF, bFGF, VEGF).

The results of this study are a dynamic model of the flow tissue culture. We cultivated the tissue of PTC and normal thyroid gland in the system ACSYS/ST with reinculturizing modified culture medium F10. Each chamber contained 50 µl of the moist tissue. After the rinsing with fresh medium (for 60 min.), we started the 8 hours stimulation with TSH (thyrotopin) and EGF (epidermal growth factor), succeeded by another rinsing (for 60 min.). We detected running levels of bFGF and HGF in the medium, using ELISA method.

RESULTS

Serum concentrations of growth factors

Average values of growth factors serum concentrations in patients with thyroid adenoma and papillary thyroid cancer and in healthy people.

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Adenoma</th>
<th>Papillary Adenoma</th>
<th>Healthy</th>
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</thead>
<tbody>
<tr>
<td>IGF-1 (ng/ml)</td>
<td>105.5 ± 38.17</td>
<td>131.4 ± 47.20</td>
<td>163.6 ± 42.94</td>
</tr>
<tr>
<td>HGF (pg/ml)</td>
<td>1496 ± 810</td>
<td>1137 ± 882</td>
<td>361 ± 83</td>
</tr>
<tr>
<td>TGFß1 (ng/ml)</td>
<td>35.87 ± 10.48</td>
<td>37.73 ± 12.51</td>
<td>28.98 ± 16.73</td>
</tr>
<tr>
<td>bFGF (ng/ml)</td>
<td>4.93 ± 3.42</td>
<td>5.69 ± 5.58</td>
<td>1.47 ± 1.77</td>
</tr>
<tr>
<td>VEGF (pg/ml)</td>
<td>213 ± 197</td>
<td>210 ± 179</td>
<td>227 ± 231</td>
</tr>
</tbody>
</table>

We found significantly lower serum concentrations of IGF-1 in patients with thyroid adenoma compared to the healthy population (p=0.02).

There were significantly higher serum concentrations of HGF (p=0.001) and bFGF (p=0.001) in group of patients with both thyroid adenoma and PTC compared to the healthy population. There were no significant differences of HGF and bFGF serum levels between groups of patients with thyroid adenoma and PTC.

We found no significant differences of TGFß1 and VEGF serum concentrations between all examined groups of subjects.

Flows tissue culture

We proved the successive decrease of HGF production by normal thyroid tissue during the TSH stimulation. The stimulation by EGF had a similar effect.

In PTC, we found a transient increase of HGF production during the both TSH and EGF stimulation.

The bFGF production by normal thyroid gland and PTC was similar during the stimulation by both TSH and EGF. After the short-term stimulation and during the late stimulation, there was a transient increase of the bFGF production followed by long-term inhibition. There was another short-term increase after the stimulated period.

DISCUSSION

Our detected IGF-I serum levels are in contrast with literary data about the IGF-I production detected directly in the thyroid tissue. This may be due to the IGF-I participation in a large number of various physiological processes in the organism and its peripheral blood levels are not specific for a particular disease.

Proliferative and de-differentiating effects of HGF take part especially in the phase of rapid growth and this is just the most common indication for total thyroidectomy in patients with nontoxic goitre. According to this fact, we found high HGF serum concentrations in patients with thyroid adenoma and PTC. We proved in a dynamic model of the flow tissue culture, that TSH increases the HGF production in PTC. HGF seems to be important for the maintaining of malignant potential of PTC, if it probability does not initiate the malignant transformation of normal follicular cells.

TGFß1 and VEGF have an antiproliferative effect on thyrocytes. They are involved in the process of goitre volume stablization, their production increases successivelly and, at the final level, the goitre slows to grow. We found no significant differences of TGFß1 and VEGF serum concentrations between all examined groups of subjects. Patients with nontoxic goitre are often operated in the early phase of rapid growth. That is the time, where TGFß1 and VEGF concentrations are still low.

The bFGF production increases in the phase of a rapid goitre growth. Similarly to HGF, higher bFGF production was described in thyroid adenomas and cancers by many authors, while this production is relevant in the normal thyroid gland tissue. We also found higher HGF serum levels in patients with thyroid adenoma and PTC compared to the healthy population. The bFGF production by thyroid tissue could be dependant on actual metabolic requirements.

CONCLUSION

• The growth factors production in the organism is ubiquitous, they are not specific for particular tissues or diseases. Their serum concentrations express all physiological and pathological processes in the organism.
• Higher growth factor’s consumption in the tissue can be reflected by its lower serum concentration. This negative relationship might be dependent on the expression of growth factor’s receptors in the tissue.
• If it will be confirmed in more extensive studies, HGF and bFGF could be accepted as sensitive (but probably not specific) peripheral markers of papillary thyroid cancer. This could be used mainly in the early diagnosis of PTC recurrence.
• Affecting the HGF and/or bFGF binding to their receptors could contribute to the stop of the papillary thyroid cancer growth. Nevertheless, it probably can not prevent the PTC origin.

REFERENCES