The expression of vascular endothelial growth factor (VEGF)-A, VEGF-C and VEGF-D in both experimental and clinical models of head and neck squamous cell carcinoma (HNSCC) has been evaluated in relation to microvascular parameters, with particular reference to cervical nodal metastasis. Varying degree of expression of markers has been shown to correlate with pathologic staging and prognosis.

INTRODUCTION

Objective

VEGF acts through a complex system of receptor tyrosine kinases, which can be membrane-bound or soluble. New data concerning the receptor system are still emerging, thus contributing to the complexity of the system. Recently, a soluble form of VEGF-2, termed sVEGFR-2, which is a result of alternative splicing, has been discovered. This newly observed soluble variant of VEGF-2 binds to the lymphangiogenic growth factor VEGF-C and thus inhibits VEGF-C induced activation of VEGF-3, consequently inhibiting lymphatic endothelial cell proliferation. 1 It is interesting to note that sVEGFR-2 can be expressed in both normal and malignant lymphatic endothelial cells of tumors, which indicates that sVEGFR-2 may be involved in lymphatic metastasis. This correlation has been found during the downregulation of sVEGFR-2 and the malignant progression of neuroblastoma, which is characterized by hypervascularization and invasion of lymphatics into the cornea. 2 Therefore, sVEGFR-2 may be involved in lymphatic metastasis in neuroblastoma.

Methods

sVEGFR-2 expression was identified in all squamous and cervical carcinomas of the head and neck. Expression was specific to the endothelial cells in blood vessels as well as adjacent normal tissue. sVEGFR-2 was not expressed in lymphatic vessels. This varied contrast expression was also expressed in papillary thyroid cancer cells and in the basement membrane of papillary thyroid cancer cells. This secreted protein was also expressed in lymphatic vessels, but was abundant in the basement membranes of papillary thyroid cancer cells. This correlated with peritumoral vascularity and was inversely related to lymphatic vessel density.

RESULTS

Samples

One hundred and ten paraffin-embedded tissue samples from patients with malignant tumors were analyzed: 61 squamous cell carcinomas of the larynx, 16 oral cavity, 20 oropharynx, 5 hypopharynx, 1 nasopharynx, 4 papillary, 2 medullary and 1 follicular thyroid carcinomas. Papillary (4), follicular (1) and medullary (2) thyroid cancers were also studied.

Objective

1) Evaluate the expression pattern of sVEGFR-2 in lymphatic vessels in thyroid cancer and correlate the expression of sVEGFR-2 with lymphatic vessel density in thyroid cancer.

2) Examine the relationship between sVEGFR-2 expression and lymphatic vessel density in peri-tumoral stroma, measured by podoplanin expression.

sVEGFR-2 was not expressed in lymphatic vessels, but was expressed in endothelial cells of blood vessels as measured by CD34 expression. sVEGFR-2 was minimally expressed in normal thyroid tissue but was abundant in the basement membranes of papillary thyroid cancer cells. This correlated with peritumoral vascularity and was inversely related to lymphatic vessel density.

Table 1. Tissue samples analyzed for sVEGFR-2 expression

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Tissue Type</th>
<th>Podoplanin</th>
<th>CD34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid Cancer</td>
<td>Papillary Medullary Follicular</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Head and Neck Malignant Tumors</td>
<td>Squamous Cell Carcinoma</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Conclusion

We have provided the first evidence of VEGFR-2 expression in head and neck malignant tumors. Its expression parallels with lymphatic vessel density in malignant tumors and ongoing studies will reveal the precise function of sVEGFR-2 in nodal metastasis.

REFERENCES


2. Albuquerque RJ, Hayashi T, Cho WG, et al. Alternatively spliced vascular endothelial growth factor-A (VEGF-A) is associated with the progression of neuroblastoma, which is characterized by lymphogenic metastases in progressed stages. 3 Virchows Arch 2005; 446:304-312.

3. Albuquerque RJ, Hayashi T, Cho WG, et al. Alternatively spliced vascular endothelial growth factor-A (VEGF-A) is associated with the progression of neuroblastoma, which is characterized by lymphogenic metastases in progressed stages. 3 Virchows Arch 2005; 446:304-312.

4. Albuquerque RJ, Hayashi T, Cho WG, et al. Alternatively spliced vascular endothelial growth factor-A (VEGF-A) is associated with the progression of neuroblastoma, which is characterized by lymphogenic metastases in progressed stages. 3 Virchows Arch 2005; 446:304-312.

5. Albuquerque RJ, Hayashi T, Cho WG, et al. Alternatively spliced vascular endothelial growth factor-A (VEGF-A) is associated with the progression of neuroblastoma, which is characterized by lymphogenic metastases in progressed stages. 3 Virchows Arch 2005; 446:304-312.

6. Albuquerque RJ, Hayashi T, Cho WG, et al. Alternatively spliced vascular endothelial growth factor-A (VEGF-A) is associated with the progression of neuroblastoma, which is characterized by lymphogenic metastases in progressed stages. 3 Virchows Arch 2005; 446:304-312.

7. Albuquerque RJ, Hayashi T, Cho WG, et al. Alternatively spliced vascular endothelial growth factor-A (VEGF-A) is associated with the progression of neuroblastoma, which is characterized by lymphogenic metastases in progressed stages. 3 Virchows Arch 2005; 446:304-312.

8. Albuquerque RJ, Hayashi T, Cho WG, et al. Alternatively spliced vascular endothelial growth factor-A (VEGF-A) is associated with the progression of neuroblastoma, which is characterized by lymphogenic metastases in progressed stages. 3 Virchows Arch 2005; 446:304-312.

9. Albuquerque RJ, Hayashi T, Cho WG, et al. Alternatively spliced vascular endothelial growth factor-A (VEGF-A) is associated with the progression of neuroblastoma, which is characterized by lymphogenic metastases in progressed stages. 3 Virchows Arch 2005; 446:304-312.

10. Albuquerque RJ, Hayashi T, Cho WG, et al. Alternatively spliced vascular endothelial growth factor-A (VEGF-A) is associated with the progression of neuroblastoma, which is characterized by lymphogenic metastases in progressed stages. 3 Virchows Arch 2005; 446:304-312.