Expression of the Kv3.4 channel subunit in head and neck cancer

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ABSTRACT

The survival rate for patients with head and neck squamous cell carcinoma (HNSCC) has improved only marginally despite major advances in diagnosis and treatment. Novel markers are needed to distinguish differences in tumor condition and behavior. The implication of ion channels in tumor cell biology and the concept of ion channels as membrane therapeutic targets and diagnostic/prognostic biomarkers has attracted increasing interest. Kv3.4 has been linked to a human neurovascular disease, paroxysmal nocturnal hemoglobinuria and Alzheimer disease. In addition, increased Kv3.4 mRNA levels have been reported in oral and oropharyngeal squamous cell carcinomas. In the context of HNSCC, Kv3.4 mRNA expression at both mRNA and protein levels was found in 15 (54%) out of 28 tumors compared to the corresponding normal epithelia (Figures 4A and 4B). All HNSSC-derived cell lines expressed Kv3.4 although mRNA levels varied depending on the cell line (Figure 1C).

RESULTS

Increased Kv3.4 mRNA levels were found in 15 (54%) out of 28 tumors. Increased Kv3.4 protein expression was observed in 34 (40%) of 84 carcinomas and also at early stages of HNSCC tumorigenesis. Thus, 35 (52%) of 67 laryngeal lesions displayed Kv3.4-positive staining in the dysplastic areas, whereas normal laryngeal/pharyngeal squamous cell carcinomas and 67 patients with laryngeal dysplasias. Molecular alterations were correlated with clinicopathological parameters and patient outcome.

Table 1.

<table>
<thead>
<tr>
<th>Kv3.4 protein expression</th>
<th>Clinicopathological parameters</th>
<th>Site</th>
<th>Patients with positive expression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>No differences in disease-specific survival or overall survival were observed when comparing patients with positive vs. negative Kv3.4 expression.</td>
<td></td>
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<tr>
<td>Negative</td>
<td>No differences in disease-specific survival or overall survival were observed when comparing patients with positive vs. negative Kv3.4 expression.</td>
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</table>

METHODS AND MATERIALS

Kv3.4 mRNA expression was analyzed by real-time PCR in 32 primary HNSCC tissue specimens and patient-matched normal epithelium. Normal pharyngeal mucosa obtained from non-oncologic patients was also included as a control (no exposure to tobacco carcinogens). Kv3.4 expression was also expressed in 12 HNSSC-derived cell lines. Kv3.4 protein expression was analyzed by immunohistochemistry in paraffin-embedded tissue specimens from 84 patients with HNSSC and 67 normal epithelia. Molecular alterations were associated with clinicopathological parameters and disease outcome.

To investigate the role of Kv3.4 in the proliferation of HNSSC-derived cell lines, transfected SCC42B cells were transfected with either Kv3.4 siRNA, siControl or nothing (as indicated), and Kv3.4 protein expression (A) and mRNA levels (B) were respectively analysed 48 h and 24 h post-transfection. (C) Tetrazolium-based MTS proliferation assay in SCC42B cells was performed (as indicated). (D) A laryngeal dysplasia with strong Kv3.4 staining (D).

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CONCLUSIONS

These data demonstrate for the first time that Kv3.4 expression is frequently increased during HNSSC tumorigenesis and correlated with a higher cancer risk. Our findings support a role for Kv3.4 in malignant transformation and provide original evidence for the potential clinical use of Kv3.4 expression as a biomarker for cancer risk assessment.