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Does Loss of LEKTI Expression Correlate with Increased Perineural Invasion in Squamous Cell Carcinoma of the Skin?

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Abstract

Perineural invasion (PNI) is a unique route of tumor metastasis that is strongly associated with poor prognosis in several solid malignancies including head and neck squamous cell carcinoma (HNSCC). Recently, we investigated the pattern of Lympho-Epithelial Kazal-Type-Inhibitor (LEKTI) expression in primary tumor specimens of patients with SCC of the oral tongue in

correlation with PNI and showed a strong association between absence of LEKTI expression and occurrence of PNI. Based upon the negative correlation of LEKTI expression with PNI in SCC of the tongue, we hypothesized that the same correlation may exist in SCC of the skin. Here, we selected a total of 11 cases with PNI and 15 cases without PNI. Our analyses showed a strong correlation between LEKTI expression and PNI in SCC of the skin and suggested that LEKTI might also be one of the critical molecules involved in the regulation of PNI of neuroendocrine cancers including of HNSCC.

Key words: LEKTI; perineural invasion; HNSCC

Abbreviations: LEKTI; SPINK5; HNSCC; PNI

Introduction

Perineural growth or invasion (PNI) is a unique route of tumor metastasis that is diagnosed by the presence of tumor cells inside the neural space and shown to be strongly associated with poor prognosis in several solid malignancies including HNSCC. PNI was shown to be as high as 63% in head and neck squamous cell carcinoma (HNSCC) and strongly correlates with increased local recurrence and decreased disease-free survival [1]. PNI most likely occurs by the attachment of tumor cells to components of the extracellular matrix (ECM) and by degradation of ECM by proteinase enzymes elaborated into the tumor microenvironment [2-7]. These enzymes including serine proteases, cysteine proteases, and matrix metalloproteinases (MMPs) are tightly regulated by their endogenous inhibitors in the tumor microenvironment [8-14]. Indeed, several proteinase inhibitors have shown importance in a range of cancer types by the loss of expression correlating with advanced tumor progression [15-23].

An inhibitor of multiple serine proteinases, lymphoepithelial kazal-type inhibitor (LEKTI), was identified and cloned in our laboratory on the basis of its constitutive expression in normal oral mucosa and loss of its expression in matched head and neck squamous cell carcinoma (HNSCC) specimens and multiple HNSCC lines [24]. It was also shown by several investigators that LEKTI protein was encoded by SPINK5 gene and mutations in SPINK5 has been linked to the inherited disorder known as Netherton Syndrome [25-41]. We produced recombinant full length LEKTI and several of its fragments using baculovirus expression system

and established that recombinant human LEKTI inhibits a battery of serine proteinases in vitro including plasmin, trypsin, cathepsin G, human KLKs, and elastase, enzymes implicated in the activation of MMPs [42-47].

Recently, we investigated the pattern of expression of LEKTI in primary tumor specimens of patients with SCC of the oral tongue in correlation with perineural growth and clinical outcomes. Our results showed a heterogeneous expression of LEKTI and a strong association between absence of LEKTI expression and occurrence of perineural growth in SCC of the oral tongue.

Hypothesis

Based upon the negative correlation of LEKTI expression with perineural invasion (PNI) in Head and Neck Squamous Cell carcinoma (HNSCC) of the tongue, we hypothesized that the same correlation may exist in SCC of the skin.

Methods

Briefly, the primary tumor specimens were recut and stained with a purified mouse anti-LEKTI monoclonal antibody. Specimens were stained for LEKTI with an automated stainer. Briefly, sections (4 μ m thick) were deparaffinized, dehydrated, antigen retrieved using microwave methods, immersed in 0.3% H₂O₂ for 10 min at room temperature in methanol, and washed with PBS. The sections are incubated with 3% BSA in PBS, washed twice, and then incubated with a mouse monoclonal anti-PCNA antibody (Dako) for 1 h at room temperature. The 1C11G6 mAb, which is specific for LEKTI, is detected using the Vectastain ABC-alkaline phosphatase kit according to supplier's instructions (Vector Laboratories, Burlingame, CA). Two investigators examined the stained specimens independently. In each case, three arbitrary separate microscope fields ($\times 200$) are examined to count immunoreactive tumor cells and the total number of tumor cells. The average percentage of immunostained cells are defined as the labeling index (LI) and used for statistical analysis. Slides were reviewed and categorized by two independent investigators. LEKTI scoring was done as follows: Tumors with weak to no LEKTI staining in $> 95\%$ cells were considered negative; Tumors with moderate LEKTI staining in $> 5\%$ of cells or strong staining restricted to more differentiated tumor were considered

intermediate; Tumors with strong LEKTI staining in > 5% of cells, not restricted to more differentiated areas were considered strongly positive. The surgical pathology reports were reviewed for histopathologic features of the primary tumor. Medical records were reviewed for covariate and clinical follow-up data.

Results and Discussion

We examined for LEKTI protein by IHC in HNSCC specimens and the results are shown in Figure 1. We observed intense suprabasal staining of LEKTI in non-malignant squamous mucosa in specimens from patients 1 and 2 (A and B), while there is reduced staining in an adjacent dysplastic area in the specimen from patient 2 (C). By contrast, tumors from patients 3, 4, and 5 (D, E, and F) were negative for LEKTI, except for a highly keratinized foci of tumor cells (single arrow) in F. On the other hand, we noticed intermediate LEKTI staining defined by orderly expression of LEKTI confined to more differentiated areas within tumor nests (double arrows) in the tumor from patient 1 (G), while tumor specimens from patients 6 and 7 (H and I) exhibited heterogeneous but strong expression of LEKTI independent of differentiation. Tumor and adjacent non-malignant tissue shown were from patients with SCC of the tongue (A, B, C, D, E, F, G), larynx (D, I), and floor of mouth (H)

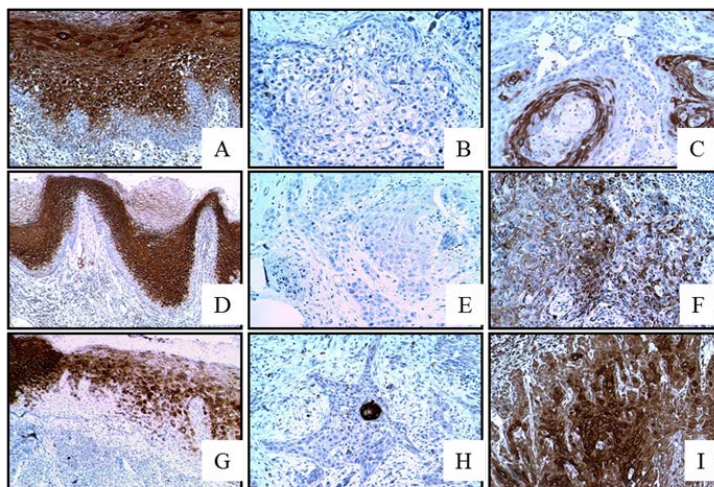


Fig 1. LEKTI expression is lost or altered in HNSCC specimens. Tumor and adjacent tissue shown were from patients with SCC of tongue (A, B, C, D, E, F, G), larynx (D, I), and floor of mouth (H).

Next, we investigated expression of LEKTI in primary tumor specimens of 81 patients with SCC of the oral tongue in correlation with PNI and clinical outcomes. We demonstrated that

LEKTI expression is negative in 31, intermediate in 44, and strong in 6 patients. Our correlative analyses between LEKTI expression and PNI demonstrated that the relative risk of PNI was 3.2 (95% CI, 1.2 to 8.9, $p = 0.007$ by Chi Square Test) in patients with LEKTI-negative tumors compared to those with LEKTI-positive tumors. Based upon the negative correlation of LEKTI expression with PNI in SCC of the tongue, we hypothesized that the same correlation may exist in SCC of the skin. Here, we present data from a case control pilot study using archival specimens from patients with SCC of the skin. We selected a total of 11 cases with PNI and 15 cases without PNI. We performed LEKTI staining in these samples by IHC. IHC analyses have shown that LEKTI expression is negative in 11, intermediate in 6, and strong in 9 patients (Table 1).

Table 1. LEKTI expression pattern in PNI (-) and PNI (+) tumors from skin case control pilot

LEKTI expression	PNI (-)	PNI (+)	Total
Negative	4 (6.4) *	7 (4.6)	11
Intermediate	6 (3.5)	0 (2.5)	6
Strong	5 (5.2)	4 (3.8)	9
Total	15	11	26

* (Numbers in parenthesis indicate expected values based upon probability)

$p = 0.039$ by Chi-square analysis; PNI is not independent of LEKTI pattern

Higher than expected number of PNI + in LEKTI negative tumors

Lower than expected number of PNI + in LEKTI intermediate tumors

Table 2. Summary of Tongue Cohort and Skin Pilot

Parameters	Tongue Cohort	Skin Pilot
Number of Cases	81	26
Site	fixed	Varied, with ear (38%), lip (19%), other (45%)
Percent PNI +	22.2%	42.3%
p=	0.018 when tumors classified as negative, intermediate, and strong	0.039 when tumors classified as negative, intermediate, and strong

Our correlative analyses showed a strong correlation between LEKTI expression and PNI in SCC of the skin (Table 1) as we demonstrated for SCC of the tongue (Table 2). As we

demonstrated for SCC of the tongue cohort, we observed much higher than expected number of PNI + in LEKTI negative tumors and much lower than expected number of PNI + in LEKTI intermediate tumors in SCC of the skin also (Table 1). Moreover, our results discovered that the incidence of PNI is much higher in skin tumors (42 %) compared to tongue tumors (22 %). A large body of evidence in the literature discussed various factors implicated in perineural growth of cancer. These factors include brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 and -4, glial cell-line derived neurotrophic factor (GDNF), the neural cell adhesion molecule (NCAM), substance P (SP), and chemokines [48]. SHH overexpression is also shown to be involved in PNI in pancreatic cancer [49]. Now our data from SCC of the tongue and skin confirm our in vitro and in vivo findings and strongly support that the loss of LEKTI expression in HNSCC correlates with a locally aggressive biologic behavior [50-55]. Our results suggested that LEKTI might also be one of the critical molecules involved in the regulation of perineural growth of neuroendocrine cancers including of HNSCC.

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Authors Column



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