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Reduced syndecan-1 expression is correlated with the histological grade of malignancy at the deep invasive front in oral squamous cell carcinoma

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BACKGROUND: Although many histopathological characteristics of oral squamous cell carcinoma (O-SCC) have been identified as prognostic factors, no factor is completely accurate and unequivocal. This study evaluated the association between the loss of syndecan-1 expression and the histological grade of malignancy at the deep invasive front in O-SCC.

METHODS: The expression of syndecan-1 at the invasive tumor front of O-SCC was examined immunohistochemically using archived tissue from 72 cases. The mean age of the patients was 62.5 years (range: 23–90 years) and the male–female ratio was 1.3:1 (41 men, 31 women). There were 26, 24, 11, and 11 cases classified as stages I–IV respectively. The correlation between the intensity of syndecan-1 immunostaining and the clinicopathological factors, especially the histological grade of malignancy at the deep invasive front (invasive front grade) was analyzed.

RESULTS: Of the 72 cases, seven (9.7%), 29 (40.3%), 36 (50.0%) showed strong, intermediate, and weak or negative syndecan-1 staining respectively. There were significant differences between syndecan-1 expression and prognosis, differentiation, and pattern of invasion at the deep invasive front. Moreover, the invasive front grade scores, based on the intensity of syndecan-1 staining, were 5.6 ± 1.0, 8.0 ± 2.1, and 10.2 ± 2.3 points with strong, intermediate, and weak or negative intensity respectively; and the difference was significant ($P < 0.0001$). Patients with intermediate or strong intensity for syndecan-1 had significantly better prognoses than did those with negative or weak intensity ($P = 0.0138$).

CONCLUSION: This study demonstrated that the reduced expression of syndecan-1 seems to be a useful marker of histological malignancy at the deep tumor invasive front and may be a useful prognostic factor in O-SCC.

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Keywords: oral squamous cell carcinoma; syndecan-1 expression; histological grade of malignancy; deep invasive front

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Introduction

Several reports have examined the usefulness of clinical and pathological factors in determining the prognosis of oral squamous cell carcinoma (O-SCC) (1–7). In particular, the histological features of O-SCC may differ widely from area to area within the same tumor (8–10), and it is believed that the most useful prognostic information can be deduced from the invasive front of the tumor, where the deepest and presumably the most aggressive cells reside (11–14). Tumor cell proliferation activity is believed to indicate the degree of aggressiveness of a tumor (15). The proliferative activity of carcinoma cells is generally considered to be related to the degree of malignancy of carcinoma tissue (14–16). Recent seminal studies by Bryne et al. (17) suggest that the invasive tumor front is the region of the tumor with the highest prognostic utility. Similarly, we previously showed that the histological grade of malignancy at the deep invasive front (invasive front grade, IFG) had a high prognostic value for squamous cell carcinoma of the tongue (18).

Syndecans are a family of four cell-surface heparan sulfate proteoglycans that interact with extracellular matrix components, other cell surface components, and growth factors, including basic fibroblast growth factor (19, 20). Syndecan-1 is thought to function as a matrix receptor that transduces information between the

extracellular matrix and the inside of the cell (21, 22). Its down-regulation relative to the expression in normal epithelium has been reported in squamous cell carcinomas of the head and neck (21–24). This study is a retrospective review of clinical and pathological data to evaluate the association between the loss of syndecan-1 expression and the histological grade of malignancy at the deep invasive front in O-SCC.

Patients and methods

Tissue specimens were surgically removed from 85 patients with O-SCC at Kyushu Dental College Hospital between 1990 and 1999. Excluded from this study were 13 patients with disseminated disease, other serious illnesses, or a poor general condition that precluded treatment with curative intent. This study focused on the remaining 72 patients (41 men, 31 women, mean age: 62.5 years, range: 23–90 years) for which the biopsy specimens had confirmed tumor infiltration into the connective tissue of sufficient quantity. All of the patients were treated with surgical excision of the tumor and immediate reconstruction using skin grafts, myocutaneous flaps, or free flaps. None of the patients received preoperative treatment. Classical or modified radical neck dissection was performed in all patients with clinically positive neck nodes. The tumors were located in the tongue (43 cases), maxillary gingiva (13 cases), oral floor (6 cases), mandibular gingiva (five cases), and buccal mucosa (five cases). There were 26, 24, 11, and 11 cases classified as stages I–IV respectively. The mean of follow-up time for patients in this series was 61.2 months (range: 10–73 months).

Histopathologic evaluation

Paraffin-embedded specimens were retrieved from the archives, and 4 to 6-μm-thick serial sections were cut. Alternate sections were stained with hematoxylin and eosin (H & E). The initial biopsy for histological diagnosis was performed so that the excised specimen included a portion that was as deep as possible with respect to the border between the tumor and normal tissue, and contained a representative portion sufficient to determine the histological grade of the malignancy.

The histological grade of malignancy at the deep invasive front (IFG) was determined using the method of Bryne et al. (17). For each tumor, the degree of keratinization, nuclear polymorphism, pattern of invasion, and host response (degree of leukocyte infiltration) were graded and given scores between 1 and 4, which were summed to yield the total IFG score. Two pathologists and two oral surgeons, who were all blind to the clinical data, reviewed all of the pathological specimens. The histological assessments were judged by agreement among three or more reviewers.

Immunohistochemical studies

The tissue sections were deparaffinized and incubated in methanol with 3% hydrogen peroxidase for 5 min to eliminate endogenous peroxidase activity. Antigen was retrieved by autoclaving the sections used for sydecan-1 immunostaining at 121° in 0.01 M citrate buffer (pH 6.0) for 10 min. The sections were treated with normal goat serum for 15 min to block non-specific binding, and then incubated overnight at 4° with the primary antibodies. The monoclonal antibodies used were anti-syndecan-1 (CD138, M15, DAKO, Denmark: diluted 1:100) (22, 23). The Envision Plus Kit (DAKO, Tokyo, Japan) was used to apply the secondary antibody, according to the manufacturer instructions, and the reaction products were visualized by immersing the sections for 3–10 min in 0.03% diaminobenzidine (DAB) solution containing 2 mM hydrogen peroxide. The sections were then briefly counterstained with Mayer's hematoxylin, dehydrated, and mounted. The sections from normal epithelium with syndecan-1 expression were used as positive control. The negative control was done by omission of the primary antibody.

The syndecan-1 staining intensity was classified as negative, weak, intermediate, or strong relative to the staining intensity of normal oral epithelium (23–25).

Statistical analysis

All data were tabulated and statistical tests were performed using the Stat View software package (SAS Institute, Inc., Cary, NC, USA). Fischer's exact test and the Kruskal–Wallis tests were used to assess the significance within each group. The correlation between syndecan-1 expression and disease-free survival was analyzed using the log-rank test. Survival curves were plotted using the Kaplan–Meier method (26). The prognostic significance of clinicopathological factors on disease-free survival was assessed using Cox's multivariate proportional hazards regression analysis. The results were considered significant when $P < 0.05$.

Results

Strong syndecan-1 expression was observed in stratified normal epithelium. Of the 72 cases, seven (9.7%), 29 (40.3%), and 36 (50.0%) showed strong, intermediate, and weak or negative staining respectively (Fig. 1).

The relationship between syndecan-1 expression and clinicopathological factors is shown Table 1. Syndecan-1 expression was correlated with prognosis, differentiation, and pattern of invasion at the deep invasive portion. However, syndecan-1 expression was not correlated with gender, clinical site, tumor size, nodal status, or stage classification (Table 1, Fig. 2). Moreover, the IFG scores, based on the intensity of syndecan-1 staining were 5.6 ± 1.0, 8.0 ± 2.1, and 10.2 ± 2.3 points with strong, intermediate, and weak or negative intensity respectively; and the differences were significant (Fig. 3; Kruskal–Wallis test, $P < 0.0001$). Fig. 4 shows the disease-free survival according to syndecan-1 expression. Patients with intermediate or strong syndecan-1 intensity had significantly better prognoses than did those with negative or weak staining intensity (log-rank test, $P = 0.0138$). Disease-free survival was correlated with nodal status ($P < 0.0001$), differentiation ($P = 0.004$), pattern of invasion ($P = 0.0204$), syndecan-1 expression ($P = 0.0082$), and IFG

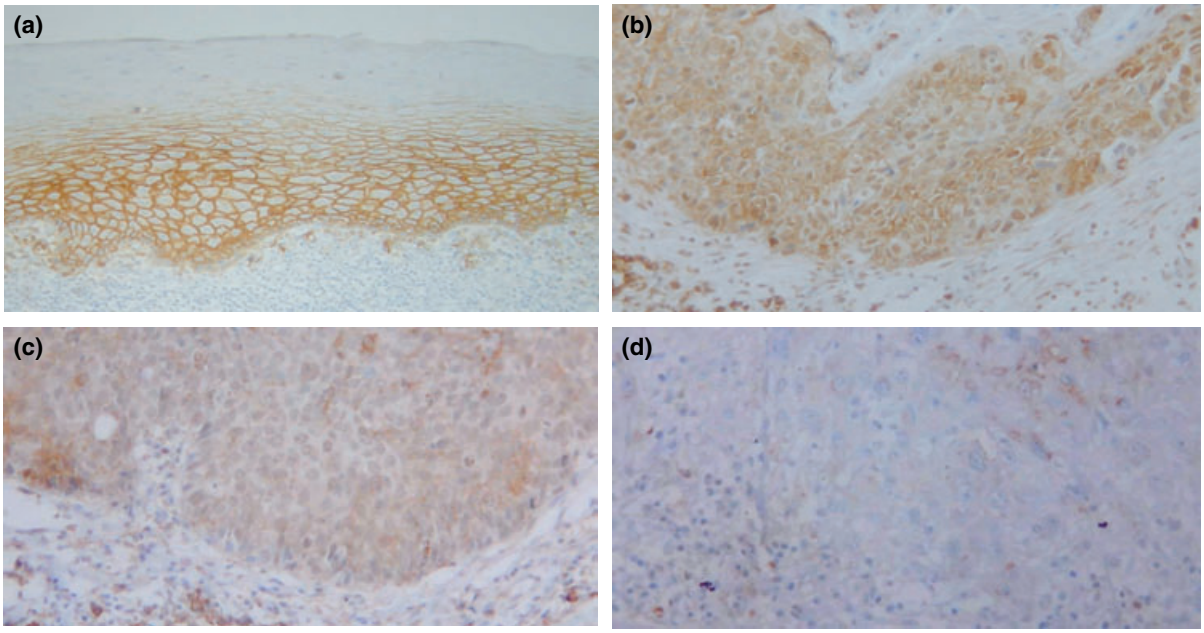

Figure 1 Immunohistochemical localization of syndecan-1 (original magnification ×150). (a) Strong syndecan-1 expression in normal epithelium. (b) Strong syndecan-1 expression at the deep invasive front of oral squamous cell carcinoma (O-SCC) (IFG score: five points). (c) Intermediate syndecan-1 expression at the deep invasive front of O-SCC (IFG score: eight points). (d) Negative syndecan-1 expression at the deep invasive front of O-SCC (IFG score: 11 points).

Table 1 Correlation of syndecan-1 expression with clinicopathological factors

	Syndecan-1 expression (no. of patients)			
Factors	*Weak (or negative)*	*Intermediate*	*Strong*	*P-value*
Gender				
Male	20	17	4	0.9696
Female	16	12	3	
Clinical site				
Tongue	25	15	3	0.4478
Maxillary gingiva	4	6	3	
Oral floor	2	4	0	
Mandibular gingiva	2	2	1	
Buccal mucosa	3	2	0	
Tumor size				
T1, T2	33	24	7	0.3231
T3, T4	3	5	0	
Nodal status				
N0	22	25	6	0.0504
N1–3	14	4	1	
Stage classification				
I, II	23	21	6	0.4683
III, IV	13	8	1	
Prognosis				
Alive	20	23	7	0.0215
Dead	16	6	0	
Differentiation				
Well	7	15	6	0.0035
Moderately	20	12	1	
Poor	9	2	0	
Pattern of invasion				
Score 1, 2	4	13	3	0.0001
Score 3	7	14	3	
Score 4	25	2	1	

($P < 0.0001$). Cox's proportional hazards regression analysis of these five factors demonstrated that nodal status ($P = 0.0013$), syndecan-1 expression ($P = 0.0078$), and IFG ($P = 0.0156$) had predictive values (Table 2).

Discussion

Recent evidence suggests that cells present at the invasive tumor front of carcinomas have different molecular characteristics compared with those in superficial areas of the tumor, making the invasive front the most important area of the tumor for determining the prognosis (11–13). Bryne et al. (17) first described a multiple-factor histological grading system of the invasive front of tumors of the head and neck: it consisted of the pattern of invasion, the degree of keratinization, nuclear polymorphism, and the host response. Bryne et al. (17) and Kearsley et al. (27) reported a strong correlation between total malignancy grading scores based on several pathological parameters and the prognosis in O-SCC. Furthermore, Kurokawa et al. (18) reported that elevated IFG scores were highly prognostic in cases of squamous cell carcinoma of the tongue. These findings suggest that cells present at the invasive tumor front of the carcinoma have different molecular characteristics than those in superficial areas of the tumor and that IFG scoring usefully evaluates the most important area of the tumor for prognostic purposes.

Syndecans are a family of four cell-surface heparan sulfate proteoglycans (19, 20, 24). Inki et al. (20) showed that syndecan-1 expression was reduced in epidermal keratinocytes during experimental skin carcinogenesis in mice. Furthermore, in human squamous cell carcinoma, marked down-regulation of syndecan-1 expression was detected in carcinomas of the head and neck, as well as

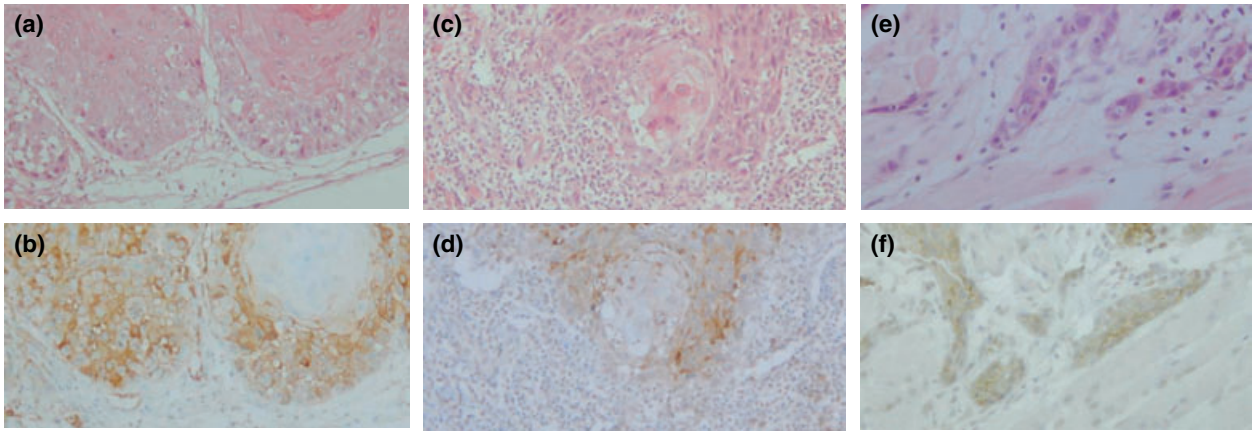

Figure 2 Immunohistochemical localization at the deep invasive front of O-SCC (a, c, e: hematoxylin-eosin stain, b, d, f: immunostaining with anti-syndecan-1 antibodies; original magnification ×115). (a) Well-differentiated O-SCC with score 1 invasion mode. (b) Strong syndecan-1 expression is seen in an adjacent section. (c) Well-differentiated O-SCC with score 2 invasion mode. (d) Intermediate syndecan-1 expression in an adjacent section. (e) Poor-differentiated O-SCC with score 4 invasion mode. (f) Weak or negative syndecan-1 expression in an adjacent section.

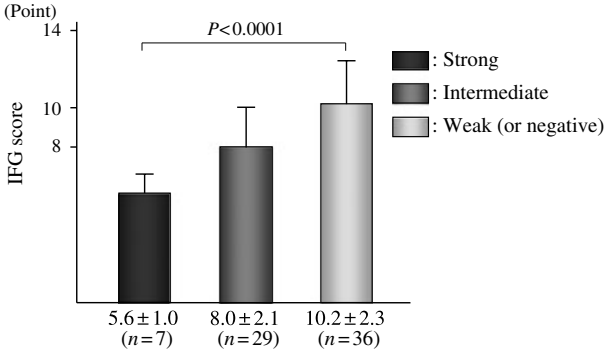

Figure 3 Correlation of syndecan-1 expression with IFG score.

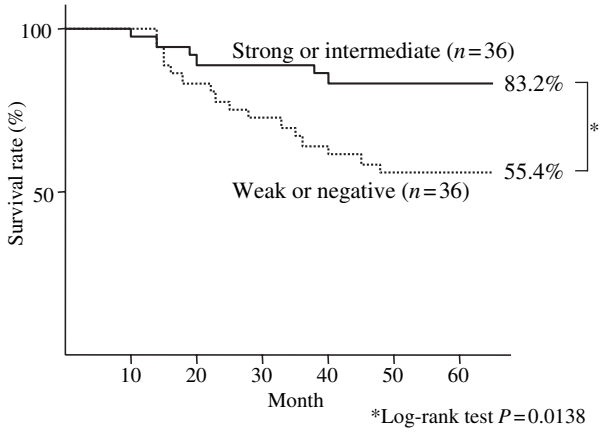

Figure 4 Disease-free survival curves in relation to syndecan-1 intensity.

in the uterine cervix, when compared with syndecan-1 expression in the corresponding normal epithelium (22, 23). Soukka et al. (24) suggested that syndecan-1 was a useful marker for evaluating pre-malignant lesions of the head and neck region. We also found a significant

Table 2 Univariate analysis and Cox's multivariate proportional hazards regression analysis of disease-free survival

Factors	*Univariate analysis (P-value)*	*Multivariate analysis*	
		Hazards ratio	*P-value*
Gender	0.1927		
Clinical site	0.8169		
Tumor size	0.0740		
Nodal status	< 0.0001	8.62	0.0013
Differentiation	0.0004	1.23	0.2552
Pattern of invasion	0.0204	1.96	0.4185
Syndecan-1 expression	0.0082	5.30	0.0078
IFG score	< 0.0001	4.62	0.0156

correlation between the down-regulation of syndecan-1 expression and the grade of oral epithelial dysplasia (25). Recent *in vitro* studies have indicated that syndecan-1 plays a role in inhibiting cell invasion and suppressing the growth of carcinoma cell lines (28–31). In addition, immunohistochemical studies have demonstrated absent or decreased expression of syndecan-1 in many kinds of carcinomas with more aggressive characteristics (22, 32–37). However, few studies have used syndecan-1 expression to evaluate the value of histological malignancy and prognostic ability of invasive front in O-SCC. Soukka et al. (24) reported that 65% of O-SCC cases showed negative or weak staining for syndecan-1, of which 35% were totally negative. In our study, 36 of the 72 cases (50%) were negative or weakly intense for syndecan-1 expression. Inki et al. (20) and Soukka et al. (24) reported that intermediate and strong positive staining for syndecan-1 was localized on cell surfaces, especially in cell–cell contact sites. Moreover, they stated that the positively stained areas were more common in well differentiated than in moderately differentiated tumors and that only weak and patchy immunostaining was noticed in poorly differentiated tumors. We also found that the normal epithelium of

each specimen was strongly positive, while the infiltrating neoplastic islands of the invasive portion in O-SCC were either weakly positive or negative for syndecan-1.

Tumor cell proliferation activity is believed to indicate the degree of aggressiveness of a tumor (15). The proliferative activity of carcinoma cells is generally considered to be related to the degree of malignancy of carcinoma tissue (14–16). Considering the relationship between cell proliferation and cell migration, Natarajan et al. (38) reported that the expression of the cell cycle regulating protein p16 was associated with some premalignant lesions and occurred consistently in areas of microinvasion and at superficial margins of invasive SCC. Incidentally, syndecan-1 is involved in the regulation of cell morphology, adhesion, and differentiation, and the loss of syndecan-1 from transformed cells might be associated with uncontrolled proliferation, reduced adhesion, and the disturbed differentiation of tumor cells (30, 38). Furthermore, there are many ways by which to evaluate the biological behavior, such as cell proliferation, apoptosis, and signal transduction, of a carcinoma (30, 38–41). Of these, cell–cell and cell–matrix adhesions are very important, because reduced adhesion can induce progression and metastasis (30, 38). In our study, the down-regulation of syndecan-1 expression was significantly correlated with IFG scores. Moreover, syndecan-1 expression was significantly associated with nodal metastasis, differentiation, and mode of invasion at the deep invasive portion. These results suggested that syndecan-1 is involved in the regulation of cell morphology, proliferation, and differentiation and that the loss of syndecan-1 expression at the deep invasive front could be associated with the histological grade of malignancy in O-SCC. Furthermore, we suggest that the decreased syndecan-1 expression contributes to tumor cell invasion and the development of metastases in O-SCC.

Some investigators have demonstrated that syndecan-1 expression correlates significantly with the histological differentiation grade of a tumor and can be a useful prognostic factor in SCC of the head and neck (26, 38). We also found a statistically significant correlation between the down-regulation of syndecan-1 expression and prognosis, differentiation and pattern of invasion at the deep invasive front in O-SCC. Moreover, the 5-year disease-free survival rates differed significantly between intermediate or strong intensity for syndecan-1 expression and negative or weak intensity. These results suggest that the down-regulation of syndecan-1 expression is a useful prognostic factor in O-SCC.

In conclusion, we have shown that the down regulation of syndecan-1 expression in the tissue at the deep invasive tumor front is associated with the histological grade of malignancy and provides useful prognostic information in O-SCC.

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