High expression of EZH2 is associated with tumor proliferation and prognosis in human oral squamous cell carcinomas

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Summary Enhancer of zeste homolog 2 (EZH2) is a member of the polycomb group of genes and is important in cell cycle regulation. Overexpression of EZH2 protein has been associated with biological malignancy of prostate cancer and several other cancers. The aim of the present study was to evaluate the expression of EZH2 protein in human oral normal mucosa, dysplasia and oral squamous cell carcinoma (OSCC) with clinicopathological profiles. EZH2 expression was assessed by Western blotting and immunohistochemistry in 3 OSCC cell lines, 10 normal mucosae, 50 dysplasias and 102 OSCCs. The labeling indices (LIs) of EZH2, Ki-67, P53, and the apoptotic index (AI) were evaluated by immunohistochemistry and the terminal deoxynucleotidyl transferase (TdT)-mediated dUTP-digoxigenin nick-end labeling (TUNEL) method. Western blot analysis detected EZH2 protein as a single band at 91 kDa in the 3 OSCC cell lines, but it was almost absent in non-tumoral oral mucosa. The LI of EZH2 was highest in the OSCCs, followed by the dysplasias (<0.05) and normal mucosae (<0.05) with significant difference. The LI of EZH2 correlated with the clinical stage, tumor size, lymph node metastasis and LIs of Ki-67 and P53, but not with the AI in OSCCs, and inversely correlated with the histological differentiation of OSCCs. The survival rate calculated by the Kaplan–Meier method revealed that OSCC

Keywords EZH2; Oral squamous cell carcinoma; Ki-67; P53; Apoptosis; Prognosis

Abbreviations AI, apoptotic index; LI, labeling index; OSCC, oral squamous cell carcinoma; EZH2, enhancer of zeste homolog 2; TUNEL, terminal deoxynucleotidyl transferase (TdT)-mediated dUTP-digoxigenin nick-end labeling.

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patients with higher EZH2 expression showed poorer prognosis than those with a lower EZH2 expression ($p < 0.01$). These results suggest that overexpression of EZH2 is correlated with malignant potential and poor prognosis in OSCCs. EZH2 might serve as a novel biomarker for predicting prognosis in patients with OSCCs.

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Introduction

Oral squamous cell carcinoma (OSCC) is the most frequently occurring malignant tumor of the oral cavity. In spite of recent advances in radiotherapy and/or chemotherapy, the prognosis of patients with OSCC has not improved (there is an estimated five-year survival rate of 56%). The reason for this unsatisfying outcome is that OSCC often exhibits extensive local invasion and frequent regional lymph node metastasis at the time of initial diagnosis. OSCC is thought to develop from precancerous dysplastic lesions by multistep carcinogenic processes in which oncogene activation and loss of the tumor suppressor gene are the key features. Detecting genetic abnormalities in OSCCs might be an important prognostic indicator of patient survival. In the future, indicators or markers could be clinically helpful for choosing initial treatment and for tailoring individual tumor specific therapies.

In OSCC, tumor size, histological differentiation, and mode of carcinoma invasion are known to correlate with tumor metastasis and patient prognosis. In recent years, many studies on factors controlling the cell cycle, cell proliferation, and apoptotic pathways have provided an increased understanding of the pathogenetic mechanisms leading to cancer, and many molecular studies have been performed to reveal useful prognostic factors. As a result, P53 and Ki-67 have been identified as markers of malignancy in OSCC. Overexpression of these proteins is commonly associated with an aggressive clinical course. Some reports, however, have not shown any relationship between prognosis of OSCC patients and expression of P53, and Ki-67. The search for molecular factors that are highly correlated with prognosis may lead to the discovery of factors that can help to predict patient survival. We focused on a new marker, enhancer of zeste homolog 2 (EZH2), which might have potential for cancer screening and for prediction of patient survival.

EZH2 is a member of the polycomb group of genes which are important for transcriptional regulation through nucleosome modification, chromatin remodeling, and interaction with other transcription factors. EZH2 functions as a methyltransferase for lysine 27 of histone H3. In a recent report, overexpression of EZH2 was consistently associated with malignancy of tumors and prognosis in human prostate, breast, gastric, hepatic, and bladder cancers.

In this study, we examined the expression of EZH2 in oral normal mucosae, dysplasias and SCCs, and analyzed their clinicopathologic significance with respect to histological differentiation, mode of invasion, lymph node metastasis and patient prognosis in human OSCCs, comparing these with apoptosis and expression of Ki-67 and P53.

Materials and methods

Human OSCC cell lines

Three human OSCC cell lines, HSC3 (poorly differentiated), HSC4 (well differentiated) and SCCKN (moderately differentiated) were cultured in Dulbecco’s modified Eagle’s medium (Nissui, Tokyo, Japan) supplemented with 10% fetal bovine serum (JRH, Lenexa, KS, USA), 100 U/ml penicillin, 100 μg/ml streptomycin and 292 μg/ml L-glutamine.

Protein sample

We obtained frozen tissue samples of two pairs of oral non-neoplastic tissues and well-(T1), or poorly differentiated (T2) SCCs. The frozen tissue samples and three oral SCC cell lines were solubilized in lysis buffer (50 mM Tris–HCl pH 7.4, 125 mM NaCl, 0.1% NP-40, 1 mM PMSF, 1 ng/ml leupeptin, 1 ng/ml aprotinin) with a homogenizer on ice. Lysates were centrifuged at 12,000 rpm for 10 min and then supernatants were decanted. Protein concentration was determined using the Bradford protein assay (Bio-Rad Lab, Richmond, CA, USA) with bovine serum albumin as the standard protein.

Western blot analysis

Fifty micrograms of protein was separated by electrophoresis on a 12% sodium dodecyl sulfate–polyacrylamide gel. The protein was then electro-transferred onto a polyvinylidene difluoride membrane (Immobilon; Millipore, Bedford, MA). After 1 h incubation in blocking solution (5% non-fat dry milk in PBS, 0.5% Tween 20), the membrane was blotted with anti-beta-actin monoclonal antibody (1:1000; AC15, Sigma, St. Louis, MO) and anti-EZH2 antibody, (1:1000; clone 11, BD Biosciences, San Jose, CA). The blots were developed with peroxidase-labeled secondary antibodies. After extensive washing, specific bands were detected using an enhanced chemiluminescence system (ECL detection system, Amer sham Biosciences, UK).

Tissue samples

We analyzed tissue samples of 10 pieces of normal oral mucosa, 50 dysplasias and 102 OSCCs. All specimens were obtained from the Division of Oral and Maxillofacial Biopathological Surgery, Tottori University Faculty of Medicine. All specimens were fixed in 10% buffered formalin and embedded in paraffin wax. Paraffin blocks were sectioned in 4 μm slices. All tumors were classified according to the International Union Against Cancer (UICC) tumor size nodal metastasis distant metastasis (TNM) classification. Histological diagnoses of
OSCC and dysplasia were made according to the criteria of the World Health Organization for the histological typing of cancer and precancer of the oral mucosa. The histological mode of invasion was classified according to the classification of Jakobsson.

Immunohistochemistry

Paraffin-embedded tissue sections were immunostained using the streptavidin–biotin–peroxidase complex (SAB) technique with a mouse monoclonal antibody against EZH2 (1:25, BD Biosciences, clone 11, San Jose, CA), Ki-67 monoclonal antibody (1:50, MIB-1, Immunotech, Cedex 9, France) and P53 monoclonal antibody (1:50, DO7, Dako, Kyoto, Japan). The sections were deparaffinized, and antigens were retrieved by autoclaving in 10 mM citrate buffer (pH 6.0) at 121°C for 10 min. Endogenous peroxidase activity was blocked by immersing the slides in 0.3% hydrogen peroxide in methanol for 30 min. The sections were reacted with each primary antibody overnight at 4°C. Tissue sections were treated with secondary antibody and biotin–streptavidin complex for 30 min each at 37°C. Diaminobenzidine was used as the chromogen for the immunoperoxidase reaction. The slides were counterstained with hematoxylin.

At least 1000 normal squamous, dysplastic or SCC cells were counted, and the percentage of cells showing positive staining was designated as the labeling index (LI) (%). EZH2 immunoreactivity was classified into two groups: lower expression, when positive cells were less than 50%; and higher expression, when positive cells were 50% or more.

TUNEL analysis

For the detection of apoptotic cells in situ, terminal deoxynucleotidyl transferase (TdT)-mediated dUTP-digoxigenin nick-end labeling (TUNEL) was performed using an Apop Tag Plus in situ apoptosis detection kit (Chemicon International, Temecula, CA). Briefly, after deparaffinization, incubation was carried out with 20 μg/ml protease K (Wako Pure Chemical Industries, Osaka, Japan) for 10 min at 37°C. Then, the sections were incubated with terminal deoxynucleotidyl transferase, digoxigenin-11-DUTP and dATP in a moist chamber for 60 min at 37°C. Incubation with anti-digoxigenin antibody peroxidase for 30 min at room temperature was employed for the detection of digoxigenin-11-DUTP labeling, followed by color development with a solution containing 3,3′-diaminobenzidine and H2O2. Hematoxylin was used for counterstaining.

At least 1000 normal, dysplastic or SCC cells were counted, and the percentage of cells showing positive staining was designated as the apoptotic index (AI) (%).

Statistical analysis

Statistical analyses were performed using Mann–Whitney’s U test and the Kruskal–Wallis test. The probability of survival by EZH2 expression was determined using the Kaplan–Meier method. Different survival curves were compared using the log-rank test. A difference of p < 0.05 was considered statistically significant.

Results

Expression of EZH2 in oral SCC

Western blot analysis detected EZH2 protein as a single band with a molecular weight of 91 kDa. As shown in Figure 1, EZH2 protein was found in HSC3 (well-differentiated SCC), HSC4 (poorly differentiated SCC), SCCKN (moderately differentiated SCC) cell lines and both resected SCC tissue specimens. In contrast, the expression of EZH2 protein was almost absent in non-neoplastic mucosae compared to the corresponding OSCCs.

Expression of EZH2 in normal epithelia, dysplasias and SCCs

Immunohistochemistry was performed to examine the expression of EZH2 protein and its distribution in human oral mucosae and OSCC. Immunoreactivity for EZH2 was observed in the nuclei of normal epithelial cells and dysplastic cells and SCC cells (Fig. 2). EZH2-positive cells were distributed in basal and suprabasal cell layers in normal mucosae (Fig. 2a) and in both basal cell and prickle cell layers in dysplasia (Fig. 2b). EZH2-positive cells extended from the lower layer to the upper layer, correlating with the grade of dysplasia. EZH2-positive cells were observed mainly in peripheral portions of cancer nests in well- and moderately-differentiated OSCCs (Fig. 2d and g). In contrast, no specific distribution of positive cells was noted in poorly differentiated OSCC (Fig. 2j). Interestingly, the frequency of

![Figure 1](image-url)
EZH2-positive cells was higher than Ki-67-positive cells in each differentiation of OSCC (Fig. 2).

Table 1 shows the LIs of EZH2, Ki-67 and P53 and the AI in oral normal mucosae, dysplasias and SCCs. The mean LI of EZH2 was 19.4 ± 1.4, 25.9 ± 3.0, and 50.7 ± 2.1 in normal mucosae, dysplasias and OSCCs, respectively. The LI of EZH2 was significantly higher in OSCCs than in normal mucosae and dysplasias, respectively (p < 0.05), but no significant difference was noted between normal mucosae and dysplasias. The LI of EZH2 was highest in OSCC, followed by dysplasias and normal epithelia. EZH2 LIs also correlated with the histological grade of dysplasia and OSCC, being highest for severe dysplasia and poorly differentiated OSCC. Similar results were also obtained for LIs of Ki-67 and P53, but the value of EZH2 LI was highest among those factors. On the other hand, no significant difference was noted between AIs among normal mucosa, dysplasia and OSCC.

**Correlation of EZH2 expression levels with clinicopathological parameters in OSCCs**

Immunohistochemical results and their associations with clinicopathological features in 102 OSCCs are summarized in Table 2. The cut-off level of EZH2 LIs was fixed at 50%,
which was almost the median (49.6%) for all cases. Fifty-one cases had a higher expression of EZH2, which significantly correlated with histological differentiation \((p = 0.002)\), clinical stage \((p = 0.018)\), tumor size \((p = 0.038)\) and lymph node metastasis \((p = 0.041)\), but not with age, sex and mode of invasion.

**Correlation among LIs of EZH2, Ki-67, P53 and AI in oral SCC**

Table 3 shows the correlation between EZH2 expression and the LIs of Ki-67 and P53, and AI in 102 OSCCs. The mean LIs of Ki-67 and P53 were 35.1 ± 2.1 and 29.3 ± 2.9 in the 51 SCCs with higher EZH2 expression, and 25.1 ± 1.8 and 19.9 ± 2.2 in the 51 SCCs with lower EZH2 expression. There was a positive correlation between EZH2 expression and the LIs of Ki-67 and P53 in OSCC, respectively \((p < 0.01)\). Table 3 shows that the Spearman’s correlation coefficient between EZH2 and Ki-67 was \(rs = 0.38\) \((p < 0.01)\) and P53 was \(rs = 0.29\) \((p < 0.01)\). There was a statistically significant difference between LIs of EZH2 and Ki-67 or P53 in OSCC patients \((p < 0.01)\). Table 3 shows that the Spearman’s correlation coefficient between EZH2 and Ki-67 was \(rs = 0.38\) \((p < 0.01)\) and P53 was \(rs = 0.29\) \((p < 0.01)\). There was a statistically significant difference between LIs of EZH2 and Ki-67 or P53 in OSCC patients \((p < 0.01)\). In contrast, no significant correlation was noted between LIs of EZH2 and AI.

**Survival analysis**

We performed a prognostic analysis in 83 patients with stages II–IV OSCCs. We excluded the 19 stage I cases, because of their favorable prognosis. Kaplan–Meier survival curves showed the 100-months survival rate analysis of OSCCs. We examined the correlation between the expression of EZH2, Ki-67, P53 and the AI with cumulative survival. The median value (EZH2 = 50%, P53 = 19.5%, Ki-67 = 28.2%, AI = 0.43%) was set as the cut-off value. As shown in Figure 3a, higher LI of EZH2 showed a significantly poorer prognosis in cumulative survival time. On the other hand, there were no significant differences in the Kaplan–Meier survival curves of Ki-67 and P53 LIs, although prognosis tended to be poor with higher LIs of Ki-67 and P53 (Fig. 3b and c). The value of AI did not correlate with the cumulative survival time in OSCC patients (Fig. 3d).

**Discussion**

The present study clearly demonstrated EZH2 protein expression in the three OSCC cell lines and surgical specimens in human OSCC tissues by Western blotting, which showed a clear single band at 91 kDa, indicating the specificity of the antibody used in this study. The expression of EZH2 was clearly higher in the OSCCs than in the corresponding non-tumoral regions, suggesting that the overexpression of EZH2 might be a tumor-related factor in OSCCs.

Immunohistochemistry revealed that EZH2 expression in normal mucosa was observed in the nuclei of epithelia located in basal and suprabasal layers, in the generative zone of oral mucosa. In dysplastic mucosae, EZH2-positive cells were distributed from basal cell to prickle cell layers, consistent with the expression pattern of Ki-67-positive proliferative cells reported by Kodani et al. These data suggested that the increased number of EZH2-positive cells might reflect cell proliferative activity in oral mucosae and dysplasia. In OSCC, the distribution of EZH2-positive cells was also similar to that of Ki-67-positive cells, located in the peripheral portions of cancer nests, considered to be
proliferative areas in OSCC. Our immunohistochemical findings coincided with the previous observation that EZH2 expression has a positive relationship with high cell proliferation rate in breast, endometrial, prostate and bladder carcinomas. Indeed, the LIs of EZH2 was significantly higher in OSCC than those in dysplasia and normal mucosa. Moreover, LI increased along with the histological grade of dysplasia and with histological dedifferentiation of OSCCs. In vitro studies also revealed that overexpression of EZH2 enhanced the proliferation of Ramos cells, a B cell lymphoma cell line, and antisense oligonucleotides directed against EZH2 blocked the growth of HL60 cells, a granulocytic cell line. Taken together, our data strongly supported the idea that EZH2 expression might be associated with the proliferative activity of oral epithelial and carcinoma cells.

Table 2 The relationship between EZH2 expression and clinicopathological data in 102 oral SCCs

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases</th>
<th>EZH2 Higher (≥50%)</th>
<th>Lower (&lt;50%)</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>Grade 4</td>
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Higher: positive cells are 50% or more and lower: positive cells are less than 50%.<sup>a</sup> p < 0.05 was regarded as statistically significant in Kruskal–Wallis test.

Table 3 Correlation between EZH2 expression and LIs of Ki-67/P53 and AI in oral SCC

<table>
<thead>
<tr>
<th>EZH2</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Spearman correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher (N = 51)</td>
<td>Lower (N = 51) (mean ± SE)</td>
<td>rs</td>
</tr>
<tr>
<td>Ki-67LI 35.1 ± 2.1</td>
<td>25.1 ± 1.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>P53LI 29.3 ± 2.9</td>
<td>19.9 ± 2.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AI 0.48 ± 0.4</td>
<td>0.46 ± 0.1</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Median: mean ± SE% and rs: Spearman rank-correlation coefficient. <sup>a</sup> p < 0.01 is statistically significant in Mann–Whitney’s U test. <sup>b</sup> p < 0.01 is statistically significant in Spearman rank-correlation.

In fact, the LIs of EZH2 was significantly higher in OSCC than those in dysplasia and normal mucosa. Moreover, LI increased along with the histological grade of dysplasia and with histological dedifferentiation of OSCCs. In vitro studies also revealed that overexpression of EZH2 enhanced the proliferation of Ramos cells, a B cell lymphoma cell line, and antisense oligonucleotides directed against EZH2 blocked the growth of HL60 cells, a granulocytic cell line. Taken together, our data strongly supported the idea that EZH2 expression might be associated with the proliferative activity of oral epithelial and carcinoma cells.

The cut-off value of EZH2 LIs was fixed at 50%, which was almost the median (49.6%), this value being similar to that for gastric carcinoma. Higher LIs of EZH2 in human OSCCs were significantly correlated with the clinical stage, tumor size, and lymph node metastasis, and inversely correlated with histological differentiation. These results strongly suggested that a higher expression of EZH2 might correlate with the malignant potential of OSCCs. Similar results were also confirmed in other human carcinomas, e.g. prostate.
breast,\textsuperscript{21,22} gastric,\textsuperscript{23} hepatocellular,\textsuperscript{24} and bladder carcinoma.\textsuperscript{25,26} Although EZH2 expression was significantly associated with Ki-67 and P53, the survival rate calculated by Kaplan–Meier analysis revealed a significant inverse correlation between patients’ prognosis and LIs of EZH2, but not LIs of Ki-67 and P53, and AI, in 102 OSCCs examined in this study. These results indicate that EZH2 is more reliable as a prognostic marker than Ki-67, P53 and AI.

In summary, the present study showed for the first time the correlation of EZH2 expression with histological differentiation, clinical stage, tumor size, lymph node metastasis and unfavorable prognosis, and its reliability as a prognostic prediction marker. Furthermore, EZH2 might be not only a novel biomarker, but also a molecular target in the clinical treatment of OSCC, because polycomb group proteins, specifically EZH2, have recently been suggested as candidates for targeted treatment in human cancers.\textsuperscript{38}

Conflicts of Interest Statements

None declared.

Acknowledgments

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References

4. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and

Figure 3 Kaplan–Meier survival curves of the 83 stage II–IV oral SCCs. Patients with a higher expression of EZH2 showed significantly unfavorable prognoses (a). On the other hand, no significant differentiation was observed in the expression of Ki-67 (b), P53 (c), and the number of AI (d) in cumulative survival time.
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