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ROLE OF SURVIVIN AND CD146 IN THE PROGRESSION OF ORAL LICHEN PLANUS TO ORAL SQUAMOUS CELL CARCINOMA (IMMUNOHISTOCHEMICAL STUDY)

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Abstract

Background: The malignant transformation potential of oral lichen planus (OLP) is a subject of great controversy.

Aims: The present study aimed to assess immunohistochemically Survivin and CD146 expressions in OLP and different grades of oral squamous cell carcinoma (OSCC).

Methods: Fifty specimens of OLP and OSCC, twenty-five each, were included in the present study.

Immunohistochemical staining with anti-Survivin and anti-CD146 primary antibodies was performed. Area fraction of immunopositivity was measured by image analysis software followed by statistical analysis using ANOVA and Bonferroni's post hoc tests.

Results: All cases of OLP were immunopositive for Survivin and CD146 while in OSCC all cases were immunopositive for Survivin and only twenty cases of well and moderately differentiated OSCC were immunopositive for CD146. All cases of poorly differentiated OSCC were immunonegative for CD146. Statistically significant difference in Survivin and CD146 expressions were detected in OLP and all grades of OSCC ($P < 0.001$). Moreover, statistically significant difference in expression of both markers was detected when compared with different histopathological grades of OSCC. A statistically significant inverse correlation between Survivin and CD146 immunoexpression in both lesions was found.

Conclusion: Survivin could be an early diagnostic marker that predicts potency toward malignant transformation of OLP as well as a prognostic marker of OSCC. CD146 expression may be the cause of OLP progression into OSCC.

Keywords: oral lichen planus, oral squamous cell carcinoma, survivin, CD146.

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INTRODUCTION

Oral Lichen Planus (OLP) is a potentially malignant disease with a prevalence rate of 0.5–2.2%. It is a T-cell mediated autoimmune disease, in which cytotoxic CD8+ T cells trigger apoptosis of the basal cells of oral epithelium termed as liquefactive degeneration which is due to the proximity of subepithelial lymphocytic infiltrate. The reported progression of OLP to OSCC ranges from 0.4% to 6.5%. (Suganya et al., 2016). Oral Squamous Cell Carcinoma (OSCC) is the seventh most frequent cancer in humans and the most prevalent malignant neoplasm of the oral cavity. Up to 3-33% of OPMDs will evolve into invasive OSCC. (Bray et al., 2018).

Proliferation, differentiation and apoptosis are fundamental aspects of tumor biology. Apoptosis is a highly selective process occurring regularly which ensures a homeostatic balance between the rate of cell formation and cell death. Additionally, it plays an important role in embryogenesis and in tumorigenesis. (Hengartner, 2000).

The smallest member of the inhibitors of apoptosis proteins (IAPs), Survivin, contains 142 amino acids and is located on chromosome 17q25 in humans. Survivin prevents apoptosis through inhibition of caspases action. In addition to being a well-known IAP, it also plays a fundamental role in promoting cell proliferation and angiogenesis, proper execution of mitosis and cell division. (Kim et al., 2010).

Survivin has a high expression in the majority of human neoplasms like OSCC and gastric carcinomas and also in fetal tissues, although it is absent in normal adult differentiated cells. Survivin high expression in neoplasms has been associated with progression of cancer, poor prognosis, early recurrence and resistance to treatment. Therefore, it is considered as an important diagnostic immunohistochemical tumor marker that can predict a potency toward malignant transformation and moreover, as a prognostic marker since Survivin expression signals more aggressive and disseminated disease (Ajithkumar et al., 2019).

Cell adhesion molecules (CAMs) are a subset of cell surface proteins that maintain tissue structure and function through binding of cells with each other or with extracellular matrix, in a process called cell adhesion. CD146 is one of those CAMs (Gkretsi and Stylianopoulos, 2018).

CD146, which belongs to the immunoglobulin superfamily (IgSF), is a cell-cell adhesion protein found in both normal tissue and neoplasms. It maintains the integrity of the epithelium during many processes such as cell to cell and cell to matrix interactions, cell migration and cell signaling. Consequently, loss of CD146 protein could reduce cell-cell contact and in turn, facilitate cancer cell growth and metastasis (Wang and Yan, 2013). CD146 expression has been altered in many cancers such as esophageal SCC, melanoma, gastric, colorectal cancers and nasopharyngeal carcinoma. The expression of CD146 in the suprabasal keratinocytes of inflammatory skin diseases as in lichen planus and psoriasis was found to be increased (Weninger et al., 2000). So, this study aims to estimate the role of Survivin and CD146 in the progression of OLP to OSCC and their prognostic role in OSCC.

MATERIAL AND METHODS

• Case Selection

Fifty archival paraffin-embedded specimens of OLP and OSCC (twenty-five cases of each) (Table 1) were collected from archives of General Pathology Department, Faculty of Medicine, Ain Shams University and Oral Pathology Department, Faculty of Dentistry, Ain Shams University.

Table 1: The number of collected cases in each group.

Lesion	Number of cases
Oral Lichen Planus (OLP)	25
Well differentiated OSCC (WDOSCC)	10
Moderately differentiated OSCC (MDOSCC)	10
Poorly differentiated OSCC (PDOSCC)	5
Total	50

• Immunohistochemical Staining and Assessment

All steps of immunohistochemical (IHC) staining were done in the Oral Pathology Department, Faculty of Dentistry, Ain Shams University.

Immunostaining was performed on deparaffinized 4-um sections after antigen retrieval using microwave oven heating with citrate buffer retrieval solution (pH 4.8.). Monoclonal concentrated antibody (IHC668-100.) against Survivin was purchased from Genome Me Lab, Canada and monoclonal concentrated antibody (P1H12, ab24577.) against CD146 was purchased from Abcam Corporation, UK..

For immunostaining, the avidin-biotin-peroxidase complex method was used according to manufacturer instructions.. Immunohistochemical assessment was performed in the Precision Measurement Unit, Oral Pathology Department, Faculty of Dentistry, Ain Shams University.

For each positive section, four microscopic fields showing the highest immunopositivity were selected and photomicrographs were captured at original magnifications of 40X.

All images were captured using digital camera (EOS 650D, Canon, Japan) which was mounted on a light microscope (BX60, Olympus, Japan). Images were then transferred to the computer system for analysis. IHC evaluation was carried out using the image analysis software (Image J, 41a NIH, USA.) to measure the mean area fraction (MAF).

• **Statistical Analysis**

Data were analyzed using Statistical Package for Social Science software computer program. ANOVA and Bonferroni's post hoc tests were used for comparing between groups. Pearson's correlation coefficient was used for correlations between quantitative variables.

RESULTS

I. Immunohistochemical Results

A. Survivin

All the twenty-five cases of OLP and OSCC showed positive Survivin immunostaining. OLP showed positive Survivin immunostaining in the nuclei of basal cell layer predominantly followed by spinous cell layers. Some epithelial

cells show both nuclear and cytoplasmic reaction (Fig. 1A.).

Well differentiated OSCC (WDOSCC) showed positive nuclear immunopositivity for Survivin on the periphery of cell nests. Some epithelial cells in the center of the cell nests showed both nuclear and membranous immunopositivity for Survivin (Fig. 1B.).

Moderately differentiated OSCC (MDOSCC) showed immunopositivity in both nuclear and cytoplasmic regions of malignant epithelial cells forming the periphery of the cell nest. A few epithelial cells in the cell nest were immunonegative (Fig. 1C.).

Poorly differentiated OSCC (PDOSCC) showed cytoplasmic immunopositivity for Survivin in different malignant individual epithelial cells (Fig. 1D.).

B. CD146

All the cases of OLP, WDOSCC and MDOSCC showed positive CD146 immunostaining while all cases of PDOSCC showed CD146 immunonegativity.

OLP showed positive nuclear and cytoplasmic CD146 immunostaining in spinous cell layers while the basal and parabasal epithelial cells were immunonegative (Fig. 1E.).

Well differentiated OSCC (WDOSCC) showed positive CD146 immunostaining in nuclei and cytoplasm of the malignant epithelial cells forming periphery of cell nests. Moreover, some epithelial cells in the center of cell nest showed only cytoplasmic reaction and others showed both nuclear and cytoplasmic immunopositivity. Malignant epithelial cells forming periphery of keratin pearls showed only cytoplasmic reaction (Fig. 1F.).

Moderately differentiated OSCC (MDOSCC) showed positive nuclear and cytoplasmic CD146 immunoreactivity located in the malignant epithelial cells forming periphery of cell nests. Cells at the center of cell nests exhibited only cytoplasmic reaction (Fig. 1G.). Poorly differentiated OSCC (PDOSCC) showed negative CD146 immunostaining in the malignant epithelial cells (Fig. 1H.).

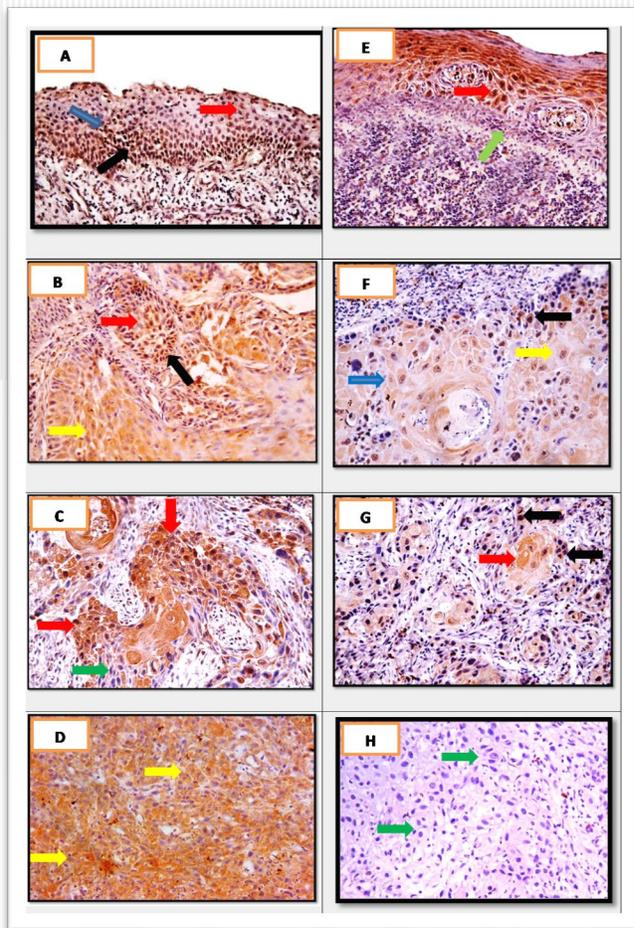


Figure (1): Photomicrographs of immunohistochemical results of Survivin (A, B, C, D) (Survivin, original magnification 40X.) and CD146 (E, F, G, H) (CD146, original magnification 40X.) in OLP and OSCC lesions. A: OLP showing positive immunostaining in the nuclei of basal cell layer predominantly (black arrow) followed by spinous cell layers (blue arrow). Some epithelial cells show both nuclear and cytoplasmic reaction (red arrow) B: WDOSCC showing positive nuclear immunopositivity on the periphery of cell nests (black arrows). Malignant epithelial cells in the center of the cell nests showed both nuclear and cytoplasmic immunopositivity for Survivin (red arrow). Some cells in the center of another cell nests showed only cytoplasmic reaction (yellow arrow). C: MDOSCC showing both nuclear and cytoplasmic immunopositivity of malignant epithelial cells forming the periphery of the cell nest (red arrows). A few epithelial cells were immunonegative (green arrow) D: PDOSCC showing cytoplasmic immunopositivity in different malignant individual epithelial cells (yellow arrows) E: OLP showing positive nuclear and cytoplasmic immunostaining in spinous cell layers (red arrow), basal and parabasal epithelial cells were immunonegative (green arrows). F: WDOSCC showing positive nuclear and cytoplasmic immunostaining of the malignant epithelial cells at periphery of cell nest (black arrows). Some epithelial cells in the center of cell nest showed only cytoplasmic reaction (blue arrow) and others showed both nuclear and cytoplasmic immunopositivity (yellow arrow) G: MDOSCC showing positive nuclear and cytoplasmic immunoreactivity located in the malignant epithelial cells forming periphery of cell nests (black arrows). Cells at the center of cell nests exhibited only cytoplasmic reaction (red arrows) H: PDOSCC showing negative CD146 immunostaining in the malignant epithelial cells (green arrows)

II. Statistical Results

A. Survivin Results:

Survivin expression data showed normal (parametric) distribution. One-way ANOVA test was used for simultaneous comparison between the expression of Survivin in different groups. On the quantitative level, the results of this study showed a statistically significant higher Survivin immunopositivity in OSCC compared with OLP (P-value < 0.001, Effect size = 0.888.). Moreover, a high statistically significant difference was revealed between different groups of OSCC (P-value < 0.001.). Pair-wise comparisons revealed that PDOSCC group showed the highest mean Survivin expression (30.51) with no statistically significant difference from MDOSCC group (25.26) and a statistically significantly higher value than WDOSCC and OLP group mean (19.27, 6.26 respectively). OLP group showed the lowest mean Survivin expression (6.26) with a statistically significant difference from different grades of OSCC (Table 2 and Fig 2.)

Table 2: Descriptive statistics showing mean and SD of the MAF and results of one-way ANOVA test for comparison between Survivin expression in OLP and different grades of OSCC. Different superscripts are statistically significantly different as demonstrated by Bonferroni's post-hoc test.

	OLP group	WDOSCC group	MDOSCC group	PDOSCC group	P value	Effect size (Partial Eta Squared)
Survivin	6.26± 2.11 ^A	19.27± 2.94 ^B	25.26± 4.93 ^{BC}	30.51± 3.69 ^C	<0.001	0.888

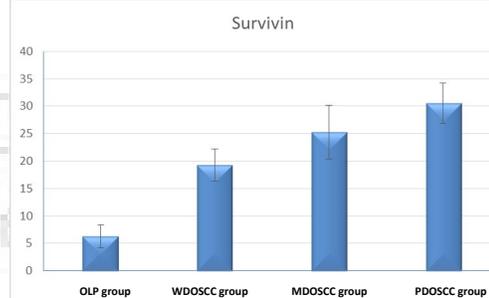


Figure 2: Bar chart representing mean and standard deviation for Survivin immunopositivity in OLP and different grades of OSCC.

B. CD146 Results:

CD146 expression data showed normal (parametric.) distribution. The mean and standard deviation of OLP and the three grades (well, moderate and poor.) of OSCC. ANOVA test was used for comparing between the expression of CD146 in different groups.

On the quantitative level, the results of this study revealed a statistically significant higher CD146 immunoeexpression in OLP compared with OSCC (P-value < 0.001, Effect size = 0.806.). Moreover, a significant difference between groups of OSCC was shown (P - value < 0.001.). Pair-wise comparisons revealed that OLP group showed the highest mean CD146 expression (25.13.) with no statistically significant difference from WDO SCC group (19.76.) and a statistically significantly higher value than MDOSCC and PDOSCC groups mean (14.13 and 2.38 respectively.). PDOSCC group showed the lowest mean CD146 expression (2.38) with a statistically significant difference from all other groups (Table 3 and Fig. 3.).

Table 3: Descriptive statistics showing mean and SD of the MAF and results of one- way ANOVA test for comparison between CD146 expression in OLP and different grades of OSCC. Different superscripts are statistically significantly different as demonstrated by Bonferroni's post-hoc test.

	OLP group	WDO SCC group	MDOSCC group	PDOSCC group	P value	Effect size (Partial Eta Squared)
CD146	25.13± 3.66 ^A	19.76± 4.56 ^{AB}	14.13± 5.36 ^B	2.38± 0.58 ^C	<0.001	0.806

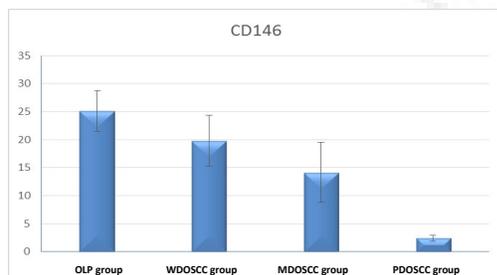


Figure 3: Bar chart representing mean and standard deviation for CD146 immunoeexpression in OLP and different grades of OSCC.

C. Correlation between Survivin and CD146 Expressions:

Pearson correlation coefficient showed an inverse highly significant correlation between Survivin and CD146 immunoeexpression in OLP and OSCC ($r = -0.839$) and (P value < 0.001) (Tables 4, 5.) (Fig.4.).

Table 4: Correlation coefficient value (r) and p-value between Survivin and CD146 expression in different groups.

	OLP group		WDO SCC group		MDOSCC group		PDOSCC group	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Survivin	6.26	3.64-8.88	19.27	15.62-22.92	25.26	19.15-31.38	30.51	21.34-39.68
CD146	25.13	20.59-29.67	19.76	14.09-25.43	14.13	7.47-20.79	2.38	0.94-3.81

Table 5: Correlation between parameters in all groups

	r	P value
CD146 with Survivin	-0.839	< 0.001

P value ≤ 0.05 is considered significant

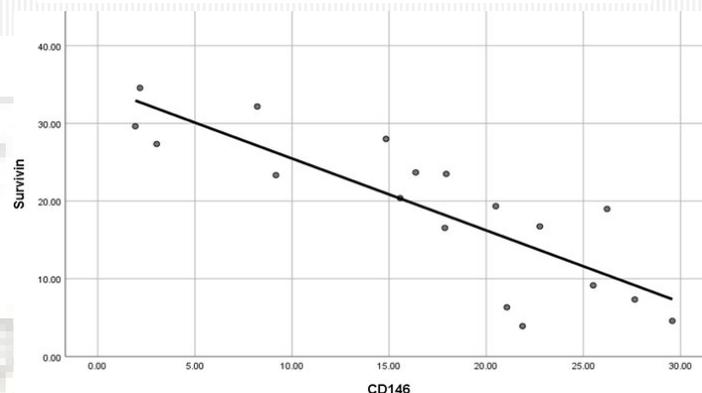


Figure 4: Scatter diagram representing inverse correlation between Survivin and CD146 expressions.

Discussion

OLP is classified as an OPMD of the oral mucosa to highlight its potential progression to oral cancer, showing around 1% overall rate of malignant transformation (Fitzpatrick et al., 2014.).

Malignant transformation of OLP into OSCC is one of the most serious complications that could happen in OLP patients. The transformation of normal epithelium to cancer is a complex multistep process that consists of intricate interactions among environmental and inflammatory mediators (Gonda et al., 2009.).

Among the head and neck cancers, Survivin is expressed in brain tumors, OSCC, B-cell lymphomas, salivary gland cancer and soft tissue sarcomas. Survivin is also found to be expressed in OPMDs (Suganya et al., 2016.).

The persistent apoptosis of basal keratinocytes is a key process in OLP pathogenesis, which also shapes its potential transformation to OSCC. The handling of such abnormal, and massive, apoptotic bodies likely poses a challenge for system-scavenging apoptotic bodies (Al-Samadi et al., 2015.). Therefore, recent research efforts have focused

on suppressing such refractory apoptotic processes in oral epithelial cells (Wu et al., 2014.).

CD146 is expressed in epithelial tumors as it could initiate or potentiate the transformation of epithelial cells into carcinomas. It is a multifunctional molecule that participates in many physiological and pathological processes (Ouhitit et al., 2009.). Based on the IHC results in this study, expression of Survivin was positive in all cases of OLP and OSCC of different grades, with a higher statistically significant difference in OSCC compared with OLP. In OLP, Survivin expressed mainly in the nuclei and cytoplasm of basal cell layers followed by spinous cell layers. Increased longevity of basal cells which acquire dysplastic changes and therefore, increases the risk of malignant transformation of this disease is the reason that explain this distribution (Suganya et al., 2016.).

In OSCC, both cytoplasmic and nuclear expressions of Survivin were found in malignant epithelial cells in WDOSCC and MDOSCC cases. However, cytoplasmic expression was found to be prevalent in PDOSCC cases. This pattern was in agreement with Li et al., 2019. The expression of Survivin evaluated immunohistochemically with respect to differentiation grades of OSCC indicate as the differentiation of cells in OSCC decreases there is increased expression of Survivin and suggest that Survivin could be a lead target for tumor diagnosis, prognosis, and anticancer therapies. Those results were in concurrence with Gayathri et al., 2017.

Survivin can travel between the nucleus and cytoplasm and it plays a cyto-protective role by facilitating Survivin interplay with the apoptotic machinery in cancer cells within the cytoplasm and also plays a role in cell division within the nucleus (Stauber et al., 2007.). The nuclear expression of Survivin is an unfavorable factor for prognosis in many tumors and OPMDs occurring in humans (Suganya et al., 2016). On contrary, Li et al., 2005 have suggested Survivin nuclear positivity as a favorable prognostic marker.

On the other hand, all the twenty-five cases of OLP showed positive CD146

immunostaining with a higher statistically significant difference in OLP compared with OSCC. This suggests that reduced CD146 expression at advanced stages may impair the cell - cell contact and facilitate the invasion of cancer cells into tissues. Therefore, we suggest that CD146 may play a major role in the transformation of OLP into OSCC. In OLP, CD146 expression was increased in the prickle cells which reveals that CD146 is tissue specific. These results were in concurrence with Weninger et al., 2000 and Pariyawathee et al., 2019.

CD146 expression is upregulated in oral epithelial cells of OLP as the adhesion between them is intact and stromal invasion is limited. With the progression of the lesions at the advanced stages, CD146 expression is decreased and this facilitates the development of invasive OSCC. This was in agreement with Pariyawathee et al., 2019.

All cases of WDOSCC and MDOSCC showed positive CD146 immunostaining while all five cases of PDOSCC showed negative CD146 immunostaining with a statistically significant difference between groups of OSCC. The lack of unique expression of genomic or proteomic component in neoplastic tissue and the somatic mutations in cancer-related genes in OSCC may underlie the different CD146 expressions in OSCC. Moreover, the heterogenic nature of OSCC tissues could be a prime cause of different expressions of CD146 protein (Santosh et al., 2016; Nakagaki et al., 2017.). Currently, to our knowledge, the CD146 expression with respect to differentiation grades of OSCC has never been mentioned in the previous studies. Pearson correlation showed a strong inverse highly significant correlation between Survivin and CD146 immunoexpression in OLP and OSCC which is in harmony with our histopathological results. This correlation could be attributed to the association between apoptotic and metastatic events of carcinogenesis. Genome expression analysis of tumors using complementary DNA microarrays revealed a significant relation between tumor progression and elevated antiapoptotic genes expression explaining that acquisition of

apoptotic resistance in cancer cells is the first requirement in tumor progression (Mehlen and Puisieux, 2006).

Conclusion

The cancer specific expression of Survivin together with its important role in inhibiting cell death and controlling cell division makes it an early biomarker that can speculate malignant transformation potentiality of OLP as well as a prognostic marker of OSCC. The loss of CD146 weakens cell-cell contact and promotes cancer invasiveness.

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