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Original Article

## Changes in the Immuno-Expression of Galectins -1, -3 and -7 in Relation to the Biological Behavior of Lip Squamous Cell Carcinoma

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### Abstract

**Objective:** To evaluate the expression through immunohistochemistry of galectins -1, -3 and -7 in cases of lip squamous cell carcinoma (SCC) in association with clinical data and morphological parameters proposed by Bryne (1998). **Material and Methods:** Thirty paraffin-embedded SCC cases were submitted to histological sections. Two independent pathologists performed the analysis of galectins -1, -3 and -7 through light microscopy evaluating the presence or absence of marking and intensity. The expressions of these proteins were submitted to statistical analysis (chi-square test, Fisher's exact test and Binomial test for the comparison of proportions). **Results:** Positive expression of galectins -1 and -3 was observed in 93.3% and 43.3% of cases, respectively. However, there was no statistically significant association between these proteins and the clinical variables used. Galectin-7 immuno-expression was present in all cases evaluated and showed statistical significance between marked cell type (parenchyma cells) and regional metastasis and between marked cell type (parenchyma cells) and histological gradation. **Conclusion:** Changes in the galectins -1, -3 and -7 expression suggest the participation of these proteins in the regulation of cellular functions and that the immuno-expression of these proteins can act as a marker of the biological behavior of lip squamous cell carcinoma.

**Keywords:** Galectins; Carcinoma, Squamous Cell; Immunohistochemistry.

## Introduction

Oral cancer is pathology with high morbidity and mortality worldwide, being a very common pathology in certain populations [1]. Clinical subtypes and the different locations of oral cancer present different etiologies, epidemiologies and survival rates [2].

Lip squamous cell carcinoma is a common pathology, accounting for about 30% of all tumors reaching the oral cavity [3]. It presents characteristics similar to skin lesions resulting from excessive and chronic exposure to ultraviolet (UV) solar radiation that promotes damage to cellular deoxyribonucleic acid (DNA) and can lead to oncogenic mutations [4]. Alcohol intake, smoking and presence of human papillomavirus (HPV) have been associated as adjuvants in the etiology of lip SCC [5].

Molecular biological markers can be valuable in the diagnosis and evolution of the prognosis of potentially malignant and malignant lesions [6]. Some mechanisms, such as biochemical and molecular changes in cells precede the establishment of neoplasms, and in this case, the deregulation of various proteins, such as galectins -1, -3 and -7. Galectins can strongly influence tumor progression through their effects on immunological surveillance, angiogenesis, cell migration and adhesion and cellular response to chemotherapy [7].

Galectin-1 has been considered a poor prognostic biomarker in a variety of cancers, including oral cancer [6,8,9]. Galectin-1 expression or overexpression in a tumor or surrounding tissue (stroma) can be considered as a sign of malignant progression with consequent unfavorable prognosis [10].

Galectin-3 is primarily found in the cytoplasm of cells. However, a significant amount of this protein may be present in the nucleus, suggesting an alternation between these two sites [11]. The location of this protein seems to be directly related to its functions, since the cytoplasmic localization influences its anti-apoptotic function, whereas nuclear localization plays an inverse role [12].

The expression of galectin-7 is an inherent feature of stratified epithelium of various natures. Positive expression of galectin-7 was observed in the epidermis, cornea, larynx, and skin and larynx squamous cell carcinomas [13].

In the oral cavity, some studies on the expression of these proteins in SCC have been performed [6,8,14-16]; however, to the best of our knowledge, there are no studies on the expression of these proteins in lip SCC. In view of the above, the aim of this study was to evaluate the expression of galectins -1, -3 and -7 by means of the immunohistochemical technique in lip SCC and to observe the role of these biomarkers in the biological behavior of this lesion.

## Material and Methods

Thirty cases of lip SCC were retrieved from the files of the Department of Pathology Anatomy - Cancer Reference Hospital, João Pessoa, Brazil, from 2008 to 2012.

Lip SCC specimens fixed in 10% formalin and embedded in paraffin were submitted to 3 µm thick histological sections for each galectin, which were placed on silanized glass slides.

Subsequently, anti-galectin-1, anti-galectin-3 and anti-galectin-7 primary antibodies (Santa Cruz Biotechnology, CA, USA) were used by the streptavidin-biotin peroxidase method according to the following laboratory steps: Deparaffinisation, hydration and recovery of antigenic sites, blocking of endogenous peroxidase with 10 vol. hydrogen peroxide for 10' at room temperature, antigen retrieval, incubation with primary antibodies for 30' at room temperature and TRIS / Tween washing, pH 7.4, revealing reactions with DAB chromogen - (Diaminobenzidine) and contra-stained with Mayer's Hematoxylin for 5' at room temperature. Washing, dehydration, diaphanization and assembly were also performed. Samples of palatine tonsils were used as positive control, one for each reaction. For negative control, primary antibodies were replaced by their diluent solutions.

Histological grading of malignancy was used [17], where more invasive regions are evaluated. The keratinization degree, nuclear pleomorphism, invasion pattern and lymphoplasmocytic infiltrate are considered as parameters. For each analyzed parameter, scores from 1 to 4 are assigned, which are summed and thus a total malignancy score is found. High final scores indicate worse prognosis and are characterized by absence of certinization (0-5% of cells), extreme nuclear pleomorphism (0-25% mature cells), marked cell invasion, disseminated and in small groups ( $n < 15$ ) and absence of lymphoplasmacytic infiltrate.

Two independent pathologists performed the analysis of galectins -1, -3 and -7 through light microscopy and evaluated the presence or absence of marking and intensity, being assigned score 0 for absence of marking, score 1 for poor marking, score 2 for moderate marking and score 3 for strong marking. The marked cell type (stromal or parenchyma) was also evaluated [18]. The marking distribution pattern was classified as focal ( $\leq 30\%$  of epithelium) and diffuse ( $> 30\%$  of epithelium) [19].

In this work, the Chi-square test ( $Q^2$ ) was used to measure associations between regional metastasis (N), histological grading of malignancy and the immuno-expressions of galectins-1, -3 and -7 in cases of lip squamous cell carcinoma. For cases where the binomial test is inappropriate (frequencies below 5 or null), the Fisher exact test was applied. In addition, to evaluate situations where there were only two categories, a test for the comparison of two proportions was used. The significance level adopted for cases studied was 95% ( $p < 0.05$ ). The Predictive Analytics Software - PASW, version 18.0 statistical software used was.

The present study was approved by the Ethics Research Committee of the Center for Health Sciences of the Federal University of Paraíba under Protocol No. 0481/12.

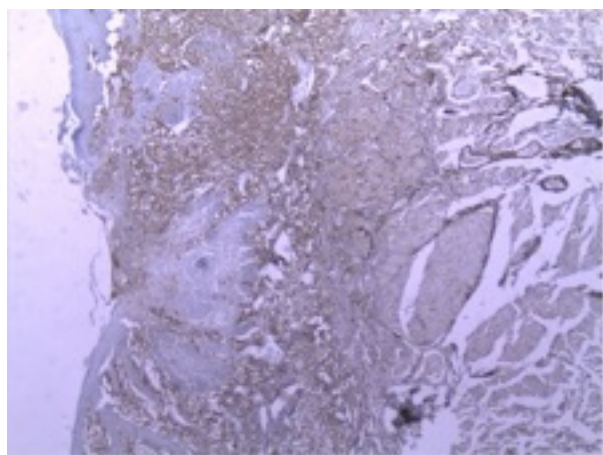
## Results

From the total number of lip SCC cases evaluated, 24 (80%) were classified as having a high grade of malignancy.

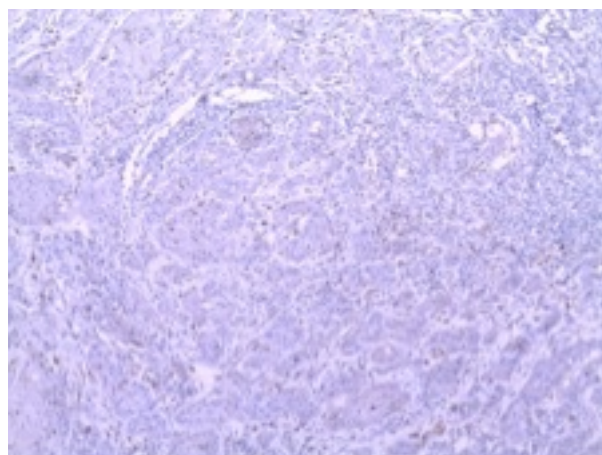
### *Galectin-1*

Of the 30 cases evaluated, 28 (93.3%) presented positive marking for galectin-1. There was no statistically significant association between galectin-1 and the clinical variables studied. Among

the 28 cases that showed positive marking, 26 (92.8%) had no regional metastasis (Table 1) and 23 (82.1%) were classified as having a high grade of malignancy (Table 2). The intensity of moderate to strong marking and cytoplasmic localization were also more prevalent in cases classified as high grade, with 86.4% and 81.5% respectively (Figure 1) (Table 2).



**Figure 1. Galectin-1 immunoreactivity in lip scc of high-grade of malignancy showing moderate stroma marking.**



**Figure 2. Lack of immunomarking of galectin-3 in lip scc of high-grade of malignancy (dab 40x).**

#### *Galectin -3*

Immunostaining for galectin-3 was considered negative in 17 (56.7%) cases (Figure 2). When there was positive immunoreactivity, the predominant distribution pattern was diffuse (76.9%) with moderate to strong intensity (53.8%). However, there was no correlation between galectin -3 expression and the clinical variables under study (Regional Metastasis (N), histological grading of malignancy).

#### *Galectin-7*

Positive expression for galectin-7 was verified in all 30 (100%) cases analyzed. There was a statistically significant association between positive expression of galectin-7 in parenchymal cells in cases with no regional metastasis (No) ( $p = 0.0000$ ) (Table 1), as well as in cases classified as high grade of malignancy ( $p = 0.0014$ ) (Table 2). Although there was no statistically significant association, the marking intensity was considered moderate to strong in 28 (93.3%) of the 30 cases analyzed, with 23.3% presenting nuclear, cytoplasmic and membrane marking (Figures 3 and 4).

**Table 1. Association between immunoreactivity of galectins -1, -3 and -7 and presence of regional metastasis (N).**

Characteristics	Galectin -1				Galectin -3				Galectin -7			
	No	N≥1	Total	p-value	No	N≥1	Total	p-value	No	N≥1	Total	p-value
Marking												
Positive	26	2	28	1.000 <sup>(2)</sup>	12	1	13	1.000 <sup>(2)</sup>	28	2	30	0.0000 <sup>(3)*</sup>
Negative	2	0	2		16	1	17		-	-	-	
Distribution												



Focal	11	0	11	0.505 <sup>(2)</sup>	3	0	3	1.000 <sup>(2)</sup>	16	0	16	0.209 <sup>(2)</sup>
Diffuse	15	2	17		9	1	10		12	2	14	
Intensity												
Weak	6	0	6	1.000 <sup>(2)</sup>	6	0	6	1.000 <sup>(2)</sup>	2	0	2	1.000 <sup>(2)</sup>
Moderate/Strong	20	2	22		6	1	7		26	2	28	
Cell type												
Parenchyma	2	0	2	0.576 <sup>(2)</sup>	3	0	3	1.000 <sup>(2)</sup>	28	2	30	0.000 <sup>(3)</sup>
Stroma	10	0	10		2	0	2		-	-	-	*
Both	14	2	16		7	1	8		-	-	-	
Location												
Cytoplasm	25	2	27	1.000 <sup>(2)</sup>	11	1	12	1.000 <sup>(2)</sup>	9	0	9	0.450 <sup>(2)</sup>
Nucleus/Cyto	1	0	1		1	0	1		9	2	11	
Cyto/Memb	-	-	-		-	-	-		7	0	7	
Nucleus /Cyto/ Mem	-	-	-		-	-	-		3	0	3	

<sup>(1)</sup>Chi-square association test; <sup>(2)</sup>Fisher exact test; <sup>(3)</sup>Binomial test for the comparison of proportions; \*Significant result at level of 5%.

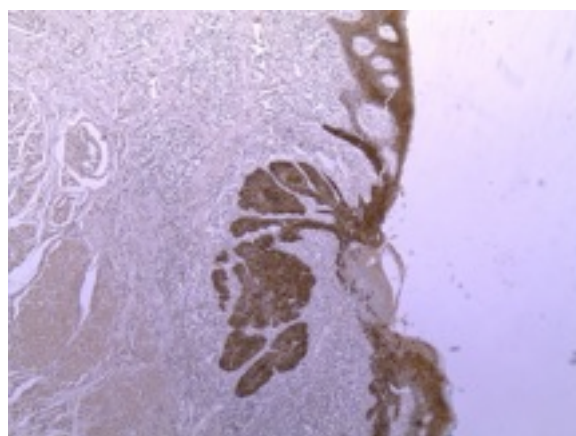
**Table 2. Association between the immunoexpression of galectins -1, -3 and -7 and histological grading of malignancy.**

Characteristics	Galectin -1				Galectin -3				Galectin -7			
	Low grade	High grade	Total	p-value	Low grade	High grade	Total	p-value	Low grade	High grade	Total	p-value
Marking												
Positive	5	23	28	0.365 <sup>(2)</sup>	3	10	13	1.000 <sup>(2)</sup>	6	24	30	0.001 <sup>(3)*</sup>
Negative	1	1	2		3	14	17		-	-	-	
Distribution												
Focal	2	9	11	1.000 <sup>(2)</sup>	2	1	3	0.108 <sup>(2)</sup>	2	14	16	0.377 <sup>(2)</sup>
Diffuse	3	14	17		1	9	10		4	10	14	
Intensity												
Weak	2	4	6	0.285 <sup>(2)</sup>	2	4	6	0.559 <sup>(2)</sup>	0	2	2	1.000 <sup>(2)</sup>
Moderate/Strong	3	19	22		1	6	8		6	22	28	
Cell Type												
Parenchyma	0	2	2	0.558 <sup>(2)</sup>	2	1	3	0.146 <sup>(2)</sup>	6	24	30	0.001 <sup>(3)*</sup>
Stroma	3	7	10		0	2	2		-	-	-	
Both	2	14	16		1	7	8		-	-	-	
Location												
Cytoplasm	5	22	27	1.000 <sup>(2)</sup>	3	9	12	1.000 <sup>(2)</sup>	2	8	10	0.783 <sup>(2)</sup>
Nucleus/Cyto	0	1	1		0	1	1		2	9	11	
Cyto/Memb	-	-	-		-	-	-		2	4	6	
Nucleus /Cyto/ Mem	-	-	-		-	-	-		0	3	3	

<sup>(1)</sup>Chi-square association test; <sup>(2)</sup>Fisher exact test; <sup>(3)</sup>Binomial test for the comparison of proportions; \*Significant result at level of 5%.



**Figure 3. Galectin-7 immunoexpression in lip scc of low-grade of malignancy showing strong parenchyma marking (dab 40x).**



**Figure 4. Galectin-7 immunoexpression in lip scc of high-grade of malignancy showing strong cytoplasmic and membrane marking (dab 100x).**

## Discussion

Tumor cells are also responsible for the secretion of some proteins [20], responsible for the degradation of the extracellular matrix and consequent spread of malignant cells and several regulatory molecules that influence cell adhesion and mobility. Thus, a protein secreted by the tumor, or its "protein signature", can be used for early diagnosis and better prognosis of the disease [21].

In relation to galectin-1, although many authors report absence of galectin-1 expression in the parenchyma [6,9,22], the findings of the present study corroborate the results of other authors in which there was positive expression of galectin-1 in both parenchyma and stroma, especially in cases classified as high grade [6,23]. Expression of this protein in stromal cells may be a result of secretion of neoplastic cells [8].

There was no statistically significant association between expression of galectin-1 and presence of regional metastases. However, cytoplasmic positive marking was observed in 25 cases with no metastasis and in 22 cases classified as high grade. In a study that analyzed the expression of Galectin-1 in cases of oral squamous cell carcinoma and its correlation with the degree of tumor differentiation, it was observed that there was a strong cytoplasmic marking in tumor cells. In addition, high expression of Galectin-1 was associated with poorly differentiated tumors [16]. Thus, galectin-1 can be used as a biomarker of worse prognosis in cases of oral squamous cell carcinoma.

Galectin-3 is expressed in a variety of tissues and cell types, being widely found in the cytoplasm. However, it may also be present in the nucleus, depending on the cell type or cell's proliferative stage [24].

No statistically significant association was observed between expression of galectin-3 and the clinical variables under study. Furthermore, in the present study, galectin-3 negative immunoexpression was observed in more than half of cases analyzed, differing from several studies in literature performed in other locations [8,15]. In samples of normal cervical tissue, low-grade intraepithelial lesions, high-grade intraepithelial lesions and cervical squamous cell carcinoma, it was observed through immunohistochemistry that galectin-3 expression was strong in all normal tissue samples, with progressive decrease according to the neoplasia progression [25].

Among the 13 cases that showed positive expression for galectin -3, 12 presented cytoplasmic marking. In samples of tongue SCC, the nuclear expression of galectin-3 decreases during transformation from normal to neoplastic epithelium, with the inverse occurring in cytoplasmic expression [15]. Such results suggest that the shift of galectin-3 cell compartment from nucleus to the cytoplasm during tumor progression may serve as a prognostic factor also in cases of lip SCC.

Galectin-7 contributes to different events associated with the differentiation and development of stratified epithelium [26]. Among galectins studied, galectin -7 was the only present in all cases of lip SCC. In addition, the immunoexpression of this protein occurred in the

parenchymal cells of 29 (96.7%) cases, with moderate to strong intensity (93.3%). These results may be justified by the fact that galectin-7 is deeply involved in the physiology of the epithelial tissue.

In this study, there was a statistically positive association between galectin-7 expression in parenchymal cells with regional metastasis ( $p = 0.000$ ) and histological grading ( $p = 0.001$ ), especially in cases classified as high grade, corroborating another study [8]. Of the 30 positive cases for this protein, 24 presented immunoexpression in parenchyma cells, being in some cases expressed in both neoplastic nests and adjacent epithelium. Although nuclear and cytoplasmic location is present in most cases, it was possible to observe the membrane immunoexpression of this protein, which did not occur with the other galectins.

The displacement of galectin-7 from the membrane to the intracellular medium suggests its involvement with progression from normal epithelium to low- and high-grade dysplasias [14]. In cases of hypopharynx and larynx squamous cell carcinoma, galectin-7 expression has been shown to increase during tumor progression. In addition, tumor progression in cases of hypopharynx squamous cell carcinoma, it was associated with a change in the location of galectin-7 from the nucleus to the cytoplasm [27]. These data demonstrate that the change in the location of this protein may be related to tumor progression, as the galectin-7 concentration in the nucleus can prevent the interference of this protein in tumor progression or regression [28].

As shown above, there is increased expression of galectin-7 in keratinocytes after exposure to ultraviolet B radiation [29]. This fact may explain the frequent expression of this protein in cases of lip SCC, thus serving as a marker of this type of lesion. In contrast, the expression of galectin-7 may decrease with tumor progression, for example in gastric cancer, where a decrease in galectin-7 expression has been observed in patients with advanced clinical staging [30]. The low expression of galectin-7 is related to the low survival rate of patients with oral squamous cell carcinoma, mainly in relation to tumor resistance to chemotherapy and preoperative radiotherapy [28]. Thus, galectin-7 may represent a promising target for research related to cancer diagnosis and prognosis.

## Conclusion

The expression of galectin-7 is very evident in cases of lip SCC, and there is a statistically positive association between the immunoexpression of this protein, regional metastasis and histological grading of malignancy. Although there was no statistically significant association between galectins -1 and -3 and the study variables, there was a positive immunoexpression of these proteins in several cases analyzed. Thus, it is suggest that galectins -1, -3 and -7 may serve as markers of biological behavior in cases of lip squamous cell carcinoma.

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