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Comparison of the Expression of Cytokeratin 6 and 16 in Oral Lichen Planus, Oral Lichenoid Lesions with Dysplasia and Oral Squamous Cell Carcinoma

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ABSTRACT

Introduction: Oral lichen planus (OLP) and oral lichenoid lesions (OLL/OLR) are chronic inflammatory disorders of the oral mucosa with potential malignant transformation. Cytokeratins 6 and 16 (CK6, CK16) are markers of epithelial proliferation and have previously been reported to be elevated in inflammation, wound healing, and epithelial tumors. This study aimed to compare CK6 and CK16 mRNA expression across reticular OLP (ROLP), erosive OLP (EOLP), oral lichenoid lesions with dysplasia (OLR + D), oral squamous cell carcinoma (OSCC), and healthy controls.

Materials and Methods: A cross-sectional study was performed on 90 archived oral tissue specimens. mRNA expression was quantified using qRT-PCR, and data were analyzed using ΔCt, ΔΔCt, and fold-change values. Statistical comparisons were made using one-sample t-tests and one-way ANOVA.

Results: CK6 and CK16 expression were significantly altered in all lesion groups compared with controls ($p < 0.001$). Fold-change analysis showed a slight decrease in CK6 expression in ROLP (0.63-fold), followed by progressive increases in EOLP (1.59-fold), OLR + D (1.85-fold), and OSCC (2.33-fold). CK16 expression increased from ROLP (1.36-fold), EOLP (1.47-fold), and OLR + D (2.00-fold) to OSCC (2.72-fold). However, no statistically significant differences were observed among the lesion groups for either gene (CK6: $p = 0.840$; CK16: $p = 0.946$).

Conclusion: CK6 and CK16 expression increases along the spectrum of oral epithelial lesions but does not reliably distinguish inflammatory, dysplastic, and malignant lesions. These cytokeratins primarily reflect generalized inflammatory and reparative processes, and their interpretation should be integrated with histopathology, clinical findings, and additional molecular markers.

Keywords: Lichen planus; Oral lichenoid lesions; Oral squamous cell carcinoma; Epithelial dysplasia; Cytokeratin.

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Introduction

Oral potentially malignant disorders (OPMDs) represent a heterogeneous group of oral mucosal conditions associated with an increased risk of progression to oral squamous cell carcinoma (OSCC) [1]. Within this group, oral lichen planus (OLP) and oral lichenoid lesions (OLLs) are of particular clinical relevance due to their prevalence and the persistent controversy surrounding their malignant potential [2-5]. OLP is a chronic immune-mediated inflammatory disorder of the oral mucosa [6,7]. OLLs, in contrast, comprise lesions that clinically and histopathologically closely resemble OLP but are linked to identifiable etiologic factors, such as dental materials, medications, or systemic conditions [2,3]. The considerable overlap between OLP and OLLs has long complicated clinicopathologic diagnosis, especially when epithelial dysplasia is present [3,8-10]. Evidence from systematic reviews and meta-analyses indicates that malignant transformation occurs more frequently in OLLs with epithelial dysplasia and in specific clinical subtypes of OLP, particularly erosive and atrophic forms [4,5,11,12].

These clinical variants often present as ulcerative or erythematous lesions, resembling chronic wound-like conditions of the oral mucosa [3,6]. Histopathological studies suggest that epithelial atrophy in these lesions is frequently accompanied by increased keratinocyte proliferative activity, reflecting a biologically stressed epithelial environment [13]. These findings emphasize the importance of identifying molecular markers that detect early epithelial alterations associated with malignant progression [14-16]. OSCC constitutes the majority of malignant tumors arising in the oral cavity and remains a significant global health concern [17-20]. In Iran, oral cancer imposes a substantial socioeconomic burden, with recent epidemiological data demonstrating a rising incidence and considerable treatment-related costs, particularly in advanced stages of disease [21-23]. Given the relatively high prevalence of OLP and OLL reported in clinical populations, improved understanding of their malignant transformation pathways is of both biological and public health importance [3,4,6,8,23]. Cytokeratins are intermediate filament proteins that play a fundamental role in maintaining epithelial structural integrity and regulating cellular proliferation and differentiation [13,14,24]. Cytokeratins 6 and 16 (CK6 and CK16) are characteristically expressed in hyperproliferative epithelia and are upregulated in conditions associated with inflammation, wound healing, and squamous epithelial malignancies [19,22]. Their expression reflects an activated keratinocyte phenotype and has been associated with epithelial stress responses and dysregulated proliferation [12,25, 26]. Although CK6 and CK16 expression have been documented in hyperproliferative and malignant epithelial conditions [12,21,26], data directly comparing their expression across OLP, dysplastic OLLs, and OSCC are limited. To date, no studies have systematically compared the expression patterns of CK6 and CK16 across OLP, dysplastic OLLs and OSCC. Therefore, the present study aimed to compare the expression of cytokeratin 6 and cytokeratin 16 in oral lichen planus, oral lichenoid lesions with dysplasia, and oral squamous cell carcinoma to clarify their potential role in epithelial proliferation and malignant transformation.

Materials and Methods

Study Design and Ethical Approval

This cross-sectional archival study investigated the relative expression of CK6 and CK16 in reticular OLP, erosive OLP, oral lichenoid lesions with epithelial dysplasia, and oral squamous cell carcinoma (OSCC). Ethical approval was obtained from the Ethics Committee of Tehran University of Medical Sciences (Approval Code: IR.TUMS.AMIRALAM.REC.1402.051). All procedures complied with institutional guidelines for the use of archived specimens.

Study Population

A total of 90 archived oral biopsy specimens collected between 2013 and 2023 were retrieved from the Department of Oral and Maxillofacial Pathology, School of Dentistry, Tehran University of Medical Sciences. The specimens were categorized into five groups, each consisting of 18 samples. Among these, 18 histologically normal oral mucosa samples were included as the control group.

Inclusion criteria:

1. FFPE tissue samples histopathologically diagnosed as reticular or erosive oral lichen planus (OLP) according to the World Health Organization (WHO) 2022 criteria.

2. FFPE tissue samples diagnosed as oral lichenoid lesions with epithelial dysplasia, presenting either unilaterally or bilaterally, based on the WHO 2022 classification.

3. Histopathologically confirmed FFPE specimens of oral squamous cell carcinoma (OSCC).

Exclusion criteria:

1. Incomplete clinical or histopathological records.

2. Tissue blocks with insufficient material for RNA extraction.

3. History of prior radiotherapy or chemotherapy.

4. Concurrent malignancy in the patient.

5. Presence of autoimmune diseases or history of medications known to induce oral lichenoid reactions.

RNA Extraction and cDNA Synthesis

Total RNA was extracted using the RNeasy Mini Kit (Qiagen, Germany) following the manufacturer's protocol. RNA purity and concentration were assessed using a NanoDrop™ spectrophotometer (Thermo Fisher Scientific), and only samples with an A260/A280 ratio between 1.8 and 2.1 were used for downstream analysis. cDNA was synthesized from 1 µg RNA using the RevertAid First Strand cDNA Synthesis Kit (Thermo Scientific, USA) with oligo (dT) primers, according to the manufacturer's instructions. Synthesized cDNA was stored at –20 °C until qRT-PCR analysis.

Quantitative Real-Time PCR

qRT-PCR was performed in a StepOnePlus™ Real-Time PCR System (Applied Biosystems, USA). Each 20 µL reaction contained SYBR Green Master Mix and gene-specific primers for CK6, CK16, and the reference gene GAPDH, which had been previously validated by the pathology laboratory.

Thermal cycling conditions were as follows:

- Initial activation: 95 °C for 10 minutes.
- 40 cycles of:
- Denaturation: 94 °C for 20 seconds.
- Annealing: 60 °C for 30 seconds.
- Extension: 72 °C for 30 seconds.
- Melt curve analysis: 60–95 °C.

Statistical Analysis

Relative gene expression was calculated using the $2^{-}\Delta\Delta Ct$ method, normalized to GAPDH. Statistical analyses were performed using SPSS v25 (IBM Corp.). The Kolmogorov-Smirnov test was used to assess the normality of ΔCt values,which confirmed a normal distribution in all gropus ($p > 0.05$). Differences in ΔCt values among the five study group were evaluated using one-way ANOVA. One sample t-test were applied to compare each lesion group with the control group. Fold change was calculated to evaluate the relative increase in CK6 and CK16 expression compared to the control group

Results

Overall, quantitative RT-PCR analysis demonstrated increased expression of CK6 and CK16 in all oral lesion groups compared with normal oral mucosa. Although a progressive increase in expression was observed from inflammatory and dysplastic lesions toward OSCC, no statistically significant differences were detected among disease groups.

Sample Characteristics

A total of 90 archived oral biopsy specimens were included and categorized into five groups: reticular oral lichen planus (ROLP), erosive oral lichen planus (EOLP), oral lichenoid lesions with epithelial dysplasia (OLR + D), oral squamous cell carcinoma (OSCC), and normal oral mucosa (control). All samples met the predefined inclusion criteria and were confirmed by an oral and maxillofacial pathologist prior to analysis. Demographic and clinical characteristics of the study population are summarized in [Tables 1–4]. In the OSCC group, tumors were predominantly well or moderately differentiated, with 45% well-differentiated, 40% moderately differentiated, and 15% poorly differentiated squamous cell carcinomas.

Melting Curve Analysis

Melting curve analysis was performed following quantitative RT-PCR amplification to assess the specificity of the CK6 and CK16 amplicons. Both genes demonstrated single, sharp melting peaks with no evidence of non-specific amplification or primer–dimer formation, confirming the specificity of the PCR reactions. [Figures 1 and 2].

ΔCt Analysis of CK6 and CK16 Expression

Mean ΔCt values for CK6 and CK16 are summarized in Table 5, with the control group used as the reference. The Kolmogorov-Smirnov test confirmed normal distribution of ΔCt values for CK6 and CK16 in all groups ($p > 0.05$). Relative expression analysis using the $2^{\wedge}-\Delta\Delta Ct$ method demonstrated altered CK6 and CK16 expression in all lesion groups compared with normal oral mucosa., with the highest expression observed in OSCC. [Tables 6 and 7]. One-sample t-tests demonstrated that the mean ΔCt values of each lesion

group differed significantly from the control group for both CK6 and CK16 ($p < 0.001$). In contrast, one-way ANOVA revealed no statistically significant differences in ΔCt values among the four lesion groups (ROLP, EOLP, OLR + D, and OSCC) for either gene ($p > 0.05$).

Fold Change Analysis

Relative expression analysis using the 2^−ΔΔCt method showed a gradual increase in CK6 and CK16 expression across disease groups, from ROLP and EOLP to OLR + D and OSCC,with CK6 slightly reduced in ROLP. Boxplot visualization illustrated this trend and showed homogeneous distributions without extreme outliers across the groups [Figures 3 and 4]. However, these apparent trends did not reach statistical significance in the ANOVA comparisons among lesion groups.

Table 1. Demographic characteristics of the reticular lichen planus group.

	Category	Number	Percentage
Gender	Male	10	55/6%
	Female	8	44/4%
Lesion Site	Buccal Mucosa	12	66/7%
	Tongue	13	16/7%
	Buccal Vestibule	1	5/6%
	Maxillary Labial Vestibule	1	5/6%
	Maxillary Labial Frenum	1	5/6%
Age Decade	Age 0-19	1	5/6%
	Age 20-39	6	33/3%
	Age 40-59	9	50/0%
	Age 60-79	2	11/1%

In the reticular lichen planus group, 55.6% of the participants were male and 44.4% were female, with a mean age of 43.5 years. The most common lesion sites, in descending order, were the buccal mucosa and tongue. Following these, the upper buccal vestibule, upper labial vestibule, and upper labial frenum were observed with equal prevalence.

Table 2. Demographic characteristics of the erosive lichen planus group.

	Category	Number	Percentage
Gender	Male	6	33/3%
	Female	12	66/7%
Lesion Site	Buccal Mucosa	13	72/2%
	Tongue	4	22/2%
	Maxillary Labial Mucosa	1	5/6%
Age Decade	Age 20-39	3	16/7%
	Age 40-59	7	38/9%
	Age 60-79	6	33/3%
	Age 80-99	2	11/1%

In the erosive lichen planus group, 33.3% of the participants were male and 66.7% were female, with a mean age of 57.6 years. The most common lesion sites, in descending order, were the buccal mucosa, tongue, and upper labial mucosa.

Table 3. Demographic characteristics of the oral lichenoid lesions with dysplasia group.

	Category	Number	Percentage
Gender	Male	5	33/3%
	Female	12	66/7%
Lesion Site	Tongue	10	55/6%
	Buccal Mucosa	6	33/3%
	Maxillary Labial Mucosa	2	11/1%
Grade of Dysplasia	Moderate	9	50/0%
	Mild	7	38/9%
	Severe	2	11/1%
Age Decade	Age 40-59	8	44/4%
	Age 60-79	10	55/6%

In the oral lichenoid lesions with dysplasia group, 33.3% of the participants were male and 66.7% were female, with a mean age of 60.1 years. The most common lesion sites, in descending order, were the tongue, buccal mucosa, and upper labial mucosa. Severe dysplasia was observed in 11.1% of participants, moderate dysplasia in 50.0%, and mild dysplasia in 38.9%.

Table 4. Demographic characteristics of the oral squamous cell carcinoma.

	Category	Number	Percentage
Gender	Male		72/2%
	Female		27/8%
Lesion Site	Tongue		50/0%
	Buccal Mucosa		11/1%
	Mandibular Ridge		11/1%
	Labial Mucosa		5/6%
	Palatal Mucosa		5/6%
	Maxillary Ridge		5/6%
	Floor of the Mouth		5/6%
	Maxillary Gingiva		5/6%
Age Decade	Age 0-19		5/6%
	Age 20-39		22/2%
	Age 40-59		16/7%
	Age 60-79		27/8%
	Age 80-99		27/8%

In the oral squamous cell carcinoma group, 72.2% of the participants were male and 27.8% were female, with a mean age of 56 years. The tongue was the most common lesion site. The buccal mucosa and mandibular ridge shared the second rank with equal prevalence, followed by the labial mucosa, palatal mucosa, maxillary ridge, floor of the mouth, and upper gingiva, which shared the third rank with equal prevalence.

Table 5. Mean ΔCt for each group.

	Mean ΔCt CK6	*Mean ΔCt CK16*
Control	*6/056*	*6/056*
ROLP	*6/722*	*5/611*
EOLP	*5/389*	*5/5*
OLR + D	*5/167*	*5/056*
OSCC	*4/833*	*4/611*

Mean ΔCt for each group. ΔCt values were calculated by subtracting the Ct of the reference gene (β-actin) from the Ct of the target gene. The mean ΔCt of the Control group was considered as the baseline for comparison with the patient groups.

Table 6. MΔΔCt CK6 values are calculated relative to the Control group; negative values indicate increased expression of the gene in the respective patient groups.

	ΔΔCt CK6
ROLP	*0/666*
EOLP	*-0/667*
OLR + D	*-0/889*
OSCC	*-1/223*

Table 7. MΔΔCt CK16 values are calculated relative to the Control group; negative values indicate increased expression of the gene in the respective patient groups.

	ΔΔCt CK16
ROLP	*-0/445*
EOLP	*-0/556*
OLR + D	*-1*
OSCC	*-1/445*

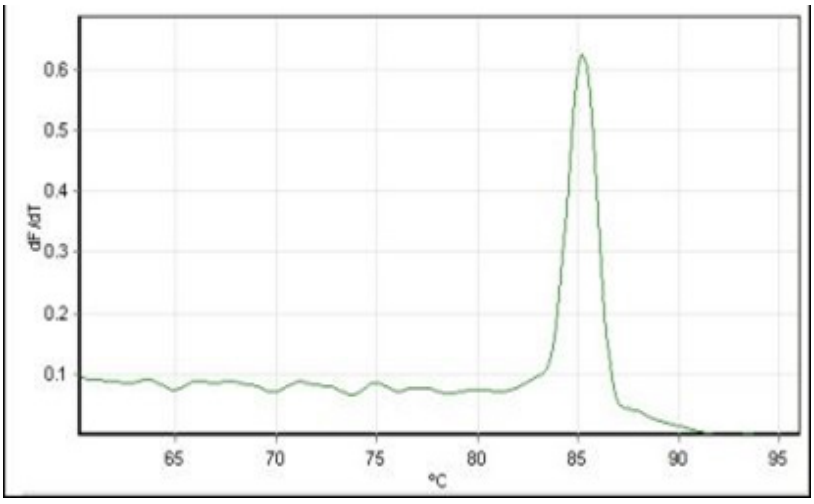


Figure 1. Melting curve related to CK6. A single sharp peak in the melting curve confirms the specificity of CK6 amplification.

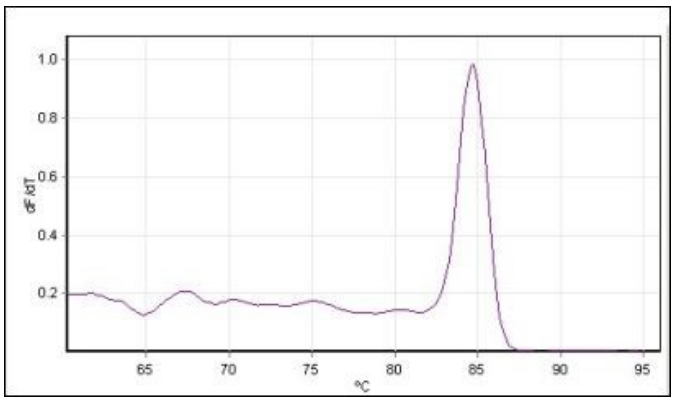
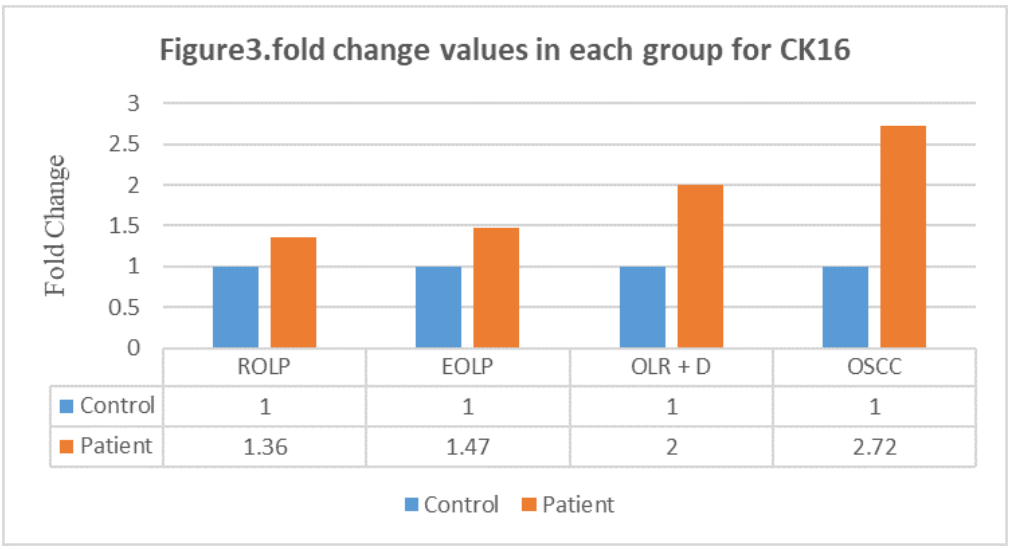
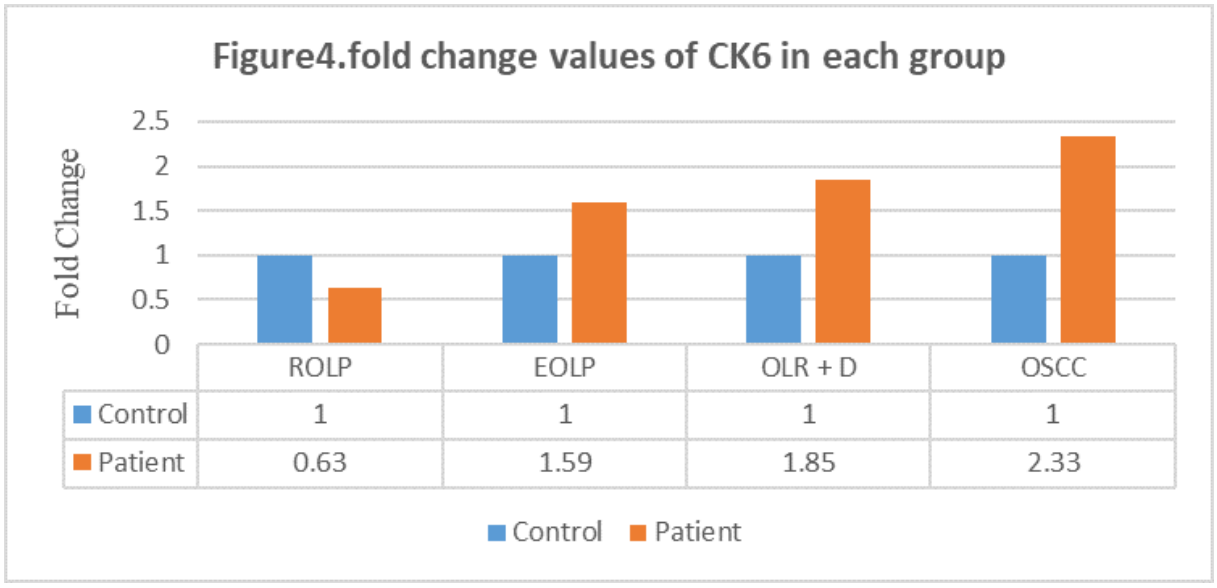


Figure 2. Melting curve related to CK6. A single sharp peak in the melting curve confirms the specificity of CK6 amplification.





Figures 3 and 4. Expression levels of CK6 (Figure 4) and CK16 (Figure 3) In patient groups relative to the Control group; values indicate fold change In expression.

Discussion

The present findings demonstrated an overall increasing trend in CK6 and CK16 expression from benign oral epithelial lesions to oral squamous cell carcinoma (OSCC). However, no statistically significant differences were observed among the four disease groups for either gene, while all lesion groups exhibited significantly higher expression than healthy controls [13,26,27,28]. These findings partially support the initial hypothesis that CK6 and CK16 expression increases during disease progression but indicate that mRNA-level expression alone may not be sufficient to distinguish between different pathological stages of oral epithelial lesions. Previous studies have consistently reported elevated expression of CK6 and CK16 in hyperproliferative, chronically inflamed, and malignant tissues. Sesterhenn AM et al. [26] demonstrated marked upregulation of these cytokeratins in head and neck squamous cell carcinoma (HNSCC) and suggested their potential use in studying circulating tumor cells and micrometastases. Zhang X et al. [13] showed strong expression of CK6, CK16, and CK17 in keratinocytes during wound healing and psoriasis, reflecting an active proliferative state and playing roles in apoptosis inhibition and regulation of immune homeostasis. The lack of statistically significant differences among disease groups in our study contrasts with these reports. It suggests that both methodological and biological factors may influence the transcriptional activity of CK6 and CK16. One explanation for this discrepancy is methodological. Most prior studies assessed protein expression by immunohistochemistry (IHC), whereas our research quantified mRNA by qRT-PCR. RNA integrity in formalin-fixed paraffin-embedded tissues can be affected by necrosis, hypoxia, fixation conditions, and storage time, particularly in OSCC samples [26,27].

Although our samples did not include necrotic or hypoxic regions, these technical factors may partially account for the absence of significant differences at the mRNA level. Moreover, Sesterhenn AM et al. [26] noted that cytokeratin RNA levels do not always correlate with protein expression, suggesting that transcriptional data may underestimate functional protein abundance. In the present study, statistical comparisons were performed on ΔCt values, in accordance with current recommendations for qRT-PCR data analysis, after verification of normality using the Kolmogorov–Smirnov test. This allowed the use of parametric tests (one-way ANOVA and one-sample t-tests), which provide greater statistical power than non-parametric methods for detecting differences between lesion groups and controls. Another critical factor is the intrinsic biological heterogeneity of OSCC. This carcinoma includes multiple subtypes with variable keratinization and differentiation. Well-differentiated, keratinized tumors often express higher levels of hyperproliferative cytokeratins than poorly differentiated or non-keratinized SCCs [26,29]. Pooling heterogeneous SCC samples may reduce average CK6 and CK16 expression, thereby obscuring measurable differences. In the present cohort, variation in histologic grade among OSCC cases may have contributed to the lack of significant differences in CK6/CK16 mRNA levels, as well-differentiated, keratinized tumors generally exhibit higher expression of hyperproliferative cytokeratins than poorly differentiated carcinomas. Additionally, EOLP and OLR + D lesions, due to chronic inflammation and epithelial repair processes, may display cytokeratin expression patterns resembling those of OSCC [2,9,13,30,31,32,33].

Despite these limitations, our findings underscore the complex regulation of CK6 and CK16, as well as the significant influence of inflammation on their expression. They highlight that these cytokeratins cannot serve as standalone transcriptional biomarkers for differentiating between inflammatory, dysplastic, and malignant oral lesions. Future research should assess CK6 and CK16 at the protein level using IHC and analyze OSCC and oral lichenoid lesion subgroups according to keratinization, inflammation, and dysplasia severity. Such stratification could clarify the relationship between CK6/CK16 expression and lesion pathology more precisely.

Conclusion

CK6 and CK16 expression does not differ significantly across oral epithelial lesions from ROLP to SCC, indicating that they play a primary role in general reparative and inflammatory responses rather than in carcinogenesis. These cytokeratins alone cannot reliably distinguish inflammatory, dysplastic, and neoplastic lesions, highlighting the need for integrated approaches that combine molecular markers with histopathology and clinical evaluation. This study provides a foundation for future research to identify additional biomarkers or multi-parameter strategies to improve diagnosis and risk assessment in oral potentially malignant disorders.

Conflict of Interest

There is no conflict of interest to declare.

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