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Original Article

Cytokine Profiling in Oral Carcinogenesis: Interleukin-1β and Interleukin-8 Expression in Premalignant and Malignant Lesions

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ABSTRACT

To evaluate IL-1β and IL-8 epithelial expression in oral premalignant lesions as predictive biomarkers for cancer development. The study examined a total of around 55 formalin-fixed, paraffin-embedded tissue specimens, which included 15 samples each of oral lichen planus (OLP), oral leukoplakia, and oral squamous cell carcinoma (OSCC), along with 10 samples of healthy oral mucosa as controls. Immunohistochemical staining was performed to detect IL-1β and IL-8 protein expression using a rabbit polyclonal anti-human IL-1β antibody (sc-7884, H-153; Santa Cruz Biotechnology) and a monoclonal anti-human IL-8 antibody (ab7747; Abcam). Differences in the count of immunostained positive cells across groups were statistically evaluated with the unpaired Student's t-test, and a p-value below 0.05 was regarded as statistically significant. Both IL-1β and IL-8 were detected in the nuclei and cytoplasm of keratinocytes across all study groups. Despite this, all lesion types exhibited a significant reduction in staining intensity compared to normal oral mucosa for both cytokines. Additionally, IL-8 expression differed significantly between oral lichen planus (OLP) and leukoplakia, as well as between these lesions and oral squamous cell carcinoma (OSCC). Epithelial levels of IL-1β and IL-8 in the oral mucosa appear to decline as the risk of malignant transformation rises.

Keywords: IL-8, IL-1β, Leukoplakia, Oral carcinoma, Inflammation, Oral lichen planus

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Introduction

The concept of "precancerous" lesions in the oral cavity has gradually been replaced by the term "potentially malignant disorders" (PMDs), acknowledging that not all lesions inevitably progress to carcinoma and that malignant changes may occur outside the visibly affected areas. PMDs encompass a variety of conditions, including leukoplakia and proliferative verrucous leukoplakia, erythroplakia, lupus erythematosus, palatal lesions associated with reverse smoking, oral submucous fibrosis, actinic cheilitis, oral lichen planus (OLP) and more recently recognized entities such as chronic hyperplastic candidosis, oral lichenoid lesions, verrucous hyperplasia, and oral manifestations of graft-versus-host disease [1].

Among these, leukoplakia and OLP are the most prevalent disorders with malignant potential. According to the World Health Organization (WHO), leukoplakia is defined as a white oral plaque of uncertain malignant potential, after excluding known lesions or conditions that do not carry an increased risk of cancer [1]. OLP is a chronic, T-cell-mediated inflammatory disorder affecting the mucosa and skin [1]. Although classified by WHO as a potentially malignant condition, OLP remains controversial in terms of its risk for malignant transformation, with reported rates ranging from 0% to approximately 8% [1].

When these lesions undergo malignant progression, they generally give rise to oral squamous cell carcinoma (OSCC), the most common head and neck

malignancy. OSCC ranks as the eighth most frequent cancer worldwide and the sixth leading cause of cancer-related mortality, with a five-year survival rate of only 40–50% [2].

Cytokines have been increasingly investigated for their role in the progression of leukoplakia and OLP to OSCC, mostly through studies evaluating salivary markers [3-8]. Tumors are known to secrete cytokines in an autocrine manner, thereby promoting angiogenesis and modulating immune responses to create a microenvironment conducive to tumor growth [9-12].

Interleukin-1β (IL-1β) and interleukin-8 (IL-8) are produced by a wide variety of cell types, including oral keratinocytes [10, 12]. Elevated concentrations of these cytokines have been reported in the serum and saliva of patients with OSCC, highlighting their potential as diagnostic or prognostic biomarkers [7, 8, 10].

IL-1β, a cytokine closely associated with cancer-related inflammation, has been shown to contribute to OSCC pathogenesis. Experimental evidence indicates that knocking down IL-1β can significantly reduce OSCC cell proliferation, with its activity regulated by genes such as TGFβ [13]. IL-1β has also been identified as a central gene within the tumor microenvironment during oral carcinogenesis [13].

IL-8, whose expression can be induced by IL-1 and other stimuli, has similarly been found at elevated levels in the saliva of OSCC patients, suggesting a role as a potential biomarker for malignant transformation in the oral cavity [14-18].

Despite these insights, there is still limited evidence supporting the use of tissue-based inflammatory markers for predicting malignant progression or guiding treatment strategies in oral cancer. In this context, the current study aims to investigate the tissue expression of IL-1β and IL-8 in leukoplakia, OLP, and OSCC.

Materials and Methods

Study group

This study included biopsies from 55 participants. Ethical approval was granted by the Bioethics Committee of the Dental School, Universidad Central de Venezuela, under protocol N° 0353–2012. Tissue samples comprised 15 cases of oral lichen planus (OLP), 15 leukoplakias exhibiting mild to moderate epithelial dysplasia, and 15 well-differentiated oral squamous cell carcinomas (OSCC), all collected following written informed consent from the patients. Additionally, 10 samples of normal gingival mucosa were obtained from healthy individuals undergoing extraction of impacted third molars, with no clinical signs of infection or inflammation, who also provided written informed consent.

Immunohistochemistry

Four-micrometer-thick sections were prepared from the paraffin blocks and subjected to an indirect biotin-streptavidin-peroxidase immunohistochemical staining protocol. Antigen retrieval was performed by heating the slides in a citrate-based retrieval solution (pH 6.1, DAKO®, Santa Clara, CA, USA) in a steamer for 60 minutes. The sections were then incubated for one hour at room temperature with the primary antibodies: a rabbit polyclonal anti-human IL-1β antibody (H-153, sc-7884; Santa Cruz Biotechnology, Dallas, TX, USA) diluted 1:50, and a monoclonal anti-human IL-8 antibody (ab7747; Abcam®) diluted 1:25. Signal detection and amplification were achieved using the EnVision system (DAKO®) for 30 minutes, followed by visualization with diaminobenzidine (DAB) chromogen (DAKO®). Counterstaining was performed with hematoxylin. As positive controls, a pilonidal cyst was used for IL-1β staining, and tonsil tissue was used for IL-8 staining.

IL-1β and IL-8 quantification

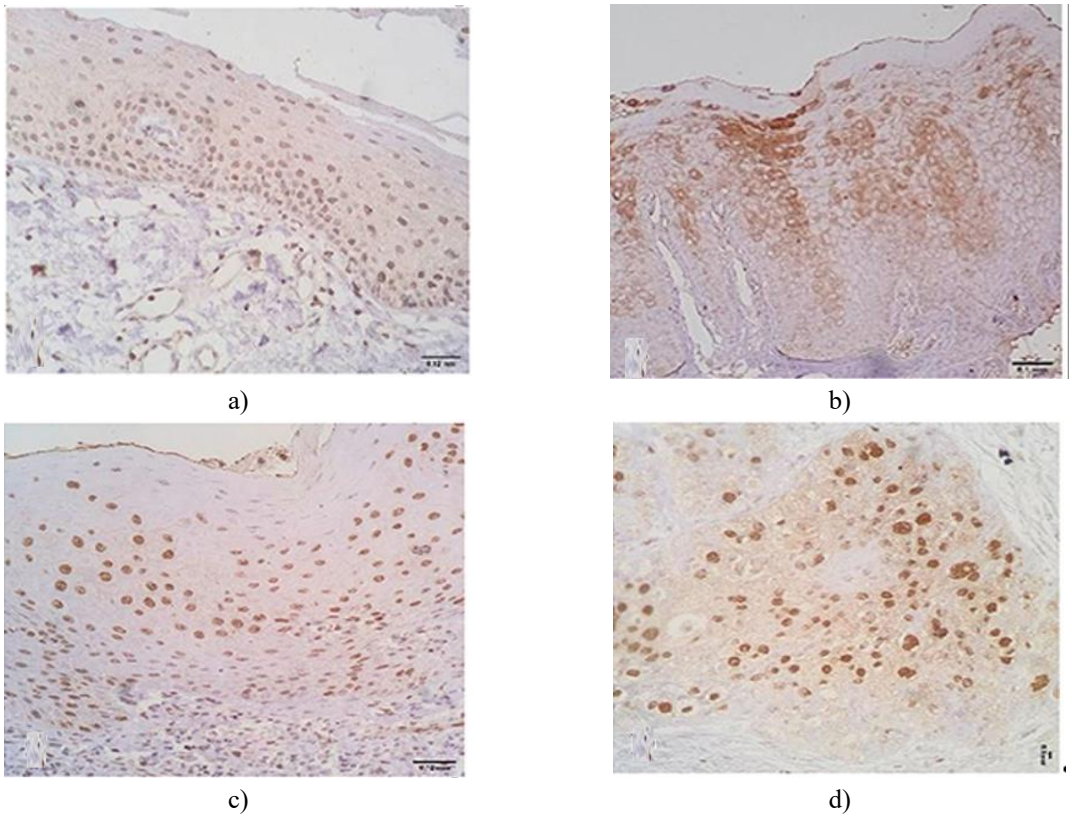
The slides were examined using an optical photomicroscope (Olympus CX41, San Diego, CA, USA) at 10×/0.25 magnification. Digital images were captured from five distinct fields per slide and saved in JPEG format. A 6 × 6 grid was overlaid on each image to facilitate counting of nuclear-positive keratinocytes [19], using the ImageJ software (version *1.46a). For each case, the average number of positively stained cells was determined.

Statistical analysis

Statistical analysis of the data was performed using SPSS software (version 18.0). Positive cell counts were reported as mean ± standard deviation (SD) and comparisons between groups were conducted using the Student's t-test for independent samples. Differences were considered statistically significant at p-values less than 0.05.

Results and Discussion

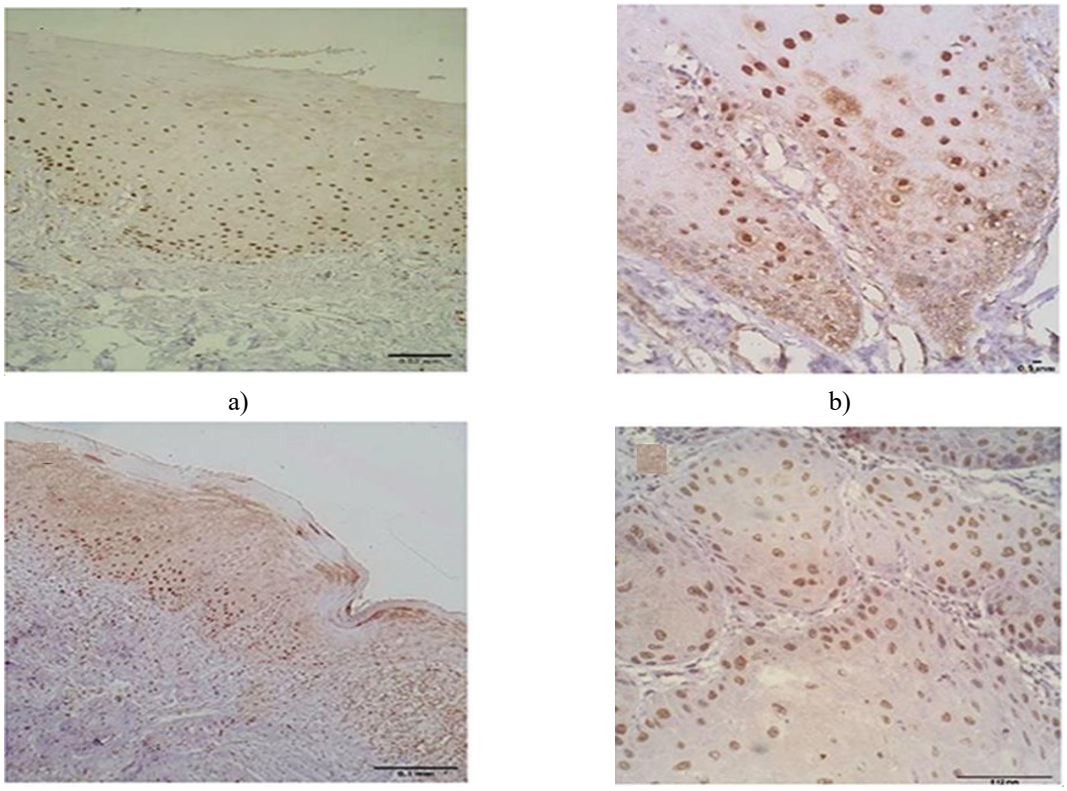
Immunostaining for IL-8 and IL-1β was observed in the cytoplasm and nucleus of keratinocytes **(Figures 1, 2).**



a) b)

c) d)

Figure 1. Immunostaining for interleukin-1β (IL-1β)-positive cells in normal oral mucosa (a), oral lichen planus (b), oral leukoplakia (OLP) (c), Distinct expression patterns are observed (OSCC) (d). and oral squamous cell carcinoma, with staining visible in both the cytoplasm and nucleus across the different tissues.



a) b)

c) d)

Figure 2. IL-8 expression in keratinocytes from oral healthy mucosa (a), OLP (b), leukoplakia (c), and OSCC (d). Both nuclear and cytoplasmic localization of IL-8 was observed across all tissue types.

IL-1β expression was most prominent in normal oral mucosa, averaging 329.25 ± 90.55 positive cells per field. In contrast, leukoplakia samples showed a lower mean of 224.60 ± 161.05 cells/field, OLP samples averaged 111 ± 101.75 cells/field, and OSCC specimens exhibited 132.07 ± 121.95 cells/field **(Figure 1, Table 1)**.

Table 1. Interleukin-8 (IL-8) and Interleukin-1β (IL-1β) keratinocyte expression.

Condition	IL-1β (positive cells/field) Mean ± SD	IL-8 (positive cells/field) Mean ± SD	p-value (overall comparison)
Normal oral mucosa	329.25 ± 90.55	389.80 ± 84.50	—
Oral Lichen Planus (OLP)	111.00 ± 101.75	230.02 ± 227.67	—
Oral Leukoplakia	224.60 ± 161.05	413.87 ± 250.78	—
Oral Squamous Cell Carcinoma (OSCC)	132.07 ± 21.95	255.00 ± 193.90	—
p-value (ANOVA/Kruskal-Wallis)	—	—	IL-1β: 0.06 IL-8: 0.046

Analysis of IL-1β levels across the study groups demonstrated a marked decrease in expression in OSCC (p = 0.001) and OLP (p = 0.0001) relative to normal oral mucosa **(Table 2)**.

Table 2. Interleukin-1β p-values comparison among groups.

Condition	Normal oral mucosa	Oral Lichen Planus (OLP)	Oral Leukoplakia	Oral Squamous Cell Carcinoma (OSCC)
Normal oral mucosa	—	**<0.0001***	0.106 (n.s.)	**0.001 (*)**
Oral Lichen Planus (OLP)	**<0.0001***	—	**0.029 (*)**	0.611 (n.s.)
Oral Leukoplakia	0.106 (n.s.)	**0.029 (*)**	—	0.087 (n.s.)
Oral Squamous Cell Carcinoma (OSCC)	**0.001 (*)**	0.611 (n.s.)	0.087 (n.s.)	—

*Statistically significant.

Analysis of IL-8 expression revealed that leukoplakia lesions had the highest mean number of positive cells (413.87 ± 250.79 cells per field), followed by healthy oral mucosa (389.80 ± 84.51 cells/field), OLP (230.02 ± 227.67 field/cells) and OSCC (255 ± 193.90 field/cells), with differences reaching statistical significance (p = 0.046) **(Figure 2, Table 1)**.

Further comparisons showed that IL-8 levels were significantly lower in OSCC compared with normal oral mucosa (p = 0.026), whereas leukoplakia exhibited a notable elevation in IL-8 expression relative to healthy tissue (p = 0.009) **(Table 3)**.

Table 3. Interleukin-8 p-values comparison among groups.

Condition	Normal oral mucosa	Oral Lichen Planus (OLP)	Oral Leukoplakia	Oral Squamous Cell Carcinoma (OSCC)
Normal oral mucosa	—	0.101 (n.s.)	**0.009***	**0.026***
Oral Lichen Planus (OLP)	0.101 (n.s.)	—	0.342 (n.s.)	0.958 (n.s.)
Oral Leukoplakia	**0.009***	0.342 (n.s.)	—	**0.043***
Oral Squamous Cell Carcinoma (OSCC)	**0.026***	0.958 (n.s.)	**0.043***	—

*Statistically significant.

Interleukin-1β (IL-1β) is a pro-inflammatory cytokine widely implicated in oral carcinogenesis [8, 20]. In this study, immunohistochemical analysis revealed interesting patterns: keratinocytes in all groups exhibited both nuclear and cytoplasmic staining, with the highest expression observed in healthy oral mucosa.

Nuclear expression of IL-1 and IL-8 in keratinocytes has been reported previously [21]. Additionally, both IL-1α and IL-1β have been detected in gingival keratinocytes in vivo and in vitro, likely reflecting a sustained response to bacterial stimuli [22-24]. Inflammasome activation is known to induce caspase-1-dependent secretion of IL-1β in keratinocytes, and gingival keratinocytes can produce IL-8 in response to IL-1β, helping maintain the tissue microenvironment [22-24]. The normal mucosa samples in this study were derived from periodontal tissue, which may explain the

consistent presence of both cytokines even under clinically non-inflammatory conditions.

The oral cavity functions as an immunologically active organ, containing elements such as mucosa-associated lymphoid tissue, a diverse microbiota, and saliva rich in secretory IgA and other biomarkers [18]. Oral keratinocytes can also express major histocompatibility complex class II molecules, functioning as antigen-presenting cells capable of producing and secreting pro-inflammatory cytokines such as IL-1β and IL-8 [25-27]. Although using gingival mucosa as a control might reflect a mildly pro-inflammatory environment rather than a completely "healthy" baseline, the observed cytokine expression was still lower than in the studied potentially malignant disorders.

In a rat model, Wu *et al*. [13] reported IL-1β positivity in keratinocytes from healthy mucosa, leukoplakia, and OSCC, with stronger staining in disease states compared to healthy tissue, suggesting that increased cytokine expression is associated with malignant transformation. Given that IL-1β expression and secretion are inflammasome-dependent, this cytokine may contribute to cell death through pyroptosis, a process essential for epithelial turnover and oral mucosa protection [28]. The activation of the inflammasome, resulting in IL-1β secretion, may exert tumor-suppressive effects [28], which could explain the significant reduction of IL-1β expression observed in this study. This decrease may indicate impaired pyroptosis, favoring keratinocyte proliferation in OLP and leukoplakia, a critical factor in OSCC development.

A dual role for IL-1β in cancer has been suggested, with involvement in both tumor growth and suppression [28, 29]. Gasparoto *et al*. [30] chemically induced squamous cell carcinomas in mice and found that inflammasome-related proteins contributed to antitumor defense, with their loss impairing tumor suppression. Conversely, Dantas *et al*. [31] reported higher IL-1β immunostaining in metastases and lymph nodes compared to tumor resection margins, while Singh *et al*. [32] observed weak IL-1β staining in most non-metastatic oral carcinomas. These findings indicate that the presence and role of IL-1β in oral epithelial tissues remain complex and context-dependent.

IL-8 is also implicated in carcinogenesis, exhibiting angiogenic and chemotactic properties and being produced by a variety of cells, including keratinocytes. Nuclear and cytoplasmic IL-8 expression has been described in OSCC keratinocytes [33]. While IL-8 levels have been studied in saliva and serum from patients with potentially malignant disorders and OSCC [16, 17], tissue-based immunohistochemical studies are limited, and results may differ. Jenkins *et al*. [34] evaluated NF-κB and IL-8 in esophageal adenocarcinoma, Barrett esophagitis, and adjacent squamous tissue, observing decreased IL-8, similar to the trends seen in the present study.

In this study, IL-8 immunohistochemical patterns mirrored those of IL-1β. Prior research [11, 18, 24, 25] indicates that IL-1β induction is among the co-stimulatory signals driving IL-8 production, suggesting a mechanistic link. As a chemoattractant for polymorphonuclear neutrophils and lymphocytes [11, 35], reduced IL-8 expression in disease states, particularly OSCC, may reflect impaired antitumor immune surveillance, thereby facilitating carcinogenesis. Supporting this, Lee *et al*. [35] demonstrated in a mouse model of human ovarian cancer that IL-8 overexpression suppressed tumor growth, potentially via neutrophil-mediated cytotoxicity.

The observed decrease in IL-8 expression may relate to reduced IL-1β levels, which normally stimulate its synthesis. This reduction could compromise chemotactic activity, weakening antitumor responses mediated by neutrophils and lymphocytes. IL-1β findings further suggest that OSCC patients may exhibit epithelial loss of this cytokine, potentially due to inflammasome deactivation in keratinocytes, leading to diminished IL-1β expression, secretion, and pyroptosis, thus promoting carcinogenesis.

In OLP, several studies have reported abnormal expression of inflammatory cytokines, including IL-1β and IL-8, in tissue, saliva, and serum [7, 12, 36]. In the present study, OLP lesions displayed the lowest tissue expression of these cytokines, likely reflecting the chronic inflammatory nature of the disease. Interestingly, despite reduced tissue levels, multiple reports have shown elevated IL-8 in saliva and serum from OLP patients [7, 12, 36, 37], suggesting that cytokines may play a larger role in systemic immune responses than in local lesions. Furthermore, salivary IL-8 levels are lower in OLP patients with epithelial dysplasia compared to those with OSCC [12, 37], indicating that non-invasive salivary measurement could serve as a useful tool to monitor malignant transformation in OLP.

Conclusion

The epithelial expression of IL-1β and IL-8 in the oral mucosa appears to decline as the risk of malignant transformation increases. IL-1β may contribute to oral carcinogenesis through its activity in keratinocytes. Notably, this study revealed that gingival keratinocytes

express both cytokines even under normal or minimally inflamed conditions.

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Conflict of Interest: None

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Ethics Statement: None

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