



# Pro-inflammatory Cytokines and Oral Lichen Planus

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## Abstract:

Pro-inflammatory Cytokines are powerful mediators which play a central role in both innate and adapted immune responses. Aberrant productions of cytokines may lead to the onset of immune deficiency, allergy or autoimmunity, which are involved in the mechanisms of various immune-mediated inflammatory diseases. Oral lichen planus (OLP) is a chronic inflammation disease affecting the oral mucosa with unknown aetiology. Previous studies have described the abnormal expression patterns of various inflammation-related cytokines, such as IL-1, 2, 4, 6, 8, 10, 12, 17, 18, TGF- $\beta$ , IFN- $\gamma$  and TNF- $\alpha$ , in lesions, saliva, serum and peripheral blood mononuclear cells from patients with OLP, which may reflect the immune dysregulation status and emerge as central players in the immunopathogenesis of OLP. Besides, the gene polymorphisms of several cytokines such as IFN- $\gamma$ , TNF- $\alpha$ , IL-4, IL-10 have been found to be involved in the susceptibility of OLP. The aim of this paper is to briefly present the characteristics and a current description about the involvement of these pro-inflammatory cytokines in the pathogenesis of OLP leading to understand the eventual malignant transformation of OLP to Oral Cancer.

**Keywords:** Pro-inflammatory Cytokines, Oral Lichen Planus, Malignant Transformation, Oral Cancer, Interleukines

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## Introduction

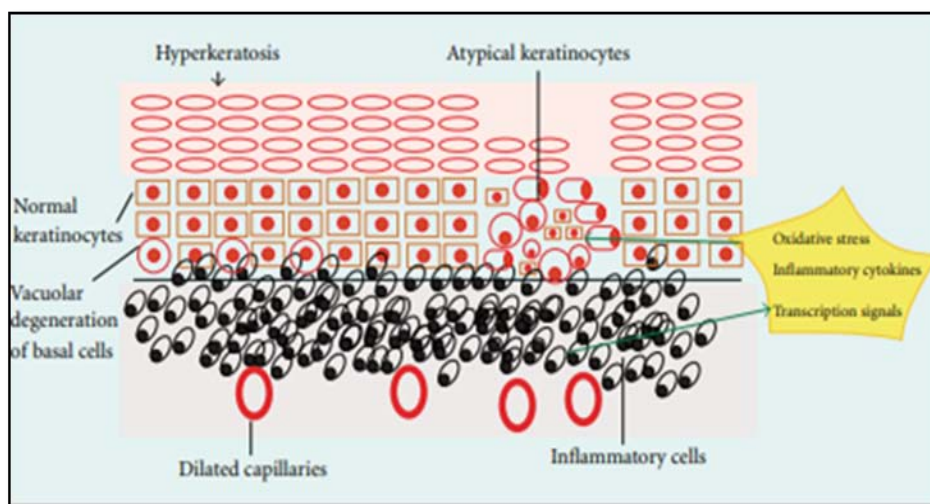
Oral lichen planus (OLP) is a chronic inflammatory oral condition of unknown aetiology characterized by T-cell-mediated chronic immune response and abnormal epithelial keratinization cycle [1]. The OLP lesions may coexist with cutaneous and genital lesions, or may be the only disease manifestations [2]. The epidemiology of OLP is not easy to calculate with reported incidence ranging between 1-2% of the general population.

The OLP lesions are consistently more persistent than the dermal lesions and have been reported to carry a risk of malignant transformation to oral squamous cell carcinoma (OSCC) of 1-2% (reported range of malignant transformation 0– 12.5%) [3,4]. Clinically, OLP appears more commonly with the classic reticular form, which results from coalition of papules and may be asymptomatic or may cause mild discomfort. Erythema, erosions, and ulceration could also appear and these are the most painful OLP manifestations, while if the lesions become chronic they may become hyperplastic or atrophic [4]. The lesions of OLP tend to present symmetrically and bilaterally especially in the buccal mucosa [5]. Histological examination of OLP reveals, dense inflammatory infiltrate in the upper lamina propria, mainly consisting of T-cells, liquefaction degeneration of basal keratinocytes and basal membrane hyperkeratosis or atrophy of the keratin layer [6,7]. The pathogenesis of OLP is very complex and involves possible antigen presentation by the oral keratinocytes that could be either of an exogenous or an endogenous origin [8–10]. This antigenic trigger is accompanied by a mixed inflammatory response comprising mainly T-cells, macrophages, and mast cells, as well as the associated cytokines and cytotoxic molecules [4, 8–10]. Officially, the World Health Organisation (WHO) classifies OLP as a “potentially malignant disorder” with unspecified malignant transformation risk and suggests that OLP patients should be under close monitoring [11].

## Carcinogenesis in OLP

Oral Squamous Cell Carcinoma (OSCC) arises occasionally at the site of a pre-existing OLP lesion, although it is unlikely that OLP is inherently pre-malignant. The cause of increased oral cancer risk in OLP patients is unknown, although the oral mucosa affected by OLP may be more sensitive to exogenous mutagens in tobacco, alcohol, betel quid, and *Candida albicans*. Studies have recently identified TGF- $\beta$ 1 expression in the subepithelial lymphocytic infiltrate in OLP. T-cell-derived TGF- $\beta$ 1 may inhibit growth and induce differentiation and apoptosis of oral mucosal keratinocytes, thereby suppressing tumor formation. T-cells in OLP also express IFN- $\gamma$  and TNF- $\alpha$ . While many other studies have shown that TNF- $\alpha$ , IFN- $\gamma$ , and IL-12 inhibit tumor growth and metastasis. Hence, TGF- $\beta$ 1, TNF- $\alpha$ , IFN- $\gamma$ , and IL-12 may inhibit carcinogenesis in OLP.

The possible premalignant nature of OLP has been the subject of numerous studies and great controversies [4, 5]. Treatment of OLP is remarkably unsatisfying; topical steroids are the first treatment choice and systemic corticosteroids and immunosuppressants are the second line agents, but none of them can result in significant long-term disease control [12]. Severe erosive disease leaving mucosal atrophy and requiring systemic treatment is reported to carry the highest risk of malignant transformation [13]. There is no definite malignant transformation mechanism identified in OLP. The current hypothesis is that chronic stimulation from the inflammatory and stromal cells is providing the signals that are causing epithelial cells to derange their growth control and in cooperation with oxidative stress, from oxidative and nitrative products, it provokes DNA damage resulting in neoplastic changes [4, 14–17] (Figure 1). Recently, OLP has been proposed to be an ideal model of inflammation induced cancer [18]. The advances in molecular information on this pathologic condition have shed new light on the complex pathogenesis of OSCC arising in OLP and this article is an attempt to review the currently available data.



**Figure 1** Development of dysplasia and cancer in OLP

## Cell Cycle Control in OLP

Apoptosis of basal keratinocytes, caused by the activity of cytotoxic T-cells, could be a possible explanation for one of the histopathologic hallmarks of OLP that is the vacuolar degeneration of basal membrane [8]. This is also supported by several molecular studies demonstrating the presence of apoptotic signals in OLP [10, 19, 20]. Nevertheless, if apoptosis was the main cellular event, then all cases of untreated OLP would end up with severe and extensive oral mucosa erosions [21]. However, this is not the case in the majority of OLP, as the most common clinical form of OLP is reticular lichen planus, while the erosive forms usually are limited in one or two oral sites [4, 5]. Therefore, a counterbalancing mechanism is expected as a response from the oral epithelium to maintain its integrity. In fact, several molecular studies indicated evidence of increased cellular turnover rate, in the form of increased cellular proliferation, in epithelial cells of oral lichen planus [21–24]. In addition, other authors have demonstrated mixed patterns of both apoptosis and increased cellular proliferation occurring simultaneously [25–27].

## The Role of pro-inflammatory Cytokines in the pathogenesis of OLP

Although the etiopathology of OLP is still unknown, a significant body of evidence has supported a central role of immune dysregulation in the pathogenesis of OLP, in which antigen-specific and nonspecific mechanisms are involved [28-29]. Immune dysregulation in OLP is largely mirrored by the aberrant productions of a wide variety of inflammatory mediators in both lesions and peripheral blood, which may play a regulatory role in the interactions between keratinocytes, T cells and many other cell types [30-33]. Of these inflammatory mediators, pro-inflammatory cytokines are the most important types. (Mon mémoire)

Cytokines are small peptide proteins that can be synthesized and secreted by various immune and non-immune cells [34]. They function as key signaling molecules in cell-to-cell communication by binding to

specific receptors on target cells and initiating signaling cascades, leading to changes in phenotype and function of target cells via modification of gene regulation [35].

Most pro-inflammatory cytokines are pleiotropic molecules and can exert distinct effects depending on the types of target cells and the environment [36]. They can also mutually induce production in autocrine, paracrine and endocrine modes, to form complex regulatory networks. In the immune system, cytokines are potent regulators and play a role in controlling the orientation, extent, and innate and adapted immune responses [34]. An aberrant production of cytokines can lead to the appearance of deficiency, allergy, autoimmunity, inflammation, which are involved in the pathogenesis of various inflammatory phenomena [37].

Pro-inflammatory cytokines (IL-1 $\alpha$ , IL-6, IL-8, TNF- $\alpha$ ) have been found increased in whole unstimulated saliva and other oral fluids of OLP patients [38] and also in OSCC patients these observations are suggestive for a role of pro-inflammatory cytokines in the inflammatory process of OLP and possibly also in the malignant transformation of OLP [39]. TNF is one of the most studied cytokines linking chronic inflammation and cancer by inducing neoplastic cellular phenotypes, and angiogenesis [37]. TNF involvement in the pathogenesis of OLP has been proposed for more than 21 years ago [39]. Since then, several studies demonstrated findings supporting the TNF involvement in OLP pathogenesis. These include TNF genetic polymorphisms with OLP susceptibility, elevated serum and saliva TNF levels in patients with OLP, and in situ detection of TNF in OLP epithelium. Its role is also supported by the favorable results of anti-TNF agents in patients with OLP. IL-6 expression in serum and saliva of OLP patients is considered indicative of a Th2 cellular involvement in OLP, [40] a fact that was underestimated initially in the pathogenesis of OLP. Similarly, IL-6 has been associated with promoting colon cancer development in inflammatory bowel diseases. Furthermore, IL-6 and IL-8 expression is associated with the senescence phenotype and has been suggested that they promote senescence-related growth arrest [41].

## Conclusion

All the findings so far are indicative that the OLP is a preneoplastic inflammatory disorder. The fact that OLP lesions are found in an open cavity, such as the oral cavity, that is, accessible to regular monitoring and biopsy, is feasible without complications and high cost, render OLP an ideal disease to study the relationship between chronic inflammation malignant potential transformation to oral cancer. The presence of certain pro-inflammatory cytokines (IL-1 $\alpha$ , IL2, IL-6, IL-8, TNF- $\alpha$ ) in oral fluids, such as saliva, could be considered as a biomarker to early detect the malignant transformation of OLP to oral cancer. Large sample studies using standardized, unbiased methods and well-matched controls are required in the future.

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