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REVIEW ARTICLE

Update of the cancer-associated molecular mechanisms in oral lichen planus, a disease with possible premalignant nature

E.A. Georgakopoulou[1,2], T.G. Troupis[1], G. Troupis[1], V.G. Gorgoulis[2]

[1]Department of Anatomy, [2]Department of Histology and Embryology, Faculty of Medicine, National and Kapodistrian University of Athens, Athens, Greece

Summary

Oral lichen planus (OLP) is a relatively common inflammatory disease. Several reports of oral squamous cell carcinomas (OSCC) developing in the ground of previous OLP lesions exist in the current medical literature. Hence, there is a debate concerning the possible premalignant nature of OLP. The studies that examined the malignant potential of OLP for many years were mainly observational and were seeking to detect the percentage of OLP patients that developed OSCC. The results of these studies varied significantly with reported percents of malignant transformation of OLP ranging from 0 to 12.5%. In recent years the number of OLP studies that investigate molecular biomarkers identified in cancer is on the rise. This article is an update of the molecular pathways identified in OLP that could be suggestive of a malignant potential of this condition.

Key words: biological markers, oral lichen planus, oral tumor markers, squamous cell carcinoma

Introduction

OLP is a chronic inflammatory disease of unknown aetiology. It is a rather common oral condition reported to affect approximately 1% of the general population [1]. The possible premalignant nature of OLP was first suggested in the 1910s when the first description of OSCC arising in a patient with OLP was reported [2]. The WHO does not describe OLP as a premalignant disease but recognizes the possibility of malignant transformation and suggests close clinical surveillance of OLP patients [1]. Numerous clinical studies of OLP patient series (prospective and retrospective) have been published in the medical literature, in which variable degrees rates of malignant transformation have been reported ranging from 0 to 12.5% [3]. Unfortunately, safe conclusions from the OLP clinical studies cannot be drawn. The main reason is that they did not use the same diagnostic criteria for OLP [3]. This is not attributed to negligence in the study designs, but to the fact that no standard and widely accepted diagnostic criteria exist for OLP. Furthermore, the suggested criteria proposed by the WHO [4] (Table 1) are not universally accepted [3] due to the clinical and histological variability of OLP. The clinical manifestations of OLP range from the classic reticular (lace-like) lesions (Figure 1) to extensive oral ulceration and atrophy (Figure 2). The clinical appearance of OLP is often characteristic enough to provide a diagnosis of lichenoid lesion/reaction, but in the majority of cases the clinician cannot be certain if the patient has classic OLP or a lichenoid lesion/reaction. The term "lichenoid reaction" is used to describe reactive inflammatory lesions with clinical and histological similarities to OLP. The commonest form of lichenoid reaction is the amalgam-induced lichenoid reaction, a lichenoid lesion of the oral mucosa located in the vicinity to amalgam fillings and is attributed to "contact allergy type reaction" to dental amalgam. The term oral lichenoid lesion (OLL) has been used in a more broad sense to describe lesions with clinical and histological features similar to OLP but not typical and not necessarily attributed to amalgam or other type of allergy.

In a respectable percentage of OLP patients the oral lesions can be indistinguishable from lupus erythematosus, mucous membrane pemphigoid or leuko-

Correspondence to: Eleni A. Georgakopoulou, MD, DDS, MSc. 124b Vas. Sofias Ave, 115 26 Athens, Greece. Tel/Fax: +30 210 7794553, E-mail: egddsmd@yahoo.gr

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Table 1. The OLP modified diagnostic criteria as proposed by Van Der Meij and Van Der Waal [4]

Clinical criteria
Presence of bilateral, more or less symmetrical lesions
Presence of a lace-like network of slightly raised gray-white lines (reticular pattern)
Erosive, atrophic, bullous and plaque-type lesions are accepted only as a subtype in the presence of reticular lesions elsewhere in the oral mucosa
In all other lesions that resemble OLP but do not complete the criteria, the term "clinically compatible with" should be used
Histopathologic criteria
Presence of a well-defined band-like zone of cellular infiltration that is confined to the superficial part of the connective tissue, consisting mainly of lymphocytes
Signs of liquefaction degeneration in the basal cell layer
Absence of epithelial dysplasia
When the histopathologic features are less obvious, the term "histopathologically compatible with" should be used
Final diagnosis of OLP or OLL
To achieve a final diagnosis, clinical as well as histopathologic criteria should be included
OLP: A diagnosis of OLP requires fulfillment of both clinical and histopathologic criteria
OLL: The term OLL will be used under the following conditions:
1- Clinically typical of OLP but histopathologically only compatible with OLP
2- Histopathologically typical of OLP but clinically only compatible with OLP
3- Clinically compatible with OLP and histopathologically compatible with OLP

OLP: oral lichen planus, OLL: oral lichenoid lesion

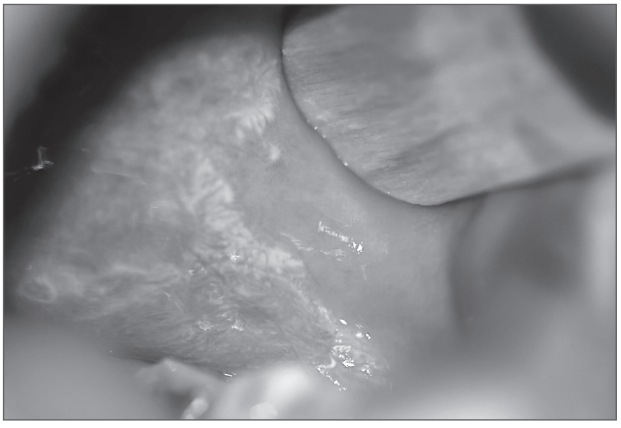

Figure 1. Reticular type OLP, buccal mucosa.

plakia. The histopathology is never pathognomonic for OLP but suggestive or compatible with lichen planus or lichenoid inflammation. Thus, it is often impossible to achieve objective interpretation of OLP lesions and this fact is a serious limitation of all clinical studies [3]. One of the main histological features of OLP is the dense inflammatory infiltrate in the connective tissue, mainly

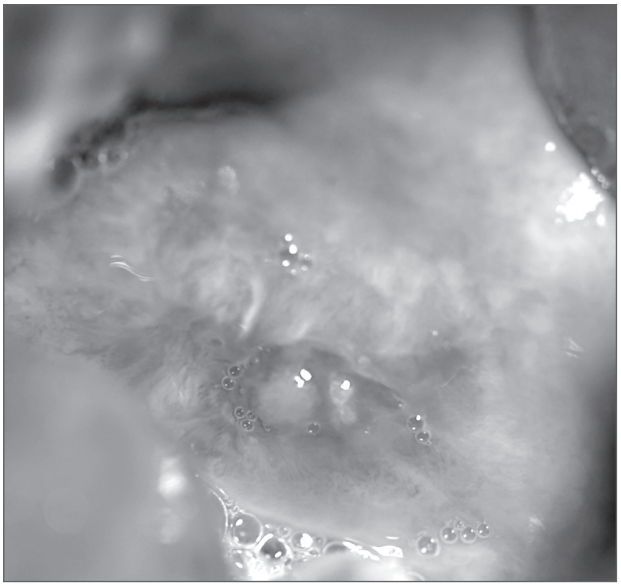

Figure 2. In this patient with erosive lichen planus the histopathologic examination revealed that this was a site of mild dysplasia (Figures 1 and 2 are from the personal archive of E.A. Georgakopoulou with the consent of the patients).

populated by lymphocytes, and it is believed by some authors that these inflammatory cells provide the molecular stimuli which enhance the development of dysplastic and malignant changes in OLP [3].

Looking for more evidence in order to investigate the possible premalignant character of OLP, the focus of studies in the last years has been the identification of molecular biomarkers of malignancy in OLP lesions. In this article the main molecular markers studied in OLP are reviewed.

Molecular markers indicative of inflammatory and/or neoplastic process in oral lichen planus

p53, Fas/FasL, Bcl2

TP53 is known as a tumor suppressor gene [5]. It encodes the tumor suppressor protein p53 that interferes in the process of cell cycle arrest and apoptosis in cells with potentially malignant DNA damage [5]. p53 has been studied to a satisfactory extent in OLP lesions. Recently, Ebrahimi et al. reviewed the studies that aimed at the detection of p53 in oral mucosa with OLP. They found 18 studies that used molecular techniques to identify p53 (most of the studies used immunohistochemistry) and the results varied from no detection to positive p53 expression in OLP samples. The results cannot be uniformly interpreted since different methodologies were used in each study [6].

Furthermore, with the use of string software, a method designed to identify genes that associate with diseases and disease interactions, it was demonstrated that TP53 and CDKN1A (cyclin-dependent kinase inhibitor that interacts with p53 to induce cell cycle arrest) are leader genes in the possible interaction between OLP and OSCC [7].

Overexpression of the antiapoptotic protein Bcl2 and downregulation of the apoptotic protein Fas (ligand of the Fas transmembrane receptor, which upon binding form the death - inducing singalling complex) have been identified to be involved in the biology of OSCC, especially in the HPV-positive types [8]. OLP-associated lymphocyte populations were expressing the Bcl-2 significantly higher than lymphocytes from healthy mucosa in a recent immunohistochemistry *in situ* study and the authors suggested that this could serve as a "suspicion-marker" for patient's closer follow up, rather than an indicator of malignancy [9]. In the same context, Fas/FasL system has been identified to be downregulated in OLP [10].

Lck, PI-3K and Survivin

Survivin is a marker that has been studied in the process of inhibition of apoptosis in cancer [11]. The SRC family (sarcoma proto-oncogenic) proto-oncogenic tyrosine kinase, Lck (lymphocyte specific tyrosine kinase), is a lymphocytic protein associated with T-cell activation [12]. Phosphatidylinositol 3-kinase (PI-3K) belongs to group of enzymes involved in the cellular communication and differentiation and has been identified as a molecule involved in one well-described apoptosis pathway [13]. Oluwadara et al. studied these biomarkers in OLP and OSCC tissue samples using of immunohistochemistry and tissue microarrays and found a possible implication of these molecules in the transformation of OLP to OSCC. Their findings are also indicative of an association between chronic T-cell-mediated inflammation and inhibition of apoptosis in the pathogenesis of OLP-related OSCC [14].

Cyclin dependent kinases and p16

Cyclin-dependent kinases (CDKs) are enzymes involved in the progression of cell cycle. Deregulation of these cell cycle regulating enzymes leads to cancer development [10]. p16 protein is an inhibitor of CDKs acting in G1 phase of the cell cycle. In more detail, p16 does not allow to the complex of cyclin-D/CDK-4/CDK-6 to phosphorylate the retinoblastoma proteins (pRbs), which is the step that leads to the disruption of the enzyme complex pRb-E2F that is crucial for the G1 phase to progress to S phase, thus leading to cell cycle arrest [13]. Recent immunohistochemistry studies have revealed significantly higher expression of p16 and CDKs 4 but not CDK 6 in OLP in comparison to healthy oral mucosa. This could have been supportive of the role of G1 cell cycle phase disturbance in the possible malignant potential of OLP [15].

NF kappaB

Nuclear factor kappa beta (NF kappaB) is a transcription factor that has been found to be activated both in inflammation and cancer [16]. Positive expression of NF kappaB has been identified both in head and neck squamous cell carcinoma and in OLP tissues, and the positive expression of NF kappaB in OLP is correlated with the level of inflammation and cytotoxicity [17]. It has also been suggested to monitor, in the saliva of OLP patients, the NF kappaB-related cytokines TNF-a, IL-1, IL-6 and IL-8, as markers of disease severity and possible malignant transformation [18].

Matrix metalloproteinases and transforming growth factor-beta1

Matrix metalloproteinases (MMPS) are enzymes of the extracellular matrix that have been implicated in inflammatory processes and in tumor invasion [13]. MMPS in OLP have been associated with the process of basal zone disruption and keratinocyte death and T-cell migration [19]. Chen et al. identified high expression of MMP9 and MMP2 in OLP lesions [20]. In the same study, MMPS expression in OLP has been correlated with increased transforming growth factor-beta1 (TGF-b1) expression [20]. Furthermore, TGF-b1 has been proposed to play a role in the pathogenesis of OLP, by inducing apoptosis of basal keratinocytes [21]. TGF-b1 has been identified to be implicated in the process of epithelial mesenchymal transition in OSCC and is probably dependent on the Snail transcription factor and related with MMPS-2 and 9 [22]. Epithelial mesenchymal transition (EMT) is a process observed in embryogenesis, cancer, and inflammatory diseases and involves the acquisition of mesenchymal characteristics by the epithelial cell. EMT is believed to play a role in the process of cancer invasion and metastasis [23].

Smad proteins, a group of intracellular proteins that act as mediators of the signals from TGFb1 receptors to the nucleus, have recently been found to be upregulated in OLP lesions, indicating possible activation of EMT process in OLP [23]. These findings also support the hypothesis of the implication of chronic inflammation in the pathogenesis of OLP-related OSCC.

Conclusion

Despite the fact that a great number of OSCC that developed in previous OLP lesions have been documented in the literature, there is still great uncertainty concerning the malignant potential of OLP [3]. As the progress in molecular biology brings new tools in our effort to understand the mechanisms that lead to cancer development, the focus of researchers that study the premalignant nature of OLP turns on that field. The results so far demonstrate that a certain number of molecular pathways activated in cancerous lesions have also been identified in OLP lesions. As these results are mostly based on individual studies, they are not yet sufficient to enough to provide definite conclusions. Nevertheless, there is no doubt that more similar studies will come up in the near feature and will shed light to the ambiguous issue of OLP and OSCC association.

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