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Gene expression based evidence of innate immune response activation in the epithelium with oral lichen planus

Guy R. Adami [a,*], Alexander C.F. Yeung [a], Grant Stucki [b], Antonia Kolokythas [b], Herve Y. Sroussi [a], Robert J. Cabay [c], Igor Kuzin [d], Joel L. Schwartz [a]

[a] Department of Oral Medicine and Oral Diagnostics, Center for Molecular Biology of Oral Diseases, University of Illinois at Chicago, 801 South Paulina Street, Chicago, IL 60612, USA
[b] Department of Oral and Maxillofacial Surgery, College of Dentistry, University of Illinois at Chicago, 801 South Paulina Street, Chicago, IL 60612, USA
[c] Department of Pathology, College of Medicine, University of Illinois at Chicago, 840 South Wood Street, Chicago, IL 60612, USA
[d] Division of Allergy/Immunology and Rheumatology, School of Medicine and Dentistry, University of Rochester, 601 Elmwood Avenue, Rochester, NY 14642, USA

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ABSTRACT

Objective: Oral lichen planus (OLP) is a disease of the oral mucosa of unknown cause producing lesions with an intense band-like inflammatory infiltrate of T cells to the subepithelium and keratinocyte cell death. We performed gene expression analysis of the oral epithelium of lesions in subjects with OLP and its sister disease, oral lichenoid reaction (OLR), in order to better understand the role of the keratinocytes in these diseases.
Design: Fourteen patients with OLP or OLR were included in the study, along with a control group of 23 subjects with a variety of oral diseases and a normal group of 17 subjects with no clinically visible mucosal abnormalities. Various proteins have been associated with OLP, based on detection of secreted proteins or changes in RNA levels in tissue samples consisting of epithelium, stroma, and immune cells. The mRNA level of twelve of these genes expressed in the epithelium was tested in the three groups.
Results: Four genes showed increased expression in the epithelium of OLP patients: CD14, CXCL1, IL8, and TLR1, and at least two of these proteins, TLR1 and CXCL1, were expressed at substantial levels in oral keratinocytes.
Conclusions: Because of the large accumulation of T cells in lesions of OLP it has long been thought to be an adaptive immunity malfunction. We provide evidence that there is increased expression of innate immune genes in the epithelium with this illness, suggesting a role for this process in the disease and a possible target for treatment.
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* *Corresponding author at*: College of Dentistry, University of Illinois at Chicago, Chicago, IL 60612, USA. Tel.: +1 312 996 6251; fax: +1 312 355 2688.
E-mail address: gadami@uic.edu (G.R. Adami).

Abbreviations: OLP, oral lichen planus; OLR, oral lichenoid reaction; LO OCV, leave-one-out cross validation; FDR, false discovery rate.

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1. Introduction

Oral lichen planus (OLP) is a disease of the oral mucosa characterized by a dysfunctional basal epithelium.[1–3] The keratinization cycle is abnormal with an elevated rate of apoptosis of the basal keratinocytes and increased cell proliferation that may be compensatory. This is accompanied by vacular degeneration of the basement membrane. The cause is believed to be an abnormal chronic inflammation marked by an intense band-like infiltration including cytotoxic T cells below the basement membrane which trigger the death of the keratinocytes. While the disease is thought to be autoimmune in nature, it is not clear what causes the infiltration and adherence of the CD8+ cells to the disease sites. Some studies of tissue from lichen planus lesions have noted higher rates of Hepatitis C Virus (HCV) infection and even Candida in lesions, which suggested an abnormal immune response to infected keratinocytes may initiate the disease.[2,4] The fact that oral lichenoid reactions (OLR), which are histopathologically indistinguishable from OLP lesions, are known to be due to an allergic reaction to drugs or dental amalgam further supports the role of adaptive immunity in OLP.[3,5] The treatment of OLP consists of topical application of corticosteroid, which shows some reduction of symptoms possibly by dampening lymphocyte migration and activation.[2]

It has long been thought that the key to determining the aetiology of lichen planus, be it in the skin or in the oral cavity, is to uncover what causes the buildup of T cells. Because the differential expression of chemokines, chemokine receptors, and adhesion molecules plays an important role in the migration and buildup of immune cells in the periphery, much effort has been made to characterize the expression of these protein types in the lymphocytes of diseased vs. normal patients. In addition, abnormalities of dendritic cells, mast cells and other immune cells, endothelial cells, and keratinocytes have all been suggested as the source of the factors that draw the T cells to the site just below the basement membrane. For example, while specialized cells like Langerhans cells play a major role in antigen processing and T cell recruitment, it is known that keratinocytes of the skin and mucosa play a fundamental immunological role as a first barrier to infection.[6] Abnormal antigen presentation by either of these cell types has been considered as a first step to this disease, which eventually results in the autoimmune-like features of OLP.[4,7]

As the first barrier to infection, the epithelium of the skin and mucosa play a role in the innate immune response that works to recognize and eliminate various microbial components.[6,8] In recent years there has been a renewed focus on the innate immune system, including its ability to affect adaptive immunity and possible roles for innate immunity in chronic inflammatory and autoimmune diseases, such as psoriasis, asthma, diabetes, and others.[9–12] A primary part of the innate immune system are the toll-like receptors (TLRs), transmembrane factors that are pattern-recognition proteins that recognize ligands that are part of microbes.[6,13,14] There are more than 11 TLRs with specificities for different organisms that, when engaged, activate cellular pathways resulting in changes in gene expression. Additional receptor proteins, such as CD14, can act as co-receptors and aid in recognizing pathogen-associated molecular patterns and also play key roles in TLR1, TLR2, and TLR4 recognition of triacylated lipoproteins[15] and the initiation of the innate immune response. Activation of the TLRs typically results in activation of NFK-B and other regulatory complexes that signal the production of inflammatory chemokines, such as CXCLs, which can recruit neutrophils for acute inflammation. Increases in certain cytokines and receptors in immune cells via TLR activation can have direct effects on T cell response in autoimmune diseases.[12,16] Some years ago Xao et al. published the only global gene expression analysis of tissue from this disease[17] and we have tried to use this as a starting point to discern genes differentially expressed in the epithelium of patients with OLP or OLR. Various factors have been shown to be associated with OLP based on changes in protein or RNA levels in OLP mucosal tissue or even protein levels in saliva.[18–23] Focusing on these and related genes we performed gene expression analysis on highly expressed genes of the oral epithelium and were able to identify a set of genes linked to OLP.

2. Materials and methods

2.1. *Clinical sampling*

Brush cytology samples were collected from 14 patients with OLP based on the clinical features of a bilateral, near symmetrical pattern of white, lacy lines on the mucosa, called Wickham's striae, which is the reticular form of OLP.[24] Several cases were of the erosive type, also referred to as the atrophic or ulcerative type, which presents as erythematous, ulcerative lesions. Care was taken to sample oral epithelium only. Most cases (12) and all ambiguous cases were verified by surgical biopsy and histopathology to show the World Health Organization criteria of a dense subepithelial lymph-histiocytic infiltrate, overlying keratinization and degeneration of basal keratinocytes.[7] While OLP in the classic presentation can be recognized without biopsy based on the lesion appearance, the lesions are typically biopsied to rule out the presence of malignancy which may be associated with the disease.[2,3,24]

Two cases were consistent with OLR while the remainder were OLP based on the case history. Diagnosis was done by one of two specialists in oral medicine. Patients were seen in the Oral and Maxillofacial Surgery Clinic and the Multidisciplinary Head and Neck Cancer Clinic in the University of Illinois Medical Centre.[25] The healthy normal group samples were from mucosa that appeared to be clinically healthy in patients there for tooth extraction. The alternative disease group consisted of 19 brush cytology samples sites of apparent mucosal abnormalities, all diagnosed after tissue histopathology.

2.2. *Brush cytology*

Brush cytology was performed on patients as they presented in the clinic. Samples were immediately placed in Trizol (Invitrogen, Carlsbad, CA, USA), mixed, and frozen. We used a

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