Expression of substance P and its relation to epithelial thickness in oral lichen planus

Thesis

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بسم الله الرحمن الرحيم

"قالوا سبحانك لا علم لنا إلا ما علمتنا إنك أنت العليم الحكيم"

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Dedication

This work is especially dedicated to my family,

My dear lovable parents,

My dear brother,

Who gave me

love, care and support throughout my life.

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Abbreviations

▪ Ag	▪ Antigen.
▪ ANOVA	▪ Analysis of variance
▪ CMV	▪ Cytomegalovirus.
▪ CNS	▪ Central nervous system.
▪ C-terminal	▪ Carboxyl-terminal.
▪ DAB	▪ 3-3’ diaminobenzidine.
▪ DG	▪ Desquamative gingivitis.
▪ EBV	▪ Epstein-Barr virus.
▪ EGFR	▪ Epidermal growth factor receptor.
▪ ERK 1/2	▪ Extracellular signal-regulated kinases 1 and 2.
▪ GPCR	▪ Guanine protein-coupled receptors.
▪ GVHD	▪ Graft versus host disease.
▪ H&E	▪ Hematoxyline & Eosin.
▪ HCV	▪ Hepatitis C virus.
▪ HLA	▪ Human leukocyte antigen.
▪ HPV	▪ Human papillomaviruse.
▪ HRP	▪ Horseraddish peroxidase.
▪ HSV-1	▪ Herpes simplex virus-1.
▪ IFN-γ	▪ Interferon-γ.
▪ IL	▪ Interleukin.
▪ LP	▪ Lichen planus.
▪ MAPK	▪ Mitogen-activated protein kinase.
▪ MHC	▪ Major histocompitability.

▪ MMP	▪ Matrix metalloproteinase.
▪ NF-κβ	▪ Nuclear factor-κβ.
▪ NK-1R	▪ Neurokinin-1 receptor.
▪ NK-2R	▪ Neurokinin-2 receptor.
▪ NK-3R	▪ Neurokinin-3 receptor.
▪ NKA	▪ Neurokinin A.
▪ NKB	▪ Neurokinin B.
▪ NPK	▪ Neuropeptide K.
▪ NPγ	▪ Neuropeptide γ.
▪ OLCLs	▪ Oral lichenoid contact lesions.
▪ OLDRs	▪ Oral lichenoid drug reactions.
▪ OLL-GVHD	▪ Oral lichenoid lesions of graft-versus-host disease.
▪ OLP	▪ Oral lichen planus.
▪ OLR	▪ Oral lichenoid reactions.
▪ PNS	▪ Peripheral nervous system.
▪ PPT gene	▪ Preprotachykinin gene.
▪ RANTES	▪ Regulated on Activation, Normal T-cell Expressed and Secreted
▪ RCA	▪ Request for cytotoxic activity.
▪ SP	▪ Substance P.
▪ TNF-α	▪ Tumor necrosis factor-α.

Introduction

Oral lichen planus (OLP), a chronic mucocutaneous inflammatory disease, usually have recognizable, distinctive clinical features and a characteristic distribution. It may be manifested in one of three clinical forms: reticular, erythematous (atrophic) and erosive (ulcerated, bullous) ***(Eisen et al., 2005 and Kim et al., 2006)***.

The histology of OLP is characterized by a dense band-like subepithelial lymphocytic infiltrate, increased numbers of intra-epithelial lymphocytes and degeneration of basal keratinocytes forming colloid (Civatte) bodies. The ultrastructure of colloid bodies suggests that they are apoptotic keratinocytes. Moreover, epithelial basement membrane changes and disruption of basal keratinocyte anchoring elements produce weaknesses at the epithelial-connective tissue interface which may result in histological cleft formation ***(Sugarman et al., 2002 and Brant et al., 2008)***.

Kawamura et al. (2003) stated that cell-mediated immune process is involved in the pathogenesis of the disease. The basal layer disruption may result from the cytotoxic effects of the CD8+ T lymphocytes by releasing cytokines [interleukin (IL)-1β, tumor necrosis factor (TNF)-α and interferon (IFN)-γ], which are mediators to its recruitment as well as to the death of basal keratinocytes ***(Brant et al., 2008)***. In addition, ***Marshman (1998)*** stated that cytokines and inflammatory mediators induce changes in keratin profile and those changes in specific keratin genes reflect hyperproliferation.

Chaudhary (2008) suggested that psychological stressors play an important role in the pathogenesis of OLP and form a starting point for the initiation of various immune reactions. Moreover, ***Niissalo et al. (2000)*** demonstrated the role

of stress in exacerbating OLP suggesting involvement of the neural-immune interaction in its pathogenesis.

In general, the neuro-immune axis is a bidirectional pathway of intersystem communication. This inter-system cross-talk is mediated via a common biochemical language of shared ligands such as cytokines and neuropeptides ***(O'connor et al., 2004)***.

Substance P (SP) is the most important member of the tachykinins, a family of neuropeptides. It was considered to be a neurotransmitter for primary sensory afferent fibers and plays an important role in the central nervous system (CNS) pathways ***(Esteban et al., 2006)***.

SP is secreted by nerves and inflammatory cells such as lymphocytes and dendritic cells and acts by binding to its receptor neurokinin-1receptor (NK-1R) ***(O'connor et al., 2004)***. SP has a wide range of functions, including regulation of neurogenic inflammation and immune response as well as participation in psychological stress pathways ***(Gonzalez-Moles et al., 2009a)***.

Rosenkranz (2007) documented that SP contribute to both the pathophysiology of inflammatory disease and the pathophysiology of depression and anxiety. Moreover, he suggested that SP dysregulation may be a point of convergence underlying the overlap of chronic inflammatory disease and mood and anxiety disorders.

SP enhances lymphocyte proliferation and differentiation, immunoglobulin production, and enhances cytokine secretion. SP-induced release of inflammatory mediators such as cytokines potentiates tissue injury and stimulates further