Review Article

THE CORRELATION BETWEEN MRNA EXPRESSIONS IN THE LICHEN PLANUS: A LITERATURE REVIEW

Ghasemzadeh Hosseini E,[1] Tavakol F,[2] Gholizadeh N[3]

1. *Resident, Department of Oral Medicine, School of Dentistry, Tehran University of Medical Science, Tehran, Iran.*
2. *Resident, Department of Oral Medicine, School of Dentistry, Tehran University of Medical Science, Tehran, Iran.*
3. *Assistant Professor, Department of Oral Medicine, Faculty of Dentistry, Tehran University of Medical Science, Tehran, Iran.*

Abstract

Recently, Lichen planus is a chronic inflammatory and relatively common disease that affects skin and mucous membranes. Oral lichen planus is a relatively common disorder of the stratified squamous epithelia. It is a chronic, immunological, muco-cutaneous disease with a wide range of clinical manifestations. The disease has most often been reported in middle-aged patients more commonly in females than males. Despite direct cellular and molecular pathogenesis of the lichen planus is not fully elicited but it is reported several mRNAs over/down regulation influence and interact its occurrence. So, the aim of the current study was to determine relationship between lichen planus and mRNAs gene expression using PubMed and Medline database English literature by the terms "Lichen planus", "mRNA". In conclusion, several of the factors studied are involved in differentiation and their deregulation suggests a disturbed differentiation pattern and this could indicate a premalignant character of lichen planus but malignant transformation of lichen planus lesions are relative rare. A lot of these factors are also involved in inflammatory processes and connected to autoimmune diseases and their mRNA deregulation in lichen planus could also support an autoimmune phenotype of the disease. Based on our studies a suggestion is that the disturbed differentiation mRNA pattern triggers the intense immune response directed against the epithelial cells seen in lichen planus.

Key words: *Lichen planus, mRNA, mi RNA.*

Introduction

Periodontitis Oral lichen planus is a chronic inflammatory immune mediated disease which affects 0.1–4% of the general adult population.[1] This disease is characterized histologically by a dense sub-epithelial lymphocyte-rich infiltrate, degeneration of basal keratinocytes, and basement membrane disruption. The exact aetiology of lichen planus is unclear, but accumulating evidence supports the role of immune dysregulation, the attraction of immune cells to the epithelial–connective tissue interface and the destruction of basal keratinocytes by cell-mediated cytotoxicity.[2] Among the six different types of oral lichen planus, the reticular type is the most common asymptomatic lesion and the erosive form is the second most common symptomatic lesion having malignant potential in the general population.[3] Based on the severity of the lesion, corticosteroids are the most commonly used group of drugs for the treatment of oral lichen planus. However, there is no curative therapy for oral lichen planus.[4] MicroRNAs (miRNA) are short non-coding RNAs, encoded in both protein coding and non-coding areas of the genome. Degradation or repressed translation of the target mRNA is then mediated by the miRNA/RISC complex. Some studies have shown that miRNAs may also act as activators of gene expression in quiescent cells and repressors of gene expression in proliferating cells. MiRNAs are involved in many biological processes such as development, differentiation and proliferation, and are also important players in different diseases.[5] It is estimated that one single miRNA may target several dozen or even hundreds of mRNAs and that the expression of a specific protein may be regulated by several different miRNAs and a recent study suggested that around 60% of human genes are regulated by miRNAs. It is known there is relationship between Lichen planus and mRNA expression.[6] So, in this literature paper we decided to review the new findings on the mRNA gene expression related in the oral lichen planus.

Material and Methods

The keywords used for the literature search for this review was peer-reviewed articles following keywords: Lichen planus × mRNA × mi RNA. Among them, the papers were fit the criteria selected and available full-text articles read. Related articles were also scrutinized. Hand search was also driven. The search was carried out using Biological Abstracts, Chemical Abstracts, and the data bank of the PubMed and Medline database updated to 2018. The references found in the search were then studied in detail.

Lichen planus

Lichen planus (LP) is defined as a subacute, chronic dermatosis characterized by small, flat topped, shiny, polygonal violaceous papules that may coalesce into plaques. It involves the skin, mucous membranes, genitalia, nails, and scalp.[7] Oral lichen planus was first described clinically by Wilson in 1869 as a chronic mucocutaneous disorder. Cutaneous lichen planus is recurrent, itchy and not contagious.[8] The clinical presentation of lichen planus has several forms, including the actinic, hypertrophic, annular, erosive, follicular, linear, pigmented, and bullous types. It affects all races equally and presents mainly in the range from 30 to 70 years of age.[9] The disease affects 0.5-2% of the population. The clinical history confirms the relationship between lichen planus and oral cancer, although the degree of the risk involved is controversial. Therefore, lichen planus should be considered a precancerous lesion, emphasizing the importance of periodic follow-ups in all the patients.[10]

Concomitant disease involving the scalp, nails, esophageal mucosa, larynx and conjunctivae occurs much less frequently. In many patients, the onset of lichen planus is

insidious, and patients are unaware of their oral condition. Some patients report a rough-ness of the lining of the mouth, sensitivity of the oral mucosa to hot or spicy foods, painful oral mucosa, red or white patches on the oral mucosa, or oral ulcerations. The clinical history includes phases of re-mission and exacerbation.[11] The clinical evaluation of the oral lesions is based on the six clinical forms described by Andreason: reticular, papular, plaque, atrophic, erosive, and bullous. Mucosal lesions, which are multiple, generally have a symmetrical distribution, particularly on the mucosa of the cheeks, adjacent to molars, and on the mucosa of the tongue, less frequently on the mucosa of the lips (lichenous cheilitis) and on the gums (the atrophic and erosive forms localized on the gums manifest as a desquamative gingivitis), more rarely on the palate and floor of the mouth.[11]

Pathogenesis

The exact pathogenesis of the disease remains unclear, but both antibodies and T-cell mediation have been implicated. Activated T cells release cytokines leading to the attraction of inflammatory cells and the destruction of keratinocyte by cell mediated cytotoxicity.[12] Recently it has been suggested that increased reactive oxygen species (ROS) and lipid peroxides may play a part in the pathogenesis of various skin diseases, such as atopic dermatitis, psoriasis and vitiligo.[13]

IL33 and IL35 mRNA in oral lichen planus

Interleukin (IL) 33 is a member of the IL1 cytokine family and functions as both a traditional cytokine and as an intracellular nuclear factor regulating gene transcription. IL35, an immunosuppressive cytokine, is a member of the IL12 cytokine family.[14] Reduction in IL35 expression has been associated with multiple inflammatory disorders such as inflammatory bowel disease and rheumatoid arthritis.[15] Within the oral lichen planus tissues, there was a significantly higher mRNA expression of IL33 than IL35. Data demonstrate the expression of IL33 and IL35 in oral lichen planus lesions.

P-glycoprotein expression

P-glycoprotein, the translated product of mdr1 (multi drug resistance gene 1), is an ATP-dependent efflux transporter, and its overexpression is a determinant of multi drug resistance (MDR) phenomenon that occurs during tumor chemotherapy or against environmental toxicants. P-glycoprotein functionality, protein expression and mRNA expression are influenced by a number of xenobiotics or endogenous compounds.[3] The mdr1 mRNA and its translated form p-glycoprotein are overexpressed in oral lichen planus subjects compared to healthy individuals. This overexpression is significantly higher in erosive than in reticular oral lichen planus patients, further confirming that the erosive form has higher risk for multidrug resistance. A higher expression is also observed in corticosteroid-treated erosive cases than similar untreated ones.[16]

Th1 Cytokines

IFN-γ and TNF-α were expressed by T-cells in the sub epithelial lymphocytic infiltrate in oral lichen planus. In addition, oral lichen planus lesional T cells contained mRNA for IFN-γ and TNF-α and secreted IFN γ and TNF-α in vitro. Oral lichen planus lesional T-cells did not secrete IL-4, IL-10, or TGF-β1 in vitro.[17] Of TNF-α in the serum of oral lichen planus patients. Clearly, the basis of this CD4+ Th1 cytokine bias in oral lichen planus warrants further investigation. A role for CD40 and CD80 expression and IL-12 secretion by MHC class II+ APC should be considered, as should CD154 (CD40 receptor), CD28 (CD80 receptor), and IL-12 receptor expression, by infiltrating CD4+ T-cells in oral lichen planus.[18] Th1 cytokine secretion by CD4+ T-cells in oral lichen planus may also be up-regulated by antigen stimulated CD8+ T-cells, i.e., cross-talk between CD8+ and CD4+ T-cells may further skew the CD4+ T-cell response toward a Th1 cytokine profile in oral lichen planus.

Matrix metalloproteinases

Matrix metalloproteinases (MMPs) are a family of zinc-containing endo-proteinases with at least 20 members. The principal function of MMPs is the proteolytic degradation of connective tissue matrix proteins. MMPs share biochemical properties but retain distinct substrate specificities. The gelatinases (e.g., MMP-2 and -9) cleave collagen IV, and the stromelysins (e.g., MMP-3 and -10) cleave collagen IV and laminin. MMP proteolysis is regulated by the action of endogenous inhibitors, including the tissue inhibitors of metalloproteinases (TIMPs), which form stable inactive enzyme-inhibitor complexes with MMPs or pro-MMPs. MMP-9 activity was confirmed by gelatin gel zymography. The in vitro activation rate of MMP-9 from oral lichen planus lesional T-cells was greater than that from peripheral blood T-cells of oral lichen planus patients and healthy control subjects, suggesting the presence of additional MMP-9 activators in the oral lichen planus lesional T-cell supernatants.[19] Hence, T-cells in oral lichen planus may be stimulated by TNF-α to secrete MMP-9. 1. Importantly, lesional T-cell MMP-9 (but not TIMP-1) mRNA levels and protein secretion increased following stimulation with TNF-a. MMP-9 activity was confirmed by gelatin gel zymography. The in vitro activation rate of MMP-9 from oral lichen planus lesional T-cells was greater than that from peripheral blood T-cells of oral lichen planus patients and healthy control subjects, suggesting the presence of additional MMP-9 activators in the oral lichen planus lesional T-cell supernatants.[19]

MMP9 and RECK

MMP-9, also known as gelatinase B, is an important member of MMPs family. Its main function is to degrade collagen type IV and layer adhesion proteins. For the histopathologic features of lichen planus is basement membrane element destruction, it is believe that MMP-9 may play an important role in lichen planus occurrence.[20] MMP-7 mRNA and protein overexpressed in oral lichen

planus lesional skin tissue compared with that in normal oral tissues. In addition, MMP-9 level also elevated in OLP and could be treated as biomarker for oral lichen planus diagnosis and prognosis. However, most investigations about the relationship between MMPs and lichen planus were concentrated in oral lichen planus.[20] MMP-9 and RECK protein expression in lesional skin and non-lesional skin showed negative correlation. MMP-9 and RECK expression was associated with lichen planus.[21]

Chemokine

Oral lichen planus lesional T-cells expressed mRNA for RANTES and TNF-α stimulation up-regulated oral lichen planus lesional T-cell RANTES secretion in vitro.[19] Mast cells expressed the CCR1 RANTES receptor in oral lichen planus in situ.[22] An unidentified factor in oral lichen planus lesional T-cell supernatant up-regulated human mast cell line (HMC-1) CCR1 mRNA expression in vitro.[22]

Transient Receptor Potential Vanilloid Type-1

Recently, the receptor for capsaicin, now called transient receptor potential vanilloid 1 (TRPV1), was identified and cloned. TRPV1 receptor is a member of the transient receptor potential (TRP) receptor superfamily. The local expression of non-neuronal TRPV1receptors was proven at mRNA level using quantitative real-time RTPCR. Since the number of TRPV1 receptor-positive non-neural cells is increased in inflammatory conditions, we hypothesize that TRPV1-receptor-mediated processes might play role in the pathogenesis of oral lichen planus.[23]

MicroRNAs

MicroRNAs (miRNAs) are a class of single-stranded non-coding RNAs of approximately 21–25 nt in length that repress gene expression by binding to recognition sequences located in the 3′ untranslated region of target mRNAs. The exponential increase in the number of publications related to miRNA profiling in human tumors. The increased expression of miR-146a in oral lichen planus lesions may be due to the NF-κB-related up regulation of the inflammatory cytokine TNF-α, which is involved in local immune disease and the persistent inflammation in oral lichen planus.[24] (Chen *et al*. 2017). MiR-21 expression is an independent prognostic factor indicating poor survival. Inhibiting miR-21 with antisense oligonucleotide in TSCC cell lines reduces survival and anchorage-independent growth, and induces apoptosis in TSCC cell lines. Simultaneous silencing of TPM1 with siRNA only partially recapitulates the effect of miR-21 antisense oligonucleotide.[25] MiR-21 is an independent prognostic indicator for TSCC, and may play a role in TSCC development by inhibiting cancer cell apoptosis partly via TPM1 silencing. hsa-miR-135a-5p, hsa-miR-128-3p, hsa-miR-218-5p, hsa-miR-125a-5p and hsa-let-7e-5p were the most promising biomarkers in oral lichen planus.[24] Also, miRNA-146a and miRNA-155 could be potential biomarkers for the immune-pathogenesis of oral lichen planus.[26]

p53 encodes mRNA

Recently it was shown that human p53 encodes at least nine different isoforms through alternative splicing, alternative initiation sites for translation and the use of an internal promoter: p53, p53b, p53c, D133p53, D133p53b, D133p53c, D40p53, D40p53b and D40p53c.19 In the first study of these novel p53 isoforms in SCCHN it was shown that p53 variant mRNAs were expressed in both normal oral epithelium and SCCHN. The most common of these isoforms being p53β, which was detected in the majority of samples. Of the other isoforms studied all but Dp53 could be detected in at least some samples from tumour and normal epithelium.[27] Levels of p63 isoforms were lower in oral lichen planus lesions compared with normal tissue, however, changes were not statistically significant.

Ki-67

Ki-67 is a nuclear, non-histone protein that can be found in two isoforms with molecular weights of 356 KDa and 320 KDa. The gene is located on chromosome 10 and is traceable in the nucleus of all dividing cells. It is not exclusive to neoplastic tissues; it is prevalent in any non-neoplastic area that is affected by uncontrollable proliferation.[28] The Ki-67 antibody is used to diagnose neoplastic diseases and is also utilized to predict some kinds of cancer; immunohistochemistry is the most common method used to evaluate this protein. Considering Ki-67 is a proliferation marker, the increased expression of Ki-67 in the oral lichen planus epithelium indicates a high proliferation rate in lichen planus lesions.[28]

Foxp3

Foxp3 is a member of the highly conserved for head/winged helix transcription protein family that controls the development, differentiation, maturation and function maintenance of CD4+CD25+ Tregs. Atrophic/erosive oral lichen planus lesions showed a higher proportion of Foxp3 mRNA expressing cells than that of reticular oral lichen planus lesions. It is indicated that Foxp3 mRNA expression in patients with oral lichen planus is associated with the severity and duration of the disorder.[29]

SOCS1 and SOCS3

The suppressors of cytokine signalling (SOCS) are inhibitors of cytokine signalling that function via the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway. To date, the cytokine-inducible SH2-domain-containing protein (CIS) and SOCS1-7 have been identified as members of SOCS family. SOCS3 was negatively correlated with the expression level of SOCS3 mRNA. Frequent methylation of the SOCS3 gene promoter, theoretically resulting in the increase of cytokines expression, might be associated with the etiological mechanism of oral lichen planus.[30]

VEGFR-3

The vascular endothelial growth factor (VEGF) family contains large quantities of growth factors, which directly

affect vascular endothelial cells and stimulate proliferation and chemotaxis of endothelial cells. VEGF was recognized as a primary molecule causing angiogenesis physiologically and pathologically. It is revealed VEGFR-3 expression might be involved in the pathogenesis of the oral lichen planus through increasing lymphatic vessels and lymphangiogenesis.[31]

Conclusions

The pathogenesis of oral lichen planus may involve both antigen-specific and non-specific mechanisms. Antigen-specific mechanisms in oral lichen planus include antigen presentation by basal keratinocytes and antigen- specific keratinocyte killing by CD8+ cytotoxic T-cells. Nonspecific mechanisms include mast cell degranulation and matrix metalloproteinase activation in oral lichen planus lesions. The initial event in oral lichen planus lesion formation and the factors that determine oral lichen planus susceptibility are unknown. Clearly, more work is required for a full understanding of the etiology and pathogenesis of oral lichen planus.

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Corresponding Author

Dr. Fatemeh Tavakol
Department of Oral Medicine,
Faculty of dentistry,
Tehran University of Medical Sciences,
Tehran, Iran.
Email Id: - shadi.dnt87@gmail.com