REVIEW

Pathogenesis of Oral Lichen Planus: A review

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Abstract

Oral lichen planus(OLP) is an inflammatory disease that affects the oral mucous membrane.It is mediated by T-cells and has a long term course. Several etiologies exist but the mechanism of development of oral lichen planus has always been a controversy.

This review focus to provide an insight into the ongoing concepts in oral lichen planus pathogenesis.

Relevant articles of last 20 years from Pubmed,Google scholar and Science direct were reviewed.

Specific and non-specific mechanisms together play a role in the pathogenesis of oral lichen planus that results in its distinctive histological picture.

Although there is significant progress in the research of Oral Lichen Planus there are still many aspects reagarding the immune microenvironment that remains unclear. Oral Lichen Planus is an entity included in Oral Potentially Malignant Disorders. Understanding about the pathogenesis of oral lichen planus is essential as it helps to get an idea regarding the different targets for treatment. Proper diagnosis and management is necessary as it has potential for malignant transformation.

Key words: Apoptosis, Autoimmune, CD8+T-cells, Chemokines,Oral lichen planus

Introduction

Lichen planus is a chronic immune mediated mucocutaneous disorder of the stratified squamous epithelium affecting the oral and genital mucous membranes, skin, nails and scalp.[1] It was first described by British Physician Erasmus Wilson in 1869. When oral lesions are present it is called oral lichen planus (OLP) and is found in about 53.6% of patients with cutaneous lichen planus. [2] More common in females above the age of 40 and in non-Asian countries. [3] Approximately 1-3% of the general population are affected. It is usually located bilaterally and is seen with higher frequency on the buccal mucosa. Other common sites are lateral margin of the tongue, gingiva, and lips. [4] Etiology is unknown even though multiple disease processes and agents have been thought off. [2] Most of the evidence on the pathogenesis of oral lichen planus supports the role of immunological processes, but still conflicts exist regarding the actual mechanisms behind it. [5] Main objective of this review is to highlight the current concepts in the pathogenesis of oral lichen planus after studying the last 20 years' articles.

Etiology

The etiology of oral lichen planus is not completely understood. [2] It may be due to autoimmune, genetic, psychiatric, endocrine or microcirculation disorders, agents such as viral and bacterial infections, medications, vaccinations, dental restorative materials, and even trace element deficiency.[2,5] Role of systemic diseases including hepatitis C infection, hypertension, diabetes, graft versus host disease and thyroid dysfunction have also been reported. [3] The disease gets exacerbated during psychological stress and anxiety. [2]

Clinical Presentation

In the oral cavity, the disease presents in various forms. Lesions appear as inflamed ulcerations that may have a white linear or lacy pattern or tree-like configuration called Wickham's striae. [4] The characteristic clinical presentation of OLP is almost always bilaterally symmetrical on sites like buccal

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mucosa, tongue, gums, lips, and palate. It commonly involves multiple sites but single-site involvement of gingiva and lips are also reported.[6] However, the buccal mucosa is the most common site of involvement. In the majority of cases, OLP follows a chronic course with recurrent episodes and aggravations, which may last for years. It is associated with significant morbidity, unlike cutaneous disease. OLP occurs more frequently than the cutaneous form, and it is generally more difficult to treat. 50% of OLP patients also have skin lesions. The presence of cutaneous lesions can be of great help in establishing the diagnosis of OLP in doubtful cases. [7] If there are only oral lesions and no lesions elsewhere in the body, it is called 'isolated' lichen planus.[8]

CLINICAL TYPES

OLP is broadly divided into two main categories, hyperkeratotic (usually asymptomatic) and erosive (commonly symptomatic). Hyperkeratotic forms include reticular, plaque-like, and papular. Erosive forms include atrophic, erythematous, and bullous types. The reticular type often presents as a lace-like network of slightly raised grey-white lines known as Wickham's striae.

Plaque-like forms appear as well demarcated homogenous white lesions mimicking homogenous leukoplakia, not always surrounded by striae. The papular type is a rare variant that usually present during the initial phase of the disease as white papules or dots with fine striae in the periphery. The erosive type appears as atrophic areas with central ulceration, erythema and striae. The atrophic form presents as poorly defined diffuse smooth erythematous areas with peripheral striae. Bullous type is the most unusual clinical form. It presents as blisters that grow and rupture to form ulcerations.[9]

PATHOGENESIS OF ORAL LICHEN PLANUS

Oral lichen planus is a T-cell mediated disease in which cytotoxic CD8+T-cells trigger apoptosis of basal keratinocytes of oral epithelium. Two mechanisms have been suggested in the pathogenesis, antigen specific and non-specific. In antigen specific mechanism antigen is presented by basal keratinocytes. This is followed later by antigen specific keratinocyte killing by CD8+T cells. Non-specific mechanisms include degranulation of mast cells and activation of matrix metalloproteinases that further promote migration of CD8+T-cells towards the basal keratinocytes. [10]

As a result of these mechanisms, there is increased accumulation of T-cells in the superficial lamina propria, disruption of basement membrane, intra epithelial migration of T-cells and finally apoptosis of keratinocytes in the lichen planus lesions.[10]

Two phases are involved in the development of oral lichen planus

1) Induction phase

2) Evolution phase

Induction phase includes the antigen specific mechanisms that initiate the disease. Evolution phase includes the non-specific mechanisms that results in the chronicity of the disease.

The first mechanism is the antigen specific mechanism and they play a major role in the pathogenesis of oral lichen planus.

I. INDUCTION PHASE

1. Antigen Expression

Primary event in pathogenesis is antigen expression or unmasking of antigen by basal keratinocytes. [11] The exact etiology is not known, but many kinds of stresses like drugs, virus, infections, anoxia etc are implicated. Due to these stresses certain self-peptides or heat shock proteins maintaining cell functions are over-expressed or unmasked in the basal keratinocyte. [12] Heat shock proteins or stress proteins are found in all organisms in low concentration and play a role in maintaining cell function. [13] They are the most prominent members of a family of proteins called Damage Associated Molecular Patterns (DAMPS). Hence, OLP is regarded as an autoimmune condition because of this expression of self-antigen. Keratinocytes express an antigen only at the site of the lichen planus lesion. So, the clinical distribution of the lesions depends on the distribution of lichen planus antigen. [13, 14, 15] As a rule of thumb antigens expressed by basal keratinocytes need to be recognized by the immune cells like T-cells to mediate an immune response. T-cells are of two types, helper and cytotoxic T-cells. They cannot recognize the antigen directly, instead they depend on antigen-presenting cells (APC's).

2. ANTIGEN RECOGNITION BY ANTIGEN PRESENTING CELLS (APC's)

2. a Antigen presenting cells

Antigen presenting cells are of two categories, immune and non-specific type. Immune type include dendritic cells and macrophages whereas non-specific type APC's are fibroblasts and epithelial cells (keratinocytes). Dendritic cells and keratinocytes play the role of antigen presenting cells in OLP.[11] Antigen specific activation of T-cells occurs either at the lesional site or at the regional lymph node by antigen presenting cells. [16]

2. b Antigen recognition

Toll-like receptors (TLRs) are expressed by antigen presenting cells. They are pattern recognition receptors (PRRs) that initially detect microbe-specific molecular signatures called pathogen associated molecular patterns (PAMPs) and molecules that are derived from the damaged cells themselves called damage associated molecular patterns (DAMPs). They are of two types - cell surface TLRs (TLR1, 2, 4, 5, 6, 10) and intracellular TLRs (TLR3, 7, 8, 9, 11, 12, 13). Cell surface TLRs mainly detect microbial membrane components such as lipids, lipoproteins and proteins. Intracellular TLRs detect nucleic acids derived from bacteria and viruses and also recognize self-nucleic acids in autoimmune diseases. [17] Heat Shock Proteins (S100A8/A9) are the DAMPs in OLP. Once expressed, they stimulate TLRs. [16] Stimulation of TLRs results in recruitment of TIR domain containing adaptor proteins like Myeloid differentiation primary response 88(MyD88) and TIR-domain containing adaptor inducing beta interferon(TRIF) that initiate signal transduction pathways. This further activates nuclear factor kappa beta(NF-κβ) and

mitogen activated protein kinases(MAP kinases) that regulate the expression of cytokines. [17] As a result cytokines like IFN-α, IL-1β and TNF-α are released from antigen presenting keratinocytes and dendritic cells. [16] The primary function of cytokine is to regulate inflammation.

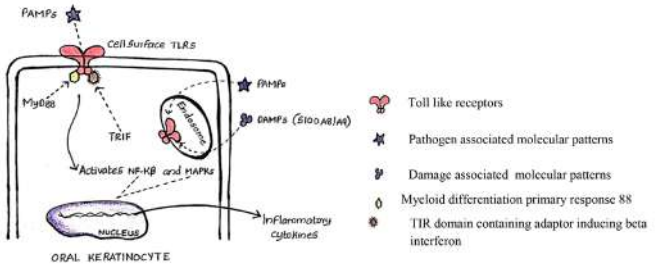


Fig. 1: Antigen expressed by the basal keratinocyte is recognized by antigen presenting cells with TLRs. Signal transduction pathways are initiated that results in the release of inflammatory cytokines.

3. ANTIGEN PRESENTATION TO T-CELLS

Once the antigens are recognized, activation of T-cells occurs by antigen presenting cells (APCs) at the lesional site as well as at the regional lymph node. [16]

3. 1 T-cell activation at the lesional site on keratinocytes

Antigen presenting cells present the antigen with major histocompatibility complex (MHC) at the lesional site for recognition by T-cells. T-cells cannot recognize an antigen unless it is presented by MHC molecules. MHC class 1 molecules are expressed on the surface of all nucleated cells and MHC class 2 molecules are selectively expressed on APC's.

There are two hypothesis that explains how T-cells encounter the antigen.

1) Chance encounter hypothesis

2) Direct migration hypothesis

One way of encounter of T-cells (mostly CD8+T-cells)with the keratinocyte antigen is by chance as a part of routine immune-surveillance in the epithelium. This is the 'Chance encounter hypothesis'. Recruitment of T-cells to the lesional site mediated by chemokines is explained by 'direct migration hypothesis'.

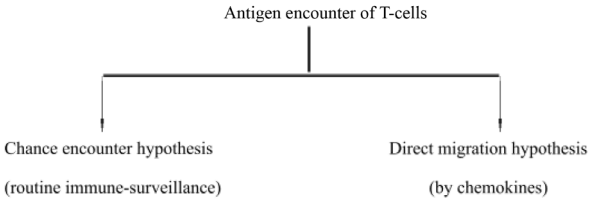


Table 1:Encounter of T-cells with the antigen

Table 1

After encounter with the antigen, CD8+T-cells recognize the antigen and are activated by two mechanisms;[16]

Direct mechanism

The antigen presenting cell with MHC Class I eg; keratinocyte present the antigen directly to CD8+T-cells and activate them.

Indirect mechanism

Antigen presenting cell with MHC class II eg; langerhan cells (dendritic cells) will indirectly activate CD8+T-cells through CD4+T-cells.

Langerhan cells with MHC Class II expression present antigens to CD4+T-cells. As a result IL-12 is produced by langerhan cells which further induces cytokine release from CD4+T-cells including IFN-γ and IL-2. This causes activation of CD8+T-cells at the lesional site. [16]

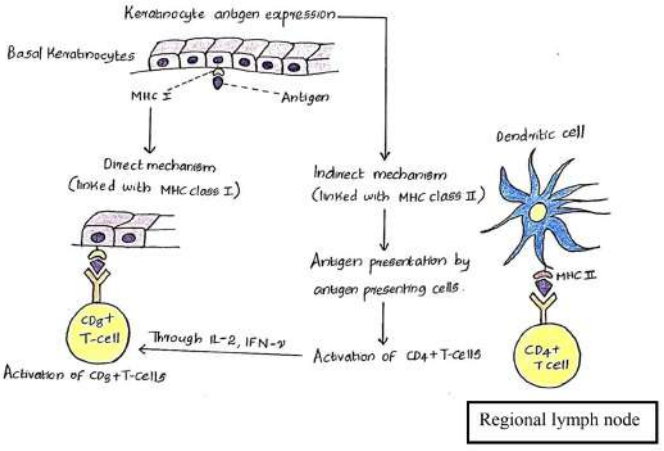


Fig. 2: Antigen presenting cells present antigen to T-cells at the lesional site on keratinocytes as well as at the regional lymph node after which T-cells gets activated.

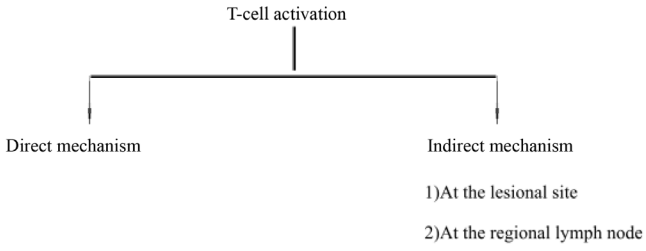


Table 2:Activation of T-cells after antigen encounter

3. 2 T-cell activation at the lymph nodes

IFN-α released by the antigen presenting cells after stimulation of TLR's activates inflammatory dentritic cells (DCs). The dendritic cells are divided into two main types, myeloid and the plasmacytoid. Myeloid type cells play the role of antigen presentation to T-cells and plasmacytoid type cells are associated with antiviral immunity. Inflammatory dendritic cells are a type of myeloid DCs. They differentiate from blood monocytes at the site of inflammation and are not present in steady state tissues. These cells migrate to the regional lymph nodes where they present the antigen to native T-lymphocytes. [16]

The dentritic cells present antigen to CD4+T-cells, and their secreted interleukin-12(IL-12) induces cytokine release from CD4+T-cells including IFN-γ and IL-2. [5] The release of IL-12 or IL-2 causes differentiation of T1 helper (CD4+T cells), T1cytotoxic (CD8+T-cells) and T17(Th17 and Tc17) lymphocytes. [16] The activated T-cells at the lymphnode enters into the blood stream.

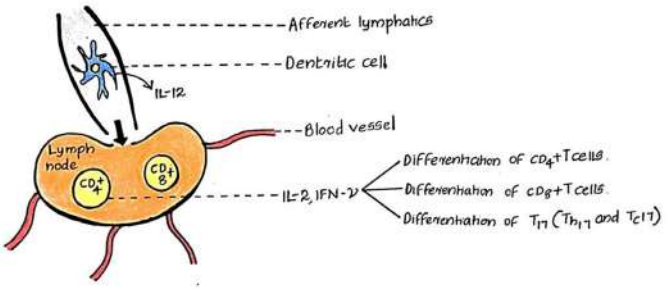


Fig. 3: Antigens are presented by dentritic cells at the regional lymph node. The activated T-cells enters the blood stream and are directed towards the lesional site on keratinocytes.

Studies showed increased aggregation of DC subsets in OLP lesions, like CD1a+/ Langerin+ (Langerhans cells), DC-SIGN+DCs, and CD123+/ BDCA2+ plasmacyte like DCs(pDCs).[16]

After entering the blood stream, T-cells are recruited to the epithelial lesional site by two different mechanisms;

1) By cytokines and adhesion molecules [18, 19]

2) Chemokine mediated self-recruiting mechanism

This migration of T-cells to the basal cell keratinocytes mediated by chemokines is explained by ***'direct migration hypothesis'.*** [6] This is another way of encounter of keratinocyte antigen by T-cells. Further activation of T-cells occur as mentioned for chance encounter.

Role of cytokines and vascular adhesion molecules in the recruitment of T-cells to the lesional site.

Resident cells like macrophages, langerhans cells and the overlying keratinocytes etc…themselves produce cytokines like TNF-α, IFN-α and IL-1β. [20] These cytokines upregulate the vascular endothelial adhesion molecules like CD62E, CD54, CD106 in the endothelial cells of subepithelial vascular plexus. This finding is supported by the fact that the lymphocytes infiltrating the basement membrane express reciprocal receptors CD11a to these vascular adhesion molecules. [21] This is referred to as ***'Cytokine-mediated lymphocyte homing mechanism'*** in the pathogenesis of OLP.

Role of chemokines in the self-recruiting process of T-cells to the lesional site(Direct migration hypothesis)

After the differentiation of T-cells at the lymph node, Type 1 CD4+, CD8+T-cells(Th1, Tc1) produces TNF-α, TNF-β, IFN-γ and IL-2. Type 2 CD4+, CD8+T-cells(Th2 and Tc2) produces IL-4, 5, 6, 10 and 13. It is now known that type 1 T-cells relatively express CCR5/CXCR3 chemokine receptors respectively. The infiltrating CD4+ and CD8+ T cells in the submucosa predominantly expressed CCR5 and CXCR3. [18]

CXCR3

It is primarily expressed on activated T lymphocytes and its specific ligands are the trio of CXC chemokines commonly inducible by the type 1 cytokine IFN-γ like interferon inducible protein-10(CXCL 10/IP-10), monokine induced by interferon-γ (CXCL9/MIG) and interferon inducible T-cell α chemoattractant (CXCL11/I-TAC)[18]

CCR5

Expressed on activated T-cells, particularly on exposure to IL-12. CCL5/RANTES (Regulated on activation, normal T-cell expressed and secreted), Macrophage inflammatory protein-1α(MIP-1α/CCL3) and MIP-1β/CCL4 are the three CC chemokines that signal via CCR5.

It was found that majority of infiltrating T-cells, particularly CD8+T-cells not only express CCR5/CXCR3 but also contain their respective ligands, RANTES/CCL5 and IP-10/CXCL10 in their cytolytic granules. These chemokine expression promote inflammatory cell recruitment. [22]

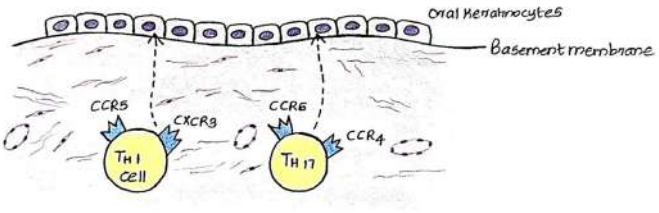


Fig. 4: Chemokines in the self-recruiting mechanism of T-cells to the lesional site on keratinocytes.

EVOLUTION PHASE

This phase gives chronicity to the disease. Cells like monocytes, macrophages and mast cells are involved. Cytokines released by these cells results in increased recruitment of T-cells to the lesional site.

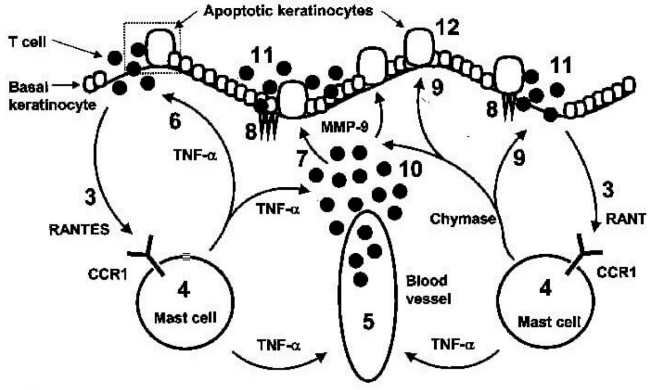
A) Role of monocytes

T helper cells(Th1)secrete cytokines like IFN-γ, IL-2 and TNF-α that recruit monocytes to the lesional areas. There they differentiate into M1 macrophages that secrete proinflammatory cytokines that upregulate the expression of adhesion molecules on endothelial cells and keratinocytes that further induce T-cell chemokine expression(RANTES). This stimulate inflammatory cell recruitment in OLP. [18]

B) Role of mast cells

Mast cells are responsible for the chronicity of the disease. They act in conjunction with T-cells in OLP pathogenesis. They are found to accumulate more in deeper areas of lamina propria, near blood vessels and areas adjacent to basement membrane disruption.[19] Activation of mast cells are by interaction with T-cells. Once activated, they degranulates and release cytokines and chemokines such as chymase, tryptase, TNF-α and

T-cell chemoattractants like IL-16, CCL4 and CCL5. According to Zhao et al, mast cell derived TNF-α upregulates T-cell adhesion and extravasation by increased expression of endothelial cell adhesion molecules and promote T-cell secretion of RANTES and matrix metalloproteinases (MMPs).[21] Mast cell derived tryptase and chymase are also potent activators of MMPs, MMP 9.[22] Mast cell derived chemokines act in conjunction with keratinocyte derived chemokines to increase the recruitment of T-cells to the lesional site.[19] RANTES causes sustained degranulation of mast cells.[23, 24, 25] This positive feed back mechanism of degranulation of mast cells and upregulation of RANTES by T-cells results in persistence of inflammation in OLP.



Courtesy:P.B. Sugerman et.al The pathogenesis of oral lichen planus:Crit Rev Oral Biol Med 13(4):350-365 (2002).

Fig. 5: Monocyte mediated upregulation of RANTES, mast cell derived tryptase and chymase that activates MMP 9 results in persistence of inflammation.

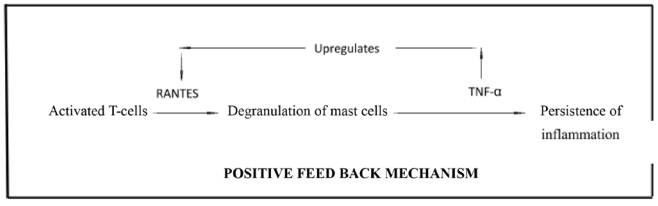


Table 3

C) Role of basement membrane disruption in OLP

A normal functioning basal cell keratinocyte maintains the integrity of basement membrane by secreting collagen 4 and laminin 5 to it. In turn the keratinocyte require basement membrane derived signal to maintain the normal living state and prevent the onset of apoptosis.[18] Matrix metalloproteinase 9(MMP 9) secreted by activated effector T-cells and degranulation products from mast cells damage the basement membrane. The increased proteolytic activity by MMPs facilitate the migration of T-lymphocytes through the extracellular matrix of lamina propria as well as through the disrupted basement membrane. These actions of MMPs result in greater access for CD8+T-cells to oral epithelium and detachment of basal keratinocyte from the basement membrane causes deprivation of normal cell survival signals to keratinocytes thereby driving apoptosis.

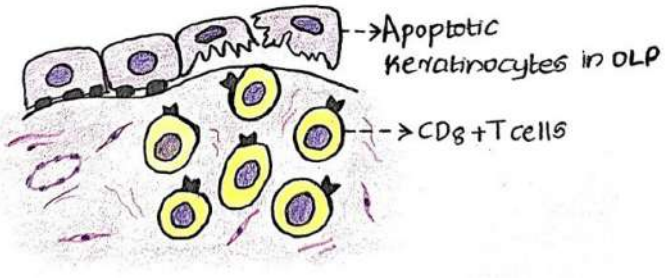


Fig. 6: Activated CD8+T-cells causes apoptosis of basal keratinocytes

MECHANISMS OF APOPTOSIS IN ORAL LICHEN PLANUS

Current evidence suggests different mechanisms by which activated CD8+T-cell induce the apoptosis of basal cell keratinocytes.

Mechanisms include;

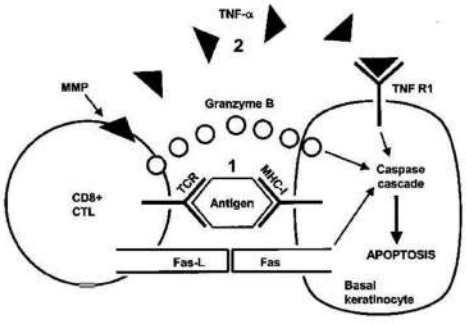
1) Interaction between CD95L(Fas L) on CD8+T-cells with CD95(Fas R) on keratinocyte cell surface resulting in activation of caspases.

2) T-cell secreted granzyme B enters the keratinocyte cytoplasm through perforin induced membrane pores.[26, 27]

Granzymes belong to the family of structurally related serine proteases stored within the cytotoxic granules of CD8+T-cells. Perforin is a pore forming protein called cytoplasmic granule toxins. Perforin facilitates the internalization of granzymes by cells. This entry of granzyme into the cell is a vital step in cell death. Granzyme B activates caspases indirectly by activating proapoptotic proteins of Bcl-2 family.[28, 29]

3)TNF-α secreted by CD8+T-cells bind to TNF receptor-1 (TNFR-1) on keratinocytes.

TNF-α is a cytokine produced by many cells like macrophages, T and B lymphocytes. Its activity is through binding of TNFR1 or 2. TNFR1 is mainly responsible for transmitting apoptotic signals and its engagement induce apoptosis through subsequent cleavage of caspase-8.[27]



Courtesy:P.B. Sugerman et.al The pathogenesis of oral lichen planus:Crit Rev Oral Biol Med 13(4):350-365 (2002).

Fig. 7: Mechanisms of apoptosis in oral lichen planus.

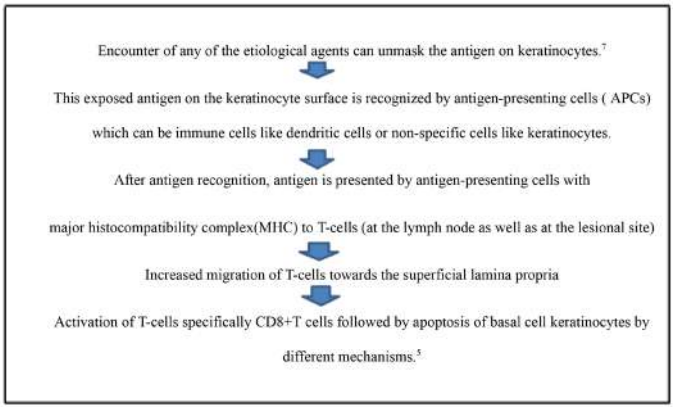


Table 4

Role of micro-RNAs

They are a group of small RNAs that regulate the expression of protein coding genes having pro-inflammatory and pro-apoptotic actions. Increased expression of mRNAs 21, 31 and 155 in the serum and saliva of OLP patients have been reported.[30]

Type II interferon response

Shao et al recently demonstrated JAK STAT dependent type II interferon response in OLP. They showed the involvement of Janus kinase 2(JAK2) and signal transducer and activator of transcription 1(STAT 1) making them therapeutic targets in the management of OLP.[31, 32, 33]

Conclusion

Lichen planus is a chronic condition affecting the skin and any lining mucosa like oral, esophageal, vaginal etc. Various etiological factors are attributed in initiating the disease. A proper diagnosis is necessary as it does carry a small risk of malignant transformation. The different concepts have been described so far in the pathogenesis of oral lichen planus but the review shows antigen-specific cytokine mediated inflammatory mechanisms play a major role.

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