International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 10; Issue 07 (C); July 2021; Page No.24835-24838
DOI: http://dx.doi.org/10.24327/ijcar.2021.4952.24838

Review Article

PATHOPHYSIOLOGY OF ORAL LICHEN PLANUS- A REVIEW

Shambhu Sharan Yadav[1] and Vaishali Hanjagi[2]

A R T I C L E I N F O

Article History:

Received 4th April, 2021
Received in revised form 25th May, 2021
Accepted 23rd June, 2021
Published online 28th July, 2021

Keywords:

Oral lichen planus, Antigen-specific, Non-specific autoimmunity, Humoral immunity.

A B S T R A C T

Oral lichen planus can be described as a non-infectious, inflammatory mucocutaneous disorder that affects both skin and mucous membrane. OLP clinically manifests as white striations, white papules, white plaques, erythema, erosions, or blisters. This condition primarily affecting the buccal mucosa, tongue and gingiva. The exact etiology of the disease is not known but it is considered that both antigen-specific and non-specific mechanisms may involve in its pathophysiology. Antigen-specific mechanisms, such as antigen presentation through basal keratinocytes or antigen-specific keratinocyte apoptosis by CD8+ cytotoxic T- cells and non-specific mechanisms such as mast cell degranulation or matrix metalloproteinase activated. In the review articles, we discuss the various mechanisms that could be involved in the pathophysiology of Oral Lichen Planus.

INTRODUCTION

Oral lichen planus can be described as a non-infectious, inflammatory mucocutaneous disorder that affects both skin and mucous membrane. The term lichen planus comes from the Greek word "leichen" which means tree moss, and the Latin word "planus", which refers to flat. Erasmus Wilson was the first to describe lichen planus, a chronic, autoimmune disease that can affect the skin, scalp, nails and mucosa with a possible rate of malignant transformation 0–2%. [1, 2, 3]

Oral lichen planus is a fairly common disease that affects between 0.5% to 2.2%.The ratio of males and females is 1 to1.4. This disease is more common in older adults, but younger children can also be affected.[4]

OLP can impact all areas of the oral cavity. The most common site is the buccal mucosa, followed by the lingual, gingival and labial mucosa. [5, 6] Bilateral symmetrical distribution of the lesions predominantly occupying posterior regions of the mouth is typical of this disease.

Oral lichen planus occurs in six clinical variants these are Reticular, Papule, Plaque-like, Bullous, Erythematous and Ulcerative. [7]

Clinically, the lesion is defined as radiating white, gray and thread-like papules. These papules can be either linear, annular or retiform and form typical lacy, irregular patches, rings and streaks on the buccal mucosa and to a lesser extent on the lips, tongue and palate.

Corresponding author:* **Shambhu Sharan Yadav

A tiny white elevated dot is frequently present at the intersection of the white lines, known as the striae of Wickham.[8]

On histopathological examination, the lesion shows hyper parakeratosis or hyper orthokeratosis with thickening of the granular layer, acanthosis with intracellular edema of the spinous cells in some instances, the development of a 'saw tooth' appearance of the rete pegs. Band-like subepithelial mononuclear infiltrate consisting of T-cells and histiocytic; increased numbers of intraepithelial T-cells; and degenerating basal keratinocytes that form colloid (Civatte, hyaline, cytoid) bodies.

Degeneration of the basal keratinocytes and disruption of the anchoring elements of the epithelial basement membrane and basal keratinocytes (e.g. hemi desmosomes, filaments, fibrils) weakens the epithelial-connective tissue interface. [8]

The etiology and pathophysiology of OLP is still unknown. However, several systemic as well as local factor, have been implicated in the etiology and several hypotheses have been proposed. The aim of this review article is to describe the various possible pathophysiology of oral lichen planus.

Pathophysiology

The exact pathophysiology of the disease is not known but it is considered that both antigen-specific and non-specific mechanisms may involve in its pathophysiology. Antigen-specific mechanisms, such as antigen presentation through basal keratinocytes or antigen-specific keratinocyte apoptosis by CD8+ cytotoxic T- cells and non-specific mechanisms such as mast cell degranulation or matrix metalloproteinase

activated. In the review articles, we discuss the various mechanisms that could be involved in the pathophysiology of Oral Lichen Planus.

1. Antigen-specific cell-mediated immune response
2. Non-specific mechanisms
3. Autoimmune response
4. Humoral immunity

Antigen-specific cell-mediated immune response

Oral lichen planus is developed by the lymphocytic infiltration (mostly activated $CD8^+$lymphocyte. Several studies have shown that activated $CD8^+$ lymphocytes trigger keratinocyte apoptosis in oral lichen planus.[9-12] But the mechanisms used by CD8+ cytotoxic T-cells to trigger keratinocyte apoptosis in OLP are still not fully known. Possible mechanisms include (i) T-cell-secreted TNF-a binding TNF-a receptor 1 (TNF R1) on the keratinocyte surface, (ii) T-cell surface CD95L (Fas ligand) binding CD95 (Fas) on the keratinocyte surface, or (iii) T-cell-secreted granzyme B entering the keratinocyte via perforin-induced membrane pores. All of these mechanisms may activate the keratinocyte caspase cascade, resulting in keratinocyte apoptosis.[13]

Non-specific Mechanisms in OLP

Epithelial basement membrane

Collagen IV and laminin V make up the epithelial basement membrane. Collagen IV and Laminin V are secreted from keratinocytes. But in the case of oral lichen planus, keratinocyte undergoes apoptosis triggered by intra-epithelial CD8+ cytotoxic lymphocytes, apoptotic keratinocytes are no longer able to secrete collagen IV and laminin V. Because of lack of collagen and laminin epithelial basement membrane is not able to maintain their cellular integrity and lead to epithelial basement membrane disruption.[14]

According to Pullan*et.al*. keratinocytes require a basement membrane-derived cell safety signal to prevent apoptosis. OLP may also be triggered by epithelial Basement membrane disruption. While it is not known which mechanism caused OLP's keratinocyte apoptosis first, either epithelial basement membrane disruption or keratinocyte basement membrane disruption.[15]

Matrix Metalloproteinases (MMPs)

MMPs are a class of zinc-containing proteinases. MMPs' primary function is to degrade collagen IV and laminin. MMP-2 and MMP-9 cleave collagen IV. MMP-3 and MMP -10 cleave both collagen IV and laminin. As we have discussed above the epithelial basement membrane is made up of collagen IV and laminin V.[13] Due to proteolytic degradation of collagen and laminin, the epithelial basement membrane is not able to maintain their cellular integrity and finally lead to epithelial basement membrane disruption which may predispose the pathophysiology of OLP.

Mast cells

TNF-α, chymase, tryptase, and other pro-inflammatory mediators are released from degranulated mast cells. TNF-α may be able to up-regulate endothelial molecule adhesion molecule (CD62E-CD54 and CD106) expression in OLP. This is important for lymphocyte adhesion onto the luminal surfaces and subsequent extravasation. T-cells might enter the OLP epithelium through basement membrane ruptures.

Zhao et.al. Carried out a study that found an increase of mast cells in OLP. About 60% were degranulated.

MMPs can be secreted as inactive enzymes and rapidly degrade after activation. MMP-9 activator Chymase is a mast-cell protease. Mast cell proteases could be directly or indirectly responsible for basement membrane disruption during OLP via activation of T-cell-secreted MMP-9. [16,17]

Chemokines

The chemokines form a superfamily with pro-inflammatory cytokines. They can be produced by nearly all somatic cells. RANTES (regulated Normal T-cells are activated. It is one of the most widely studied chemokines and plays a vital role in the recruitment of lymphocytes. The CC chemokines, including CCL5 RANTES, activate mast cell migration and degranulation.[18] Degranulation of mast cells upregulates the TNF-α which in turn up-regulates OLP lesional T-cell release of CCL5, leading again to the development of a self-perpetuating cycle, that further contributes to the chronicity of OLP.

Apart from the degranulation of mast cells, RANTES also induce PI 3-kinase. This signal transduction mechanism is responsible for both chemotaxis activation and mitogen-activated protein kinase activation.[19]

Hence, in addition to stimulating mast cell chemotaxis and degranulation, RANTES secreted by OLP lesional T-cells may also prolong the survival of inflammatory cells in OLP and thereby contribute to disease chronicity.

Autoimmune response

Breakdown of Immune Privilege in OLP

OLP's disease activity could be affected by the balance between T-cell apoptosis that is triggered by resident T-cells and keratinocyte-triggered keratinocyte apoptosis. In the case of OLP, Oral keratinocytes may fail to express enough amount of active TNF-α from the surfaces of oral keratinocytes which may result in a failure of resident keratinocytes to trigger T-cell apoptosis and infiltrating T-cells may fail to express enough amount of active TNF R1 which may result in a failure of keratinocyte apoptosis.[20]

This imbalance between keratinocyte apoptosis and T-cell apoptosis may trigger the onset of the disease.

Although the concept of insufficient keratinocyte-derived TNF-α mediated T cell lysis in OLP seems speculative, it is supported indirectly by findings that keratinocyte TNF-α expression was found in the normal oral mucosa.[21]

Deficient Antigen-specific Immunosuppression in OLP

TGF-β1 has immunosuppressive effects and it exerts its immunosuppressive effect by interfering with antigen presenting cell (APC), IL-12 production, IFN-γ secretion, and cytotoxic T-cell responses.[22]

OLP chronicity may be due to a defect in the TGF-β1 immunosuppressive pathway involving (i) insufficient numbers of TGF-β1-secreting Th3 regulatory T-cells, (ii) blockage of TGF-β1 secretion, (iii) defective or inadequate TGF-β1 receptor expression, (iv) secretion of non-functional TGF-β1, or (v) defective intracellular signaling downstream from the TGF-β1 receptors.[4] A study conducted by Khan *et.al*.

in the year 2001, found insufficient numbers of TGF-β1-secreting Th3 regulatory T-cells lymphocytes in OLP.[20]
It has been seen that the Th1 cytokine IFN-γ inhibits the immunosuppressive activity of TGF-β1 by blocking TGF-β1-induced phosphorylation of the Smad3 transcription factor.[23] Hence the balance between TGF-β1 and IFN-γ signaling may determine the level of immunological activity in OLP lesions. Local overproduction of IFN-γ by Th1 CD4+ T-cells in OLP lesions would down-regulate the immunosuppressive effect of TGF-β1 and up-regulate keratinocyte MHC class II expression and CD8+ cytotoxic T-cell activity.[4]

Keratinocyte Apoptosis and LC Maturation in OLP

Auto-reactive T-cells are responsible to develop autoimmune diseases. To stimulate T-cells response dendritic cells (DCs) and presumably Langerhans cells (LCs) must undergo a process of maturation. Maturation may be stimulated by various inflammatory mediators such as CD40L (CD154) expressed by activated T-cells, IL-1b, TNF-α, extracellular matrix degradation products, reactive oxygen intermediates, HSPs, MMP-9, mechanical trauma, Fc receptor aggregation, viral RNA, bacterial lipopolysaccharide etc. DCs and LCs endocytose apoptotic keratinocytes and migrate to the regional lymph nodes, where they present peptides derived from the apoptotic keratinocytes on MHC classes I and II molecules.

Under normal conditions, APCs (DCs and LCs) carrying self-peptides which are derived from apoptotic cells and do not receive a maturation stimulus. Therefore, do not trigger an auto-reactive T-cell response. But in the case of OLP, Antigen presenting cells endocytosis of apoptotic cells followed by maturation of dendritic cells and Langerhans cells which further activate self-reactive CD4+ T-cells that differentiate into T helper cell type 1 or T helper cell type 2 phenotypes and promote cell- or antibody-mediated autoimmune reactions against basal keratinocytes.[4]

Heat Shock Proteins in OLP

Heat shock proteins (HSPs) are present in all organisms and are released into the extracellular compartment during normal physiological conditions as well as in abnormal conditions such as oxidative stress, nutritional deficiencies, ultraviolet irradiation, and exposure to chemicals, bacterial infection, viral infection and necrosis in mammalian hosts. In the extracellular compartment, HSPs perform various functions like antigen presentation, intercellular signaling and induction of pro-inflammatory cytokines. Heat shock proteins (HSP70) are capable to induce cytotoxic T-lymphocyte response. A reaction of cytotoxic T-lymphocytes to the stressed basal cell keratinocytes may then result in tissue damage which is characteristic of OLP lesions. A study conducted by Sugeman*et.al*. in 1995, they found up-regulated HSPs in oral mucosal keratinocytes in OLP patients.[24]

Humoral immunity

Apart from cell-mediated immune response, it is considered that humoral immune response also has some role in the pathophysiology of OLP. Presences of circulating autoantibody against desmogleins 1 and 3 indicate the role of humoral immune response in the pathophysiology of OLP. But the exact role of such auto-antibody remains uncertain.[25]

CONCLUSION

Oral lichen planus is the most common mucocutaneous disease encountered by the oral physician in routine dental practice. The best treatment is possible only if the oral physician or dental practitioners have a clear understanding of the lesion's pathophysiology. OLP's pathophysiology remains a mystery. Non-specific and antigen-specific mechanisms are currently being investigated. For a complete understanding of OLP's pathophysiology and etiology, it is evident that there needs to be more work.

Financial support and Sponsorship

Nil

Conflicts of Interest

There are no conflicts of interest.

References

1. Farhi D, Dupin N. Pathophysiology, etiologic factors, and clinical management of oral lichen planus, part I: facts and controversies. Clin Dermatol. 2010;28:100–108.
2. Parashar P. Oral lichen planus. Otolaryngol Clin North Am. 2011;44:89–107.
3. Ismail SB, Kumar SKS, Zain RB. Oral lichen planus and Lichenoid reactions; etiopathophysiology, diagnosis, management and malignant transformation. J Oral Sci.2007; 49: 89–106.
4. Sugerman PB, Savage NW, Walsh LJ. *et al*. The pathophysiology of oral lichen planus. Crit Rev Oral Biol Med. 2002;13:350-65.
5. Dalirsani Z, Delavarian Z, Javadzade-Bolouri A.*et al*. Psychiatric comorbidity and pharmacotherapy in patients with oral lichen planus. In: Uehara T, ed. Psychiatric disorders worldwide advances. Rijeka: InTech; 2011:223-42.
6. Bagan JV, Eisen D, Scully C. The diagnosis and management of oral lichen planus: a consensus approach. Oral Biosci Med. 2004;1:21-7.
7. Glick M. Burket's Oral Medicine. 12e. Shelton: PMPH-USA; 2015.
8. Rajendran R. Cyst and tumors of odontogenic origin. In: Rajendran R, Sivapathasundharam B, editors. Shafer's Text Book of Oral Pathology. 7th ed. Noida: Elsevier; 2012.
9. Matthews JB, Scully CM, Potts AJ. Oral lichen planus: an immunoperoxidase study using monoclonal antibodies to lymphocyte subsets. Br J Dermatol.1984;111:587-595.
10. Kilpi AM. Activation marker analysis of mononuclear cell infiltrates of oral lichen planus in situ. Scand J Dent Res;1987; 95:174-180.
11. Kilpi AM. Characterization of mononuclear cells of inflammatory infiltrates in oral tissues. A histochemical and immunohistochemical study of labial salivary glands in Sjögren's syndrome and of oral lesions in systemic lupus erythematosus and in lichen planus. Proc Finn Dent Soc.1988; 84:5-93.
12. Jungell P, Konttinen YT, Nortamo P.*et.al*. Immunoelectron microscopic study of distribution of T cell subsets in oral lichen planus. Scand J Dent Res.1989; 97:361-367.
13. Sugerman PB, Savage NW, Zhou X.*et.al*. Oral lichen planus. Clin Dermatol. 2000;18:533-539.

14. Marinkovich MP, Keene DR, Rimberg CS.*et.al*. Cellular origin of the dermal-epidermal basement membrane. Dev Dyn. 1993; 197:255-267.
15. Pullan S, Wilson J, Metcalfe A.*et al*. Requirement of basement membrane for the suppression of programmed cell death in mammary epithelium. *J Cell Sci*. 1996;109:631-642.
16. Zhao ZZ, Sugerman PB, Zhou XJ.*et.al*. Mast cell degranulation and the role of T cell RANTES in oral lichen planus. 2001;Oral Dis 7:246-251.
17. Zhou XJ, Sugerman PB, Savage NW.*et.al*. Matrix metalloproteinases and their inhibitors in oral lichen planus. J Cutan Pathol.2001; 28:72-82.
18. Bischoff SC, Krieger M, Brunner T.*et al*. RANTES and related chemokines activate human granulocytes through different G protein-coupled receptors. *Eur J Immunol*.1993;23:761-767.
19. Kane LP, Shapiro VS, Stokoe D.*et.al*. Induction of NFkappaB by the Akt/PKB kinase. Curr Biol.1999; 9:601-604.
20. Khan A, Farah CS, Savage NW.*et.al*. Th1 cytokines in oral lichen planus. *J Oral Pathol Med*. 2003 Feb;32(2):77-83.21.
21. Kristensen M, Chu CQ, Eedy DJ.*et.al*. Localization of tumour necrosis factoralpha (TNF-alpha) and its receptors in normal and psoriatic skin: epidermal cells express the 55-kD but not the 75-kD TNF receptor. Clin Exp Immunol.1993; 94:354-362.
22. Letterio JJ, Roberts AB. Regulation of immune responses by TGF-b. Annu Rev Immunol. 1998; 16:137-161.
23. Ulloa L, Doody J, Massagué J. Inhibition of transforming growth factor-beta/SMAD signalling by the interferongamma/ STAT pathway. Nature.1999;397:710-713.
24. Sugerman PB, Savage NW, Xu LJ.*et.al*. Heat shock protein expression in oral lichen planus. *J Oral Pathol Med*.1995;24:1-8.
25. Lukac J, Brozović S, Vucicević-Boras V.*et.al*. Serum autoantibodies to desmogleins 1 and 3 in patients with oral lichen planus. *Croat Med J.* 2006;47 (1):53-58.

How to cite this article:

Shambhu Sharan Yadav and Vaishali Hanjagi (2021) 'Pathophysiology of Oral Lichen Planus- A Review ', *International Journal of Current Advanced Research,* 10(07), pp. 24835-24838.
DOI: http://dx.doi.org/10.24327/ijcar.2021.4952.24838

****