REVIEW ARTICLE

ISSN: 2456-8090 (online)
International Healthcare Research Journal 2017;1(5):3-6.
DOI: 10.26440/ihrj/01_05/100

QR CODE

Comprehensive Pathogenesis of Oral Lichen Planus: A Review

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ABSTRACT

Oral lichen planus is a chronic inflammatory disease of oral mucosa, which is autoimmune in nature and mediated by CD+8 T-cells. How these CD+8 T-cells bring about keratinocytes apoptosis and various processes occurring simultaneously result in the chronicity of the disease is always a point of discussion. This paper comprehends the various mechanisms of the complicated pathogenesis of OLP making simple to understand and helping in therapeutic approach.

KEYWORDS: Lichen Planus, Pathogenesis, Antigen-specific, Non-specific mechanism

INTRODUCTION

Lichen Planus, discovered by Erasmus Wilson in 1869[1], is a chronic muco-cutaneous disease primarily occurring due to an auto-immune mechanism. Lichen planus, in general can affect skin, genitals, nails, eyes and oral cavity. Commonly the prevalence of oral lichen planus has been seen 0.5-2% in population.[2]

There are various mechanisms to define the pathogenesis of oral lichen planus but the broader aspect of it lies in the T-cell mediated delayed Type-4 hypersensitivity reaction, which is antigen specific.[3] Pathogenesis of oral lichen planus is very elusive for researchers and clinicians, to clearly explain how several factors interact and are responsible for initiation, aggravation, and chronicity of oral lichen planus.

PATHOGENESIS

Histopathological presentation of Civatte bodies in oral lichen planus which are degenerated basal keratinocytes proves that all the pathogenesis lies in the epithelial basement membrane breaking and disruption of anchorage.[4]

This process of destruction of epithelial basement membrane is accomplished by two types of mechanisms:-
a) Antigen-specific mechanism
b) Non-specific mechanism

ANTIGEN-SPECIFIC MECHANISM (Figure 1)

The first step, in this mechanism are biochemical variations resulting in the change of keratinocyte antigen expression.[5] This altered antigen is attached to MHC class 1, which in turn is recognized by CD8+ T-cells during routine surveillance, "Chance encounter"[6,7] or by migration caused by chemokines released from keratinocytes, "Direct Migration".[8]

When T-cells encounter keratinocytes, they secrete TNF-α and CD95L (Fas Ligand) which binds to TNF-α receptor and CD95 (Fas) respectively present on keratinocyte surface, all these mechanisms, in turn, activates caspase cascade, which results in apoptosis of keratinocyte.[9]

Apart from CD8+ cytotoxic T-cells, the role of CD4+ T-cells which were non-cytotoxic was also evident.[10] These CD4+ T-cells play role in the pathogenesis by giving confirmation of antigen to CD8+ T-cells prior to cell lysis. This confirmation is initiated by hypothetical request cytokine activity (RCA) molecule when CD4+ T-cells receive antigen linked with MHC class II.[11]

When the bond between RCA and its receptor (which is present on CD8+ T-cell surface) is achieved, MHC class II initiates differentiation of Th1 cytokine of CD4+ T-cells along with some

stimulatory signals (e.g. CD40, CD80, IL-12) resulting in secretion of IL-2 and IFN-γ. These all signals are received by CD8+Tcells and initiate its cytotoxic activity.[12]

NON- SPECIFIC MECHANISM

Various non-specific mechanisms also take place in OLP lesion, where cytotoxic T-cells are not activated because of some antigen. Such mechanisms are also responsible for the virtuous cycle and chronic nature of the lesion. Following are the mechanisms:-

The Epithelial Basement membrane:
Keratinocytes secretes collagen type IV and laminin V in the basement membrane which maintains its integrity.[13] On the contrary, keratinocytes also require some signals from basement membrane to prevent apoptosis.[14] Apoptotic death of keratinocytes by cytotoxic T-cells breaks this vicious cycle and contributes to the chronicity of the condition.

Matrix Metalloproteinases:
Matrix-metalloproteinases (MMPs) are zinc-containing proteinases which degrade the proteins of connective tissue. MMP 2,3,9 and 10 have specificity for collagen IV and laminin V. These MMPs were identified in epithelial basement membrane disruption.[15] In oral lichen planus, cytotoxic T-cells stimulate TNF-α which secretes Matrix metalloproteinases primarily, MMP-9 which disrupts the epithelial basement membrane.[11]

Mast cells degranulation:
Studies have shown that mast cell degranulation in OLP is 60% as compared to normal mucosa which is 20%.[16] Various pro-inflammatory mediators such as TNF-α, chymase and tryptase are released on mast cell degranulations. These pro-inflammatory mediators upregulate adhesion molecule of endothelial cells (CD62E, CD54 andCD106) which is required for adhering lymphocytes to the lumen of blood vessels and subsequent ejection.[9,11,17]

Chemokines:
The Chemokines are superfamily members of pro-inflammatory cytokines. RANTES (regulated on activation, normal T-cell expressed and secreted) is one of the chemokine of CC family which activates T-lymphocytes, monocytes, mast cells etc. T-cells in OLP lesion express mRNA for RANTES and on stimulation by TNF-α they secrete them.[18] Mast cells possess receptors for RANTES in OLP in situ.[19]

RANTES after contacting its receptors on mast cells causes mast cell degranulations and releases TNF-α, which further upregulate T-cells in OLP lesion for RANTES secretion and this reciprocating process creates a vicious cycle and is responsible for the chronicity of the diseases.

CONCLUSION

Oral lichen planus due to its chronic and auto-immune nature is difficult to treat. Having knowledge of the pathogenesis of the disease and what all chemical mediators are involved will definitely help in therapeutic intervention and advancement.

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Source of support: Nil, **Conflict of interest:** None declared

Cite this article as:
Ahuja US, Yadav A, Singh K, Dixit C. Comprehensive Pathogenesis of Oral Lichen Planus: A Review. Int Healthcare Res J 2017;1(5):3-6.

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LEGENDS

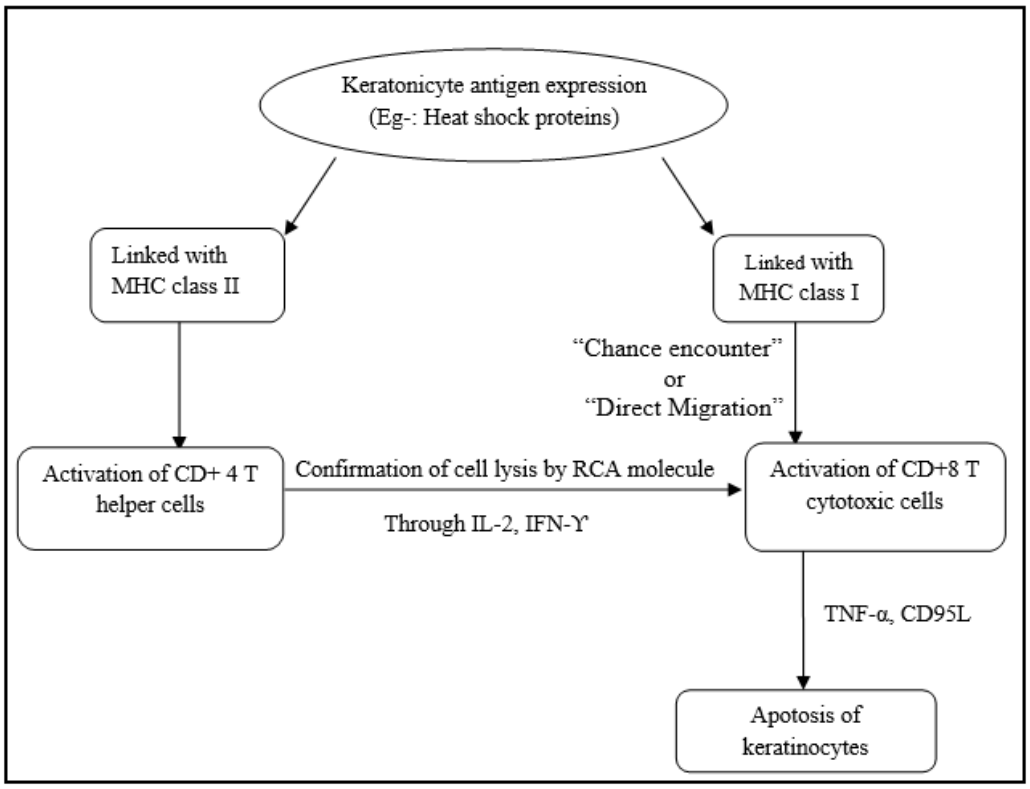

Figure 1. Antigen specific mechanism