

Review Article

Antigen presenting cells and its role in Periodontal Disease

Malathi K¹, Hemalatha J², Jenapriya R³, Annapoorani S⁴

Malathi K, Hemalatha J, Jenapriya R, Annapoorani S. **Antigen presenting cells and its role in Periodontal Disease.** J Periodontal Med Clin Pract. 2016;03: 141-146

Affiliation

- 1) Dr.K.Malathi ,MDS, Professor and Head Department of periodontics, Tamilnadu Government Dental college and Hospital
- 2) Dr. Hemalatha.J I year Postgraduate student, Department of periodontics, Tamilnadu Government Dental college and Hospital.
- 3) Dr . Jenapriya .R II year Postgraduate student, Department of periodontics, Tamilnadu Government Dental College and Hospital.
- 4) Dr S. Annapoorani III year Postgraduate student, Department of periodontics Tamilnadu Government Dental College and Hospital.

Corresponding author: Dr K.Malathi.

Email ID : malsmoni@gmail.com ,jenapriyar@gmail.com

Abstract

Periodontitis is considered to be a multifactorial disease with polymicrobial pathogenesis. Immune mechanism that prevents bacterial products from causing damage to the tissues will maintain the health of periodontal structures. Innate and adaptive response are the two types of immune response. Innate immune response is of nonspecific and the latter is of specific (adaptive) to particular microorganisms and takes over in the second phase, an orderly sequence of events. Antigen Presenting Cells are specialized cells to initiate or promote the development of lymphocytic activation. (It is also termed as professional APC) The immune system primarily contains three types of APC's namely Dendritic cells, Macrophages and B lymphocytes. As it is a vital component of immune mechanism, understanding the role of APC should be highlighted. This review summarizes the overview of APC and their role in periodontitis.

Key Words: Antigen Presenting Cells, B-lymphocytes, Dendritic cells, Macrophages,

Periodontal diseases.

Introduction

Periodontal diseases are the heterogeneous group of pathologies involving the complex interplay of various host and microbial factors. Periodontal bacteria and their by-products modify the body's immune response and in turn may increase the incidence and severity of periodontal disease. The complex immune mechanism including innate and adoptive system interfere in the development and progression of periodontal diseases.¹ Self and non-self discrimination is the basic function of the immune system. The innate immune response acts as the first line of defence and defends the body against the invading microorganisms through natural mechanism.² The adaptive/ acquired immune response requires time to respond and acts as a second line of defence. The innate immune response is mediated by influencing cytokines and chemokines and adaptive immune response is mediated by antigen specific response by T cells and B cells. The clinical expression of periodontal

disease can be either a stable lesion or the progressive one and the stable response is mediated by Th1 and dominated by the presence of T cell. The progressive lesion is dominated by B cells through the Th2 response.

Antigen Presenting Cells are specialised cells where the antigens are displayed on the surface and lymphocytic stimulation is achieved via this antigen. This in turn neutralizes the toxins produced by microorganism. Dendritic cells, macrophages and B – lymphocytes are the three types of Antigen Presenting Cells and are specialized to initiate or promote the development of lymphocyte activation. Antigen Presenting Cells express major histocompatibility(MHC) molecules for effective antigens uptake and costimulatory molecule that promote cellular interaction.

DENDRITIC CELLS

They are the cells of the immune system that are important in inflammation and host defence. They represent a large family of Antigen Presenting Cells that circulate through the blood stream and are scattered in all the tissues of the body. This leukocyte lineage cell plays a central role in the initiation of adaptive immune response. Lymphoid dendritic cells were described in 1993 by Steinman and Cohn. T lymphocytes do not recognize the antigen by itself. It needs the help of Antigen Presenting Cells.

Langerhans cells, interstitial cells, (dermal dendritic cells) and lymphoid or plasmacytoid dendritic cells are the three major dendritic cell subsets in the peripheral tissue of humans. They are myeloid lineage cells. Interstitial Dendritic cells are present in the dermis and interstitial space of all solid organs of the body such as kidney, lung and heart. Lymphoid dendritic cells

are predominantly identified in blood and langerhans cells are the major Antigen Presenting Cells in the epidermis. These cells are specialized to initiate and promote the development of lymphocyte activation are also termed as “Professional APC”. They express major histocompatibility complex molecule along with other mechanisms for effective antigen uptake and expression of costimulatory molecules that promote cellular interaction.

Dendritic cells are one of the cellular elements present in innate immune system and they are equipped with various receptors. Dendritic cells first activate T cells which in turn stimulate the B cells and they are more potent in initiating the primary and secondary T cell response. The follicular dendritic cells stimulate the memory B cells leading to stimulation of further T cell activity. Myeloid dendritic cell tends to favour a Th1 type response and have been called dendritic cell I. Precursors of plasmacytoid dendritic cells tend to favour Th2 response and were called Plasmacytoid dendritic cells II.

Lymphoid dendritic cells are isolated from secondary lymphoid tissues such as spleen, lymph nodes and peyer's patch and are potent stimulators of immune response invitro.³ The mature dendritic cells reach the paracortical areas of secondary lymph nodes via afferent lymph and to the white pulp of the spleen via blood. These areas are rich in T cells. For the T cells to take up antigen, the dendritic cells and the T cells should be encoded by the same MHC.

CD4 T cells bear MHC class II molecules and CD8 T cells bear MHC class I molecules. Optimal alteration of T cell by APC requires two major signals. They are Specific Antigen Recognition and Co stimulation.

SIGNAL I---AN APC STIMULATION

The elicitation of signal I implies that the microbes had been captured and processed by the AP. But in general, very little is known about the ability of the dendritic cells / Langerhans's cells to capture and process oral pathogens such as Porphyromonas gingivalis.

SIGNAL II ---AN APC STIMULATION - COSTIMULATION

Mature dendritic cells express a diverse array of accessory or costimulatory molecules. They play a cooperative role in activating T cells and in effective antigen presentation. Resting T cells are cells that never encountered the antigen before. They receive additional signal i.e. co stimulatory signals. Mature dendritic cells express a diverse array of costimulatory molecules and these molecules are upregulated in response to pathogen associated molecular pattern and inflammatory cytokines. If the T cell receptor signal is very strong, T cell activation might occur in the absence of signal II. Expression of B7.1 (CD80) and B7.2(CD80) by the mature dendritic cells provides an essential signal for activation of resting T cells. Expression of OB7 is also essential for induction of cytolytic activity by natural killer cells that has been implicated in the pathogenesis by periodontitis.

The adhesion molecule ICAM-1, 2 and 3 also serve as costimulatory molecule on mature dendritic cells. ICAMs are ligands for LFA 1 on T cells. ICAM-LFA-1 interaction facilitates receptor mediated signalling as well as co stimulation. Leukocyte Function Antigen-3 expressed to a higher degree in oral lichen planus than healthy mucosa. It is highly expressed in peripheral blood and lung

dendritic cells.

DENDRITIC CELLS IN AUTOIMMUNE DISEASES

They have been implicated in the immunopathology of autoimmune diseases,⁴ in graft vs host disease, contact dermatitis,⁵ chronic periodontitis⁶ and psoriasis. The very traits of dendritic cells that enable them to break tolerance of the immune system towards chronic infections and tumour antigen, also make these cells a point of potential host vulnerability.⁷ CD40 cells of the diseased periodontium other than mature dendritic cells such as fibroblast might be able to express CD40. Porphyromonas gingivalis and its lipopolysaccharides are potent activators of CD40 expression on dendritic cells. The number of dendritic cells in the gingiva is low when compared with non-keratinized oral mucosal tissues. In health, the oral biofilm comprised of gram positive bacteria and as the disease progresses the biofilm changes to a predominantly gram negative subgingival flora. According to Mougil et al in 1992 Dendritic cells number gradually increased and peaked on day 7, remained high until day 14 and decreases by day 21 as inflammation is developed. Dendritic cells infiltrate in gingival epithelium in gingivitis and then efflux into lamina propria where they undergo maturation. As the age increases Dendritic cells are significantly reduced compared young ones and there is an alteration in morphology of Dendritic cells suggesting the prevalence of periodontitis increases with age.⁸ This observation strongly suggests the role of dendritic cells in periodontitis. Human peripheral blood monocyte derived dendritic

cells can transdifferentiate into osteoclast in the presence of macrophage colony stimulating factor and RANKL in vitro, suggesting its role in osteoclastogenesis.

B CELLS AND MACROPHAGES

B cells are an essential component of the adaptive Immune system and play large role in the humoral immune response⁹ The principle function of B cells is to make antibodies against antigen, perform the role of APC and eventually develop into memory B cells after activated by antigen interaction. B cells participate in several other aspects of the host response and contribute to the activation of the immune system. B cell exhibit important immunoregulatory function, which include direct and indirect effect of other cells through Antigen Presenting Cells and production of cytokines. Plasma B cells, Memory B cells, B1 cells and B2 cells are different types of B cells. Severe form of periodontitis leading to early and considerable amount of bone loss and tooth mortality appear in 8 – 10% of adults. The response to a subgingival microbial biofilm results in inflammatory process in the periodontal tissue that mediates destruction of connective tissue attachment and alveolar bone. Plasma cells appear to be dominant cell type together with lymphocytes they represent 75-80% of all inflammatory cells. It was reported that plasma cell represents above 50% of cells in these lesions while B cells comprise about 18%. B cells serve as a well- controlled part of the adaptive host response and act on systemic regulation by T cells. Host defence mechanisms of B cells includes the transformation into plasma cells and the production of immunoglobulins that identify

and bind to antigens. The proportion of B cell is larger than that of T cells. T helper cells occur in larger number than T cytotoxic cells. Polymorphonuclear leukocyte and macrophages are found in fractions of less than 5% of all cells. With respect to cellular composition, lesions in aggressive and chronic form of periodontitis exhibit the similar feature.

Differences in disease severity, however may affect plasma cells and B cells densities in both forms of periodontitis. Thus, the proportion of plasma cells and B cells appear to be larger in lesion obtained from sites of severe periodontitis than in lesion from areas with mild to moderate periodontitis. Autoimmune reactions are involved in periodontitis and reveal that collagen type I was one of the main evaluated autoantigens. Higher levels of antibodies to collagen type I were found in the peripheral blood of patients with periodontitis than in healthy controls.

Hirschfield et al reported that the levels of anticollagen antibodies as well as numbers of anticollagen producing cells in peripheral blood were low in periodontitis subjects. Analyses made on gingival cells from periodontitis patients revealed numerous cells producing specific antibodies to type I collagen. The levels of antibodies to collagen type I was reported to be higher in gingival tissues and both IgG and IgA were found in higher concentration. B – cells following activation of T cells, undergo class switching and somatic mutation which result in a change from the production of low affinity autoantibodies to IgG autoantibodies with high affinity (VIHO V.J). CPG (Cytosine –

Phosphate -Guanine) microbial DNA reload during infection may exacerbate autoimmunity by stimulating autoreactive B cell to switch from IgM to a more pathogenic IgG isotype independent from T cells . Higher levels of antibodies to collagen type I were found in peripheral blood of patients with periodontitis than in healthy controls. Tissue destruction is one of the hallmark of periodontitis. B cells appears to contribute to the degradation of connective tissue structure in periodontitis and this will dominate in periodontitis lesions. The ability of B cell to express class II antigen and contribute to antigen presentation has been demonstrated in periodontitis. The different roles of B cells in periodontitis require further elucidation for understanding the mechanism involved in initiation and progression of the disease. B cells are the least efficient APC and present antigen via MHC II. They possess surface immunoglobulin – a specific antigen receptors.

Macrophage develop from blood monocyte, emigrate into tissues from blood. They are triggered to develop as cytokines and the activated macrophages release a product that has protective as well as destructive functions.¹⁰ Macrophages perform the functions of APC only in the presence of infection, they have receptors for specific bacterial product such as lipopolysaccharides (LPS). When lipopolysaccharides bind to their bacterial ligands, they stimulate the macrophage to upregulate MHC-II and B7. This provides strong antigen presentation properties. From subcapsular sinus the antigen enters the medullary cords of lymph nodes where it encounters medullary macrophages

and lymphatic endothelium. Macrophage migrates into follicles in response to endotoxin and stimulate B- cell response.

Macrophage do not increase in numbers and there is little evidence of its activation in advanced periodontitis compared to minimally inflamed tissues. In the progression from gingivitis to periodontitis, there is decrease in the macrophage / B cell ratio and B cell express an increasingly activated phenotype. In APC DCs induce both native and secondary immune responses, but macrophages and B cells initiate secondary responses after the induction of MHC class II molecules by interferon. The secondary immune response, that occur in gingival tissue may depend on type of APC.

CONCLUSION

In this review, a brief introduction of periodontal disease, focus on the important participation of Antigen Presenting Cells was made. The complex immune mechanism, including innate and adoptive system, production of the specific antibody response by APC was described. The DCs plays the central role in the immune response. In the immune cascade, role of DCs and its interaction with cytokines is an important component. The detailed understanding of APC is essential to fill many gaps in understanding and utilizing the knowledge that will help in developing the therapeutic strategies for various inflammatory and autoimmune diseases.

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Competing interest / Conflict of interest The author(s) have no competing interests for financial support, publication of this research, patents and royalties through this collaborative research. All authors were equally involved in discussed research work. There is no financial conflict with the subject matter discussed in the manuscript.

Source of support: NIL

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