

International Journal of Scientific Research and Reviews

Dendritic Cells: Immune Regulators in Periodontal Health and Disease

Malathi^{*1}, Prem Blaisie Rajula², Jeeva Rekha³

¹HOD Department of Periodontics, TNGDC & Hospital, Chennai, Tamilnadu, India

²Post Graduate Student, Department of Periodontics, TNGDC & Hospital, Chennai, Tamilnadu, India

³Assistant Professor, Department of Periodontics, TNGDC & Hospital, Chennai, Tamilnadu, India

ABSTRACT:

The periodontal disease is an inflammatory disease involving the complex interplay between various host and microbial factors. The transition of the immune response from innate to acquired immunity requires the production of specific antibody response. The dendritic cells bridge (DCs) this transition. Dendritic cells are one of the cellular elements present in innate immune system that are equipped with various receptors enabling them to identify various oral invaders via PAMPs (Pathogen associated molecular patterns). The adaptive immunity takes place parallel to innate immunity because the activity of innate immunity is limited in its specificity to the pathogens. Since adaptive immunity is initiated and regulated by dendritic cells, these cells play an important role in periodontitis. Here we provide an overview of dendritic cell origin, subsets, their distribution and their role in periodontitis.

KEYWORDS: dendritic cells; immune system; periodontitis; T-cells

***Corresponding author:**

Dr.K.Malathi, MDS
HOD, Department of Periodontics,
Tamilnadu Government Dental College & Hospital,
Chennai, Tamilnadu, India.
E-Mail: malsmoni@gmail.com
Mobile: +9194444040620

INTRODUCTION

Periodontal diseases are caused by bacterially derived factors and antigens that stimulate a local inflammatory reaction and activation of the innate immune system¹. Although the periodontal pathogens are required for disease initiation, they are not sufficient to cause periodontitis². The host immune response plays a central role in the destruction of periodontal tissues³.

Pathogens in the periodontal environment are monitored by the innate immune system; the first line of defense against invading pathogens⁴. The innate immune system includes epithelial barrier, secretory substances and cellular elements. Dendritic cells are one of the cellular elements present in innate immune system and they are equipped with various receptors enabling them to identify various oral invaders via PAMPs. Toll-like receptor comes under the receptors with the capability to bind several bacterial and viral molecules⁵. After the receptor triggering, the cells are activated and act in concert to induce local inflammation that eliminates the pathogen.

The adaptive immunity takes place parallel to innate immunity because the activity of innate immune cells are limited in its specificity to the pathogens. T and B lymphocytes are adaptive immune cells and they efficiently mediate pathogens clearance along with lasting immunological memory. Thus adaptive immunity plays a major role in the pathogenesis of periodontitis. Since adaptive immunity is initiated and regulated by dendritic cells, these cells represent the bridge between both immune systems⁶. Thus dendritic cells play an important role in periodontitis.

HISTORICAL PERSPECTIVE

The term “Dendritic cell” which now refers to a family of antigen-presenting cells was coined in 1973 by Ralph Steinman and Zanvil Cohn, in a description of an adherent nucleated cell from mouse spleen⁷. Steinman’s group isolated these cells to a higher degree of purity⁸ and demonstrated their unique capacity to initiate T-cell immune responses⁹. Dendritic cells relative to other immune cells make up only 0.1%-2% of human gingiva. . Dendritic cells have long finger –like processes which is similar to the dendrites of nerve cells¹⁰.

DENDRITIC CELLS ORIGIN AND THEIR SUBSETS

Dendritic cells represent a family of antigen presenting cells that circulate through the blood stream and are scattered in nearly all the tissues of body. They are distributed in both lymphoid and non lymphoid tissues¹¹. In humans, DCs are found as precursors in the bone marrow and blood whereas as more mature forms in lymphoid and non lymphoid tissues. DCs first originate from CD34 bone marrow

stem cells. In the blood, DCs are virtually indistinguishable from monocytes but in the skin or mucosa they assume a more stellate morphology. Immature DCs are called as ‘veiled cells’ because they have large cytoplasmic veils rather than displaying dendrites.

Currently dendritic cells comprise of 4 distinct subpopulations, three within the myeloid lineage (Langerhans cells, interstitial dendritic cells and myeloid dendritic cells) and one within the lymphoid lineage (Plasmacytoid dendritic cells). Another type of dendritic cell, the follicular dendritic cell does not arise in bone marrow. These dendritic cells were named for their exclusive location in organized structures of the lymph node called lymph follicles, which are rich in B cells.

From the bone marrow the precursor DCs are then seeded via the bloodstream to the tissues where they give rise to immature DCs that include Langerhans cells (LCs) and interstitial DCs¹². The various DC subsets can be identified by their anatomic location, function and expression of distinct phenotypic markers. As dendritic cells lack lineage specific markers such as CD3, CD14, CD19, CD11b, CD56 and express high levels of MHC class II molecules the phenotypic definition of dendritic cells is HLA-DR+ cells¹³.

Table No.1: Human dendritic cells in the body and phenotypic expression

Dendritic cell	Marker expression
BLOOD	
Myeloid DC	CD11c, CD1a, CD14 ⁺ , CD1c/BDCA-1, DC-SIGN
Plasmacytoid/Lymphoid	CD11c ⁻ , CD123, BDCA-2, BDCA-4, DC-SIGN
PERIPHERAL TISSUES	
Langerhans cells	CD1a, Langerin/Lag, CCR6, E-cadherin, CD621, DEC-205, intra MHCII (HLA-DR), CLA
Interstitial DC	CD80, CD83, CD86, CCR7, CD11a, CLA surface, MHCII
LYMPH TISSUES	
Veiled cells	DC-Lamp, DEC-205, CD80, CD83, CCR7
SECONDARY LYMPHOID ORGANS	
Interdigitating DC	DC-Lamp, DEC205, CD80, CD83, CD86, CCR7, DCIR, surface MHCII
GERMINAL CENTRE DC	
	CD2, CD4, CD11C, CD35, CD45RO, CD64

Abbreviations: BDCA-Blood dendritic cell antigen, DC-SIGN-Dendritic cell specific ICAM-3 grabbing non-integrin, CCR-6/7-C-Chemokine receptor, CLA-Cutaneous lymphocyte antigen, DC-LAMP-Dendritic cell lysosomal associated membrane protein., intra MHC II-intracellular MHC ClassII, MMR-macrophage mannose receptor, MHC-Major histocompatibility complex

Functionally the monocytic precursors of myeloid dendritic cells tend to favor a Th1 type response and have been called ‘dendritic cell 1’. Precursors of plasmacytoid dendritic cells tend to favor a Th2 response and were called ‘plasmacytoid dendritic cells-2’¹⁴. In case of myeloid dendritic cells,

their ability to suppress the immune response is largely dependent on the remaining immature cells¹⁵, whereas the plasmacytoid dendritic cells can induce T-regulatory cell differentiation even under mature conditions¹⁶.

DENDRITIC CELLS LINKING THE INNATE AND ADAPTIVE IMMUNITY

The innate immune system operates without any previous contact with the microorganism. It is composed of two elements:

- (1) Cells with antimicrobial functions such as epithelial cells, neutrophil, NK cells and macrophages and dendritic cells (DCs); and
- (2) Proteins such as cytokines that are produced by the immune system or complement factors that are produced by non-immune cells.

The first line of defense is provided by the surfaces of epithelial cells. The DCs are encountered once the epithelial barrier is breached. Although B and T lymphocytes recognize antigens with high degree of specificity, they do not initiate an immune response, these functions rest upon DCs¹⁷. In the peripheral tissue, the immature DCs behave as 'immunological sensors' in perceiving microbial signals. Once they have sensed a microbe, the DCs undergo considerable changes called maturation which occur while they migrate from the peripheral tissues into the draining lymph nodes. While traveling through the lymphatic system, DCs up-regulate the expression of MHC class II and co-stimulatory molecules, which enable them to present MHC bound antigens to T cells via their T-cell receptor (TCR). Upon activation and differentiation, the T cells leave the lymph nodes through the efferent lymph vessel, return to the circulation, and infiltrate the infected tissue in order to exert their functions.

DENDRITIC CELLS IN GINGIVAL HEALTH AND DISEASE

The number of DCs in the gingiva is relatively low when compared to non-keratinized oral mucosal tissues¹⁸. In health, the oral biofilm is comprised predominantly of Gram-positive bacteria and the gingival tissues are infiltrated with numerous DCs in the epithelium, with sparse dermal dendritic cells in the lamina propria. As the disease progresses, the oral biofilm changes to a predominantly Gram-negative subgingival flora. The DCs numbers gradually increased and peaked on day 7, remained high until day 14 and decreased by day 21 as inflammation developed¹⁹. During gingivitis the DCs infiltrate the gingival epithelium and then efflux into the lamina propria in chronic periodontitis, where they begin to undergo maturation. The latter process involves the expression of chemokine receptor 7 (CCR7) that mediates migration of DCs to the lymph node and upregulates MHC class II and co-stimulatory

molecules, leading to potent activation of CD4+T cells²⁰. These findings suggest that DCs leave from the oral epithelium as the inflammation increases. In older people, the number of DCs is significantly reduced compared with young people²¹ as well as there is alteration in the morphology of dendritic cell suggesting that the prevalence of periodontitis increases with age. These observations strongly suggest that DCs play a role in periodontitis.

DENDRITIC CELLS IN CHRONIC PERIODONTITIS

Although periodontal pathogens are essential for the initiation and progression of chronic periodontitis, tissue damage is caused primarily by the host immune response²². CD4+ T cells play an important role in the generation of adaptive immunity and due to their ability to support different immune functions, CD4+ T cells are termed as T helper (Th) cells. According to the instructions provided by the DCs, the T helper cells differentiate into various subsets of Th cells named Th1, Th2, Th17 and T regulatory cells (Treg)²³.

In case of periodontitis, Th1 cells amplify the killing activity of macrophages and potentiate the generation of cytotoxic CD8+ T cells which eliminate the intracellular pathogens²⁴. Th2 cells allow the elicitation of pathogen-specific antibodies by B cells. Th17 cells increase the neutrophil recruitment for effective bacterial clearance²⁵. In contrast Treg cells down-regulate T-cell responses to limit excessive inflammation and bone loss²⁶. Due to the complexity of periodontal disease, it is difficult to determine the contribution of the various CD4+ Th subsets and their cytokines. The cytokines secreted by Th1, Th2 and Th17 upon exposure to periodontal pathogen can be either beneficial or deleterious to the host. For example, *Porphyromonas gingivalis* mediated bone loss in mice is due to Th1 type immune response²⁷ whereas bone loss induced by *Tannerella forsythia* is mediated by Th2 type immune response²⁸. This shows that pathogen-induced periodontal bone loss involves diverse mechanisms of adaptive immunity depending on the type of inducing agent. This highlights the critical role of DCs in the pathogenesis of periodontitis, as DCs orchestrate the adaptive immunity following exposure to pathogens. Thus dendritic cells are important in deciding whether to respond or not and which type of immune response will develop against a particular pathogen.

As oral DCs are exposed to several types of bacteria simultaneously, several studies have investigated the effect of polymicrobial infection on DCs. It was demonstrated that Gram-ve bacteria are strong inducers of inflammatory cytokines than gram+ve bacteria²⁹. Exposure of mature DCs to different pairs of gram -ve bacteria synergizes the production of IL-6, TNF- α and IL-12²⁹. This suggests that the

outcome of polymicrobial infection on immune response depends on the characteristics of the microorganism.

DENDRITIC CELLS ROLE IN OSTEOIMMUNOLOGY OF PERIODONTITIS

Bone remodeling and homeostasis are tightly regulated and controlled by a number of cytokines, growth factors, and hormones that exert their effects via osteoblasts and osteoclasts. In health, osteoblasts and osteoclasts act together to maintain bone homeostasis. In case of periodontitis bone remodeling becomes unbalanced and is accompanied by increased osteoclasts numbers and activity, leading to irreversible bone loss³⁰. Recently identified tumor necrosis factor family molecule, RANKL, its receptor RANK, and the natural antagonist osteoprotegerin, have been shown to be the essential regulators of bone remodeling and are directly involved in the differentiation, activation, and survival of osteoclasts and osteoclasts precursors³¹. The RANKL– RANK / osteoprotegerin axis is the central pathway of controlling osteoclastogenesis in the periodontium³². In addition, RANKL–RANK signaling is involved in dendritic cell survival, lymph node formation and organogenesis, and critical dendritic cell / T-cell interactions³³. The dendritic cells have been thought to contribute indirectly to inflammation induced bone loss as antigen presenting cells (APCs)³⁴. Recent invitro studies show that human peripheral blood monocytes-derived dendritic cells can transdifferentiate into osteoclasts in the presence of macrophage colony-stimulating factor and RANKL³⁵, suggesting a direct involvement of dendritic cells in osteoclastogenesis. The search for critical genetic factors involved in dendritic cell-derived osteoclasts development is in progress and the results will likely shed some light on the regulatory mechanisms involved in dendritic cell derived osteoclasts and inflammation-induced bone loss.

CONCLUSION

Maintenance of immune homeostasis is problematic in the oral cavity, which is exposed to thousands of bacteria and other infectious agents as the host respire and eats. Dendritic cells are professional antigen presenting cells which aid in inducing and maintaining mucosal immune homeostasis. DCs are the most responsive and potent APCs that infiltrate the gingiva in case of gingivitis and periodontitis. The gingival DCs basically act to minimize the local inflammation and the mechanisms driving these cells to elicit destructive T-cell responses should be found. In addition, how repetitive exposure to periodontal pathogens impact the function of gingival DCs and the ability of DCs to preserve the immune homeostasis should also be found. This knowledge about the oral DCs will help

us in understanding the mechanisms involved in the transition of periodontal immunity from protective to destructive and to highlight their therapeutic potential in future.

REFERENCES

1. D. T. Graves and D. Cochran, "The contribution of interleukin-1 and tumor necrosis factor to periodontal tissue destruction, " *Journal of Periodontology*, vol. 74, no. 3, pp. 391–401, 2003
2. Deo V, Bhongade ML (2010). Pathogenesis of periodontitis: role of cytokines in host response. *Dent Today* 29: 60–62, 64-6; quiz 68-9.
3. Garlet GP (2010). Destructive and protective roles of cytokines in periodontitis: a re-appraisal from host defense and tissue destruction viewpoints. *J Dent Res* 89: 1349–1363.
4. Benakanakere M, Kinane DF (2012). Innate cellular responses to the periodontal biofilm. *Front Oral Biol* 15: 41–55
5. Hans M, Hans VM (2011). Toll-like receptors and their dual role in periodontitis: a review. *J Oral Sci* 53: 263–271
6. Heath WR, Carbone FR (2009). Dendritic cell subsets in primary and secondary T cell responses at body surfaces. *Nat Immunol* 10: 1237–1244.
7. Steinman RM, Cohn ZA (1973). Identification of a novel cell type in peripheral lymphoid organs of mice. I. Morphology, quantitation, tissue distribution. *J Exp Med* 137: 1142–1162.
8. Steinman RM, Kaplan G, Witmer MD, Cohn ZA. Identification of a novel cell type in peripheral lymphoid organs of mice. V. Purification of spleen dendritic cells, new surface markers and maintenance invitro. *J Exp Med* 1979; 149:1-16
9. Steinman RM, Witmer MD. Lymphoid dendritic cells are potent stimulators of the primary mixed leukocyte reaction in mice. *Proc Natl Acad Sci USA* 1978; 75:5132-5136
10. Steinman RM, Cohn ZA. Identification of a novel cell type in peripheral lymphoid organs of mice. I. Morphology, quantitation, tissue distribution *Exp Med* 1973; 137:1142-1162
11. Helft J, Ginhoux F, Bogunovic M, Merad M (2010). Origin and functional heterogeneity of non-lymphoid tissue dendritic cells in mice. *Immunol Rev* 234: 55–75.
12. De Smedt T, Van Mechelen M, De Becker G, Urbain J, Leo O, And Moser M. Effect of interleukin-10 on dendritic cell maturation and function. *Eur J Immunol* 27: 1229–1235, 1997.
13. MacDonald KP, Munster DJ, Clark GJ, Dzionek A, Schmitz J, Hart DN. Characterization of human blood dendritic cell subsets. *Blood* 2002; 100:4512-4520

14. Rissoan MC, Soumelis V, Kadowaki N, Grouard G, Briere F, de Waal Malefyt R, et al. Reciprocal control of T helper cell and dendritic cell differentiation. *Science* 1999; 283:1183-1186
15. Jonuleit H, Schmitt E, Schuler G, Knop J, Enk AH. Induction of interleukin 10-producing, nonproliferating CD4(+) T cells with regulatory properties by repetitive stimulation with allogenic immature human dendritic cells. *J Exp Med* 2000; 192:1213-1222
16. Gillet M, Liu YJ. Generation of human CD8 T regulatory cells by CD40-ligand activated plasmacytoid dendritic cells. *J Exp Med* 2002; 195:695-704
17. Lanzavecchia A, Sallusto F: Regulation of T cell immunity by dendritic cells. *Cell* 2001, 106:263-266.
18. Daniels TE (1984). Human mucosal Langerhans cells: postmortem identification of regional variations in oral mucosa. *J Invest Dermatol* 82: 21–24.
19. Moughal NA, Adonogianaki E, Kinane DF (1992). Langerhans cell dynamics in human gingiva during experimentally induced inflammation. *J Biol Buccale* 20: 163–167.
20. Steinman RM (2007). Dendritic cells: understanding immunogenicity. *Eur J Immunol* 37(Suppl 1): S53–S60
21. Zavala WD, Cavicchia JC (2006). Deterioration of the Langerhans cell network of the human gingival epithelium with aging. *Arch Oral Biol* 51: 1150–1155.
22. Gemmell E, Yamazaki K, Seymour GJ (2002b). Destructive periodontitis lesions are determined by the nature of the lymphocytic response. *Crit Rev Oral Biol Med* 13: 17–34
23. Sallusto F, Lanzavecchia A (2009). Heterogeneity of CD4+ memory T cells: functional modules for tailored immunity. *Eur J Immunol* 39: 2076–2082.
24. Garlet GP (2010). Destructive and protective roles of cytokines in periodontitis: a re-appraisal from host defense and tissue destruction viewpoints. *J Dent Res* 89: 1349–1363.
25. Yu JJ, Ruddy MJ, Wong GC et al (2007). An essential role for IL-17 in preventing pathogen-initiated bone destruction: recruitment of neutrophil to inflamed bone requires IL-17 receptor-dependent signals. *Blood* 109: 3794–3802.
26. Garlet GP, Cardoso CR, Mariano FS et al (2010). Regulatory T cells attenuate experimental periodontitis progression in mice. *J Clin Periodontol* 37: 591–600
27. Stashenko P, Goncalves RB, Lipkin B, Ficarelli A, Sasaki H, Campos-Neto A (2007). Th1 immune response promotes severe bone resorption caused by *Porphyromonas gingivalis*. *Am J Pathol* 170: 203–213.

28. Myneni SR, Settem RP, Connell TD, Keegan AD, Gaffen SL, Sharma A (2011). TLR2 signaling and Th2 responses drive *Tannerella forsythia*-induced periodontal bone loss. *J Immunol* 187: 501–509.
29. Huang CB, Altimova Y, Strange S, Ebersole JL (2011). Polybacterial challenge effects on cytokine/chemokine production by macrophages and dendritic cells. *Inflamm Res* 60: 119–125.
30. Theill LE, Boyle WJ, Penninger JM. RANK-L and RANK: T cell, bone loss and mammalian evolution. *Annu Rev Immunol* 2002; 20:795–823.
31. Lacey DL, Timms E, Tan HL, Kelly MJ, Dunstan CR, Burgess T, Elliott R, Colombero A, Elliott G, Scully S, Hsu H, Sullivan J, Hawkins N, Davy E, Capparelli C, Eli A, Qian YX, Kaufman S, Sarosi I, Shalhoub V, Senaldi G, Guo J, Delaney J, Boyle WJ. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. *Cell* 1998; 93:165–176.
32. Mahamed D, Marleau A, Alnaeeli M, Singh B, Zhang X, Penninger JM, Teng Y-TA. Gram -ve anaerobe reactive CD4+ T-cells trigger RANKL-mediated enhanced alveolar bone loss in diabetic NOD mice. *Diabetes* 2005; 54:1477–1486.
33. Anderson DM, Maraskovsky E, Billingsley WL, Dougall W, Tometsko ME, Roux ER, Teepe MC, DuBose RF, Cosman D, Galibert L. A homologue of the TNF receptor and its ligand enhance T-cell growth and dendritic-cell function. *Nature* 1997; 390:175–179.
34. Santiago-Schwarz F, Anand P, Liu S, Carsons SE. Dendritic cells (DCs) in rheumatoid arthritis (RA): progenitor cells and soluble factors contained in RA synovial fluid yield a subset of myeloid DCs that preferentially activate Th1 inflammatory-type responses. *J Immunol* 2001; 67:1758–1768.
35. Rivollier A, Mazzorana M, Tebib J, Piperno M, Aitsiselmi T, Rouboudin-Combe C, Jurdic P, Servet-Delprat C. Immature dendritic cell transdifferentiation into osteoclasts: a novel pathway sustained by rheumatoid arthritis microenvironment. *Blood* 2004; 104:4029–4037.