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Dendritic Cells: Immune Regulators in Periodontal Health and Disease

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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

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INTRODUCTION

Periodontal diseases are caused by bacterially derived factors and antigens that stimulate a local inflammatory reaction and activation of the innate immune system [1]. Although the periodontal pathogens are required for disease initiation, they are not sufficient to cause periodontitis [2].The host immune response plays a central role in the destruction of periodontal tissues [3].

Pathogens in the periodontal environment are monitored by the innate immune system; the first line of defense against invading pathogens [4].The innate immune system includes epithelial barrier, secretary 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 molecules [5.] 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 systems [6].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 spleen[7].Steinman’s group isolated these cells to a higher degree of purity[8] and demonstrated their unique capacity to initiate T-cell immune responses[9]. 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 cells [10].

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 tissues [11]. 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 DCs [12]. 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+ cells [13].

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

Dendritic cell	Marker expression
BLOOD	
Myeloid DC	CD11c,CD1a,CD14$^-$,CDic/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,CLAsurface,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 histocompatability complex

Functionally the monocytic precursors of myeloid dendritic cells tend to favors a Th1 type response and have been called 'dendritic cell 1'.Precursors of plasmacytoid dendritic cells tend to favour 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 cells [15], whereas the plasmacytoid dendritic cells can induce T-regulatory cell differentiation even under mature conditions [16].

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 DCs [17]. 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 tissues [18]. 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 developed[19].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 cells[20].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 people [21] 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 response [22].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 pathogens[24].Th2 cells allows the elicitation of pathogen-specific antibodies by B cells.Th17 cells increase the neutrophil recruitment for effective bacterial clearance[25].In contrast Treg cells down-regulate T-cell responses to limit excessive inflammation and bone loss[26].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 response [27] whereas bone loss induced by Tannerella forsythia is mediated by Th2 type immune response [28]. 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 bacteria[29].Exposure of mature DCs to different pairs of gram -ve bacteria synergizes the production of IL-6, TNF-α and IL-12[29].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 loss [30]. 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 precursors [31]. The RANKL– RANK / osteoprotegerin axis is the central pathway of controlling osteoclastogenesis in the periodontium [32]. In addition, RANKL–RANK signaling is involved in dendritic cell survival, lymph node formation and organogenesis, and critical dendritic cell / T-cell interactions [33].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 RANKL[35], 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 respires 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.

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