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DENDRITIC CELLS IN OSTEOCLAST DIFFERENTIATION

Periodontology

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ABSTRACT

Periodontitis is associated with an increase in osteoclasts formation and differentiation leading to bone resorption.Dendritic cells are antigen presenting cells crucial for adaptive and innate immune response. Once activated, they migrate to the lymphnodes where they interact with T cells and B cells to initiate and shape the adaptive immune response. Dendritic cells are derived from haematopoietic bone marrow progenitor cells. These progenitor cells initially transform into immature dendritic cells. Osteoclastarise from hematopoietic stem cells (HSC) and pass through a series of differentiation stages resulting in non-dividing, multinucleated bone resorbing cells.During disease pathogenesis of inflammatory bone disorders and in response to a complex network of signals modulated by locally released cytokines, DC develop functional OC phenotype and activities in a RANKL-dependent manner during their interactions with T-cells, stromal cells.A direct contribution of certain DC subsets to inflammation-induced bone loss may prove to be a promising therapeutic target for controlling inflammation and the subsequent amelioration of bone pathology in periodontal disease.DCs may represent a cell type further down than monocytes in the OC differentiation pathway. DCs may express unknown transcription factors that favor OC differentiation.Based on phenotypic and functional characterization studies, it is suggested that DC can act as OCp that further develop into DDOC with distinctive phenotype and behavior under the inflammatory conditions.

KEYWORDS

Dendritic cells; osteoclast; Immune response; Macrophages; Differentiation;

INTRODUCTION

Dendritic cells (DC), in addition to innate effector functions and their critical role as antigen-presenting cells (APC) involved in triggering the adaptive immune responses, they could be directly implicated as osteoclast precursors (OCp) during inflammation at the osteo–immune interface. Dendritic cells can directly contribute to inflammationinduced bone loss by acting as osteoclast or osteoclast precursors (OCp). Recent invitro and invivo studies have examined the direct contribution of dendritic cells as osteoclast precursors to inflammation-induced osteoclastogensis and bone loss in periodontal disease. **[17]**

Dendritic cells

Dendritic cells are antigen presenting cells crucial for adaptive and innate immune response to infections and for maintaining immune tolerance to self tissues.**[15]**Dendritic cells represent sparsely distributed population of bone marrow derived cells. Multiple subsets of DCs with distinct lifespan and immune functions have been identified.**[16]**

Function of Dendritic cells

Function of dendritic cells falls into three categories, each of which involve antigen presentation. The first function is antigen presentation and activation of T cells, second is inducing and maintaining immune tolerance. The third category of DCs known as follicular DCs work to maintain immune memory.Upon responding to stimuli such as bacterial products and/or inflammatory cytokines, activated DC reach maturity quickly and then migrate to the draining lymph nodes, where they interact with naive T-cells to activate adaptive immune responses.**[3]**It was shown that pDC down-regulate their expression of TLR-7 and TLR-8 and the ability to produce IFN-α, while upregulating TLR-4 expression associated with cDC-like phenotype.**[20]**

T Cell activation

Dcs process and present antigen to activate both CD4 and CD8 T cells. In case of wound accompanied by inflammation, DCs are attracted to the area of inflammation and stimulated to capture and internally process antigens. The antigen is then processed either through exogenous or endogenous pathway. For MHC class 1 presentation to stimulate CD8 T cell, the antigen is takenup by phagocytosis and further degraded in the cytosol and enter the endoplasmic reticulum where peptides bind to newly synthesized MHC class 1 molecules for presentation on the cell surface.

Osteoclastogenesis

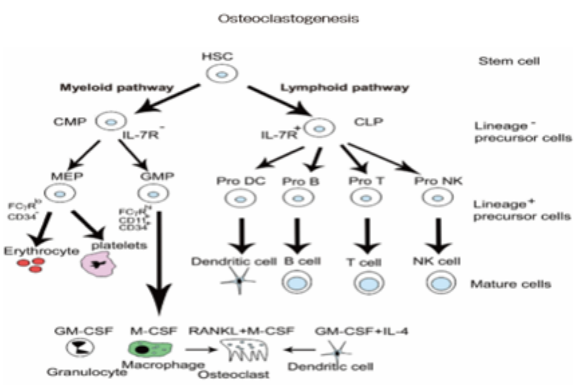


Fig – 1

Osteoclast differentiation

NFATc1 regulates OC specific genes, such as calcitonin receptor, TRAP35, Cathepsin K, OSCAR and β3 integrin. NFATc1 complexation with AP-1 is necessary for the induction of TRAP, calcitonin receptor and to enhance the auto amplification of NFATc1 itself. NFATc1 complexes with PU.1 and MITF to induce Cathepsin K and OSCAR. RANKL stimulation induces an elevation of cytosolic Ca2+, thereby activating calcineurin which mediates dephosphorylation and the nuclear translocation of NFATc1. Whereas RANKL is considered the key osteoclastogenic cytokine, NFATc1 seems to be the master of osteoclastogenic transcription factors.

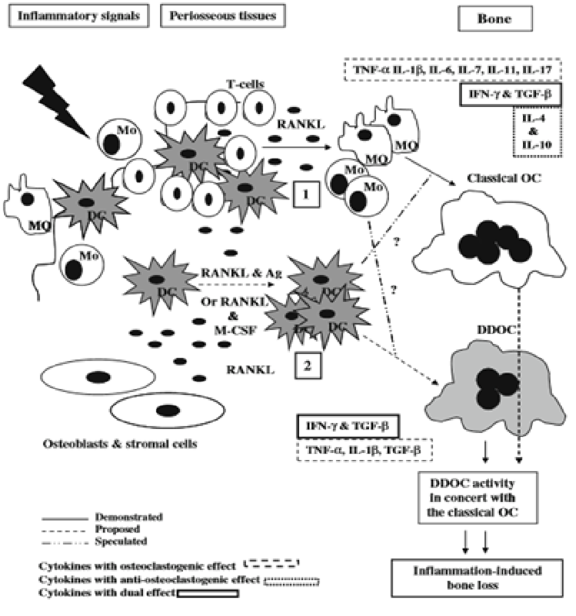
Dendritic cell derived Osteoclast (DDOC)

Several immunohistochemical studies have detected both mature and immature DC in periodontitis.**[5]**Such unique DC subsets form aggregates with T-cells in and around the inflammatory infiltrates and involve RANKL-RANK and other cytokines interactions associated with osteoclastogenesis and bone loss during different phases of disease progression.**[12]**Immature murine CD11cDC can develop into functional OC (i.e., DDOC) during immune interactions with CD4 T-cells, in response to microbial sonicates or protein Ags and the essential RANKL-RANK emodellin in the bone environment. **[13]**showed that human blood Mo-derived and murine BM-derived immature DC can transdifferentiate into functional OC in the presence of M-CSF and RANKL.At the junction of cytokine interactions during the osteo–immune cross-talks, **[14]**have recently described the effects of TNF-α, IFN-α, IFN-γ, IL-1b, IL-2, IL-4 and IL-10 on OC development from Flt3 BM precursors-derived DC.

DDOC Formation

Human immature monocytederived DCs transdifferentiate into Ocs in the presence of M-CSF and RANKL. DC-derivedOCformationis faster and more efficient in terms of fusion rate than the monocytederived OC formation pathway.. Genetic mutations of RANKL and RANK molecules result in similar phenotypes with defective OC development and severe osteopetrosis.**[6].** In experimental atherosclerosis, vascular endothelia have been shown to increase RANKL expression leading to OC formation, in association with Mo adhesion and transendothelial migration**[10]**.Its emodellin can regulate Mo as well as DC survival, lymph node formation and organogenesis, intrathymic self-tolerance, cancer cell migration and associated bone metastasis and specific DC/T-cell interactions.**[2]**

Alnaeeli and colleagues have reported that interactions of DCs with $CD4^+$ T cells and foreign antigens allow T-cell activation and the differentiation of DCs into osteoclasts in vitro.**[1]**OPG also plays a critical and protective role in the vascular system, modulating the osteo–immune interactions. M-CSF is a critical survival factor for Ocp in the Mo/MQ lineage.**[18]**M-CSF was reported to regulate the cytoskeletal organization via PI-3K and c-Src emodellin associated with the migration of MQ and OC.**[8]** In this process, the guanine nucleotide factor Vav3 becomes hyper-phosphorylated, leading to Rac-stimulated motility in Ocp.**[7]** Further, M-CSF can enhance the osteoclastogenic potential of Ocp, thereby promoting OC differentiation via the stimulation and up-regulation of RANK expression, which in turn increases their responsiveness to RANKL emodellin.**[4]**It has been shown to mediate Mo recruitment to inflammation sites by up-regulating chemokines such as CCL22 & MCP-1.**[9]**The homotrimeric TNF family member, RANKL, RANK and OPG have been shown to be the key regulators of bone emodelling and are directly involved in controlling OC differentiation, activation and survival**[19]**in the presence of macrophage-colony stimulating factor [M-CSF].TNF-α was shown to promote the proliferation and differentiation of Ocp by up-regulating c-Fms on Ocp pool in a murine model.**[11]**



CONCLUSION

During the past decade, the critical roles played by DC in regulating T-cell-mediated immunity during inflammationinduced osteoclastogenesis and subsequent bone loss have been brought to light, thereby further expanding the current paradigm of osteoimmunology. Today, emerging evidence independently suggests that specific DC subsets in mouse and human are likely involved in inflammatory bone diseases where they not only can act as potent APC for immune functions, but also directly impact bone destruction or osteolysis.. DC could become perhaps the most actively studied cell subset in the osteoimmunological research, with their active and significant roles at the immune and bone interface in periodontal disease.

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