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Malicious Interplay between Cells - Role of Osteoimmunology in Alveolar Bone Resorption

K. Malathi[1], C. Hima Bindu Reddy[2], Kiruthika. A[3], Suman Taki[4], G. Sandhya[5]

Tamil Nadu Government Dental College & Hospital

Abstract: ***Periodontal disease is a condition that involves inflammation of the tooth supporting structures. It is initiated in response to plaque and calculus on the tooth surface. The host defence system, both innate and adaptive immunity, is responsible for combating the pathologic microorganisms invading the periodontal tissue. Immune cells activate periodontal ligament cells to express the receptor activator of nuclear factor kappa - B (NF - κB) ligand (RANKL) and initiate osteoclastic activity. Osteocytes have active roles in periodontitis progression in the bone matrix. Osteoimmunology encapsulates the cellular and molecular mechanisms responsible for inflammatory osteolysis that culminates in the degradation of alveolar bone. It primarily focuses on the interplay of immune cells with bone cells during bone remodelling and regeneration. The concept of osteoimmunology is that immune cells communicate with effector bone cells - the bone resorbing osteoclasts and the bone - forming osteoblasts. This article deals with the interrelationship between the cells of the bone and the immune system and their effect on bone resorption.***

Keywords: osteoimmunlogy, Periodontitis, Osteocyte, inflammation, resorption

1. Introduction

Osteoimmunology encapsulates the cellular and molecular mechanisms responsible for inflammatory osteolysis that culminates in the degradation of alveolar bone. It primarily focuses on the interplay of immune cells with bone cells during bone remodelling and regeneration. The concept of osteoimmunology is that immune cells communicate with effector bone cells - the bone resorbing osteoclasts and the bone - forming osteoblasts. Since osteocytes have turned out to control the birth and death of the effector cells, osteoimmunology also covers the role of osteocytes in degradation of bone.1

Periodontal disease is essentially an immunoinflammatory response of the body to microbial plaque, causing destruction of periodontal soft and hard tissues. Bone resorption occurring in periodontitis is a complex interaction between various cells, it is important to decipher these pathways and the role of different cells in bone destruction. This article takes u on a journey where the basic cells of the bone are introduced and make acquainted with how Periodontitis causes bone destruction and the role of different cells responsible for bone resorption.

Bone

Bone is a metabolically active organ that is remarkably dynamic and active tissue, undergoing constant renewal in response to mechanical, nutritional, and hormonal influences.2 It is mainly composed of the cortical and trabecular or cancellous bone. Cortical bone is made up of the Haversian system (cortical osteon), which is found around central blood vessels and may branch within the cortex of the bone. Spatially, the cells in the Haversian system cover a relatively small surface area. In contrast, cells in cancellous bone occupy a large portion of the surface. This observation may explain why cortical bone exhibits lower metabolic activity than cancellous bone. Cytokine regulation is likely to be more important for trabecular bone than for cortical bone because trabecular bone is in closer proximity to the bone marrow, a rich source of cytokines.

Bone cells

Osteoblasts are cells that form bone tissue. Osteoblasts can synthesize and secrete bone matrix and participate in the mineralization of bone to regulate the balance of calcium and phosphate ions in developing bone. Osteoblasts are derived from osteoprogenitor cells.

Osteoclasts are highly specialised motile migratory bone resorptive cells, derived from haematopoietic stem cells. Pedosomes mediate the attachment of osteoclasts to extracellular bone matrix via αB13 integrin. The molecular interaction between cytoskeleton and extracellular matrix is at plasma membrane.

Osteocytes are cells derived from mesenchymal stem cells, part of an osteoblast cell lineage and account for most of the bone cells.3 When osteoblasts accomplish their role they slowly differentiate to osteocytes. Unlike osteoblasts which have a half life of 150 days, osteocytes have a half life of 25 years.

Osteocytes are mature bone cells that have become entrapped in bone matrix and mobilise calcium from matrix for transport and exchange with body fluids in response to systemic demand. The dendrites of the osteocytes reach the surface of the bone and help in communication between osteocytes and other cells. This connection establishes crosstalk between osteoclasts, osteoblasts, bone lining cells, and bone marrow cells with the osteocytes.

Overview of destruction in periodontitis

When there is plaque accumulation, within 2 - 4 days there is an acute inflammatory response that occurs at the base of the gingival sulcus. Professional phagocytes like the neutrophils and other cells like lymphocytes and mononuclear cells are recruited that help in limiting the spread of the disease. After 4 - 7 days these inflammatory

cells infiltrate the connective tissue and result in loss of collagen, additionally, fibroblasts show cytotoxic alterations. Slowly the conditions progress to chronic ginigivitis where the infiltration by inflammatory cells continue, resulting in increased connective tissue loss. However, no ultrastructural bone loss is observed. When left untreated it leads to antagonistic effects such as clinical attachment loss and bone loss. The cellular infiltrate gradually advances apically away from root surface and osteoblasts at the crest start disappearing and osteoclasts appear resulting in bone loss. Apparently cementum surface is the last tissue to get resorbed, as when compared to bone, cementum remodels slowly and also since its not vascularized the cellular infiltrate does not reach it. Infact, as cementum contains more fluoride than bone it shows greater resistance to dissolution by acids produced by osteoclasts.

RANK, RANKL, OPG

The activation and differentiation of osteoclasts are modulated by three members of the TNF ligand and receptor superfamilies: RANK, RANKL, OPG.

RANKL mediated osteoclastogenesis plays a pivotal role in inflammatory bone resorption and its expression is increased in periodontitis.4 Though the immune production of RANKL activated T lymphocytes may mediate bone resorption, in diseased periodontal tissue, activated T&B lymphocytes are one of the major RANKL inducers.

RANKL

RANKL (receptor activator of nF - □B ligand) is a member of the TNF superfamily (also known as osteoclast differentiation factor: ODF, TRANCE, and TNFSF). It is expressed by osteoblasts or stromal cells. There are 2 types of RANKL - membrane bound and soluble RANKL

When RANKL binds to its receptor, RANK, on osteoclast and preosteoclast cell surfaces, it promotes osteoclast formation by stimulating proliferation and differentiation. Membrane - bound RANKL is responsible for almost all primary functions; however, soluble RANKL has a minor role in physiological bone homeostasis. Accordingly, cells expressing membrane - bound RANKL are either near the bone surface or in contact with it.

Osteoprotegerin (OPG),

Osteoprotegerin (OPG), is a decoy receptor and a circulating protein. It is produced by a variety of cell types including osteoblasts and marrow stromal cells. It inhibits osteoclast formation by binding mRANKL and prevents the stimulatory cell - to - cell interaction with preosteoclasts and inhibiting RANKL/RANK interactions. Activation of the RANKL receptor increases the expression of TRAP, □3 integrins, cathepsin K, and calcitonin receptors on preosteoclasts.5

Role of osteocytes

The concept of osteoblasts being the primary cellular source of RANKL has shifted toward osteocytes, which serve as the primary source of RANKL in bone remodelling instead of osteoblasts. Continuous production of M - CSF in osteocytes enhances osteoclastogenesis. Osteocyte - derived M - CSF protects against excessive Nox4 - derived ROS generation and retains bone remodeling.6

Osteocytes produce RANKL during bone remodeling in periodontitis. Gram - negative bacteria - derived lipopolysaccharide interacts with toll - like receptors on the osteocyte cell surface to stimulate the mitogen - activated protein kinase/extracellular signal - regulated kinase (ERK) 1/2 signaling pathway resulting in the activation of transcription factors that upregulate IL - 6 expression. IL - 6 then activates Janus kinase through gp130, phosphorylating signaling molecules, and activator of transcription (STAT), leading to the translocation of STAT into the nucleus, enhancing RANKL expression in osteocytes.

Apart from IL - 6, TNF - α is a typical inflammatory cytokine in periodontitis that directly stimulates osteocytes to produce RANKL and induce osteoclastogenesis or promote sclerostin expression in osteocytes leading to increased osteoclastogenesis.

The precursor of osteoclasts and osteocytes attached within the collagen gel demonstrated that RANKL originates from osteocytes and is delivered to osteoclast precursor mainly via a membrane - bound form employing the dendritic processes of osteocytes in the lacunocanalicular system.

Osteocyte apoptosis recruits osteoclasts toward apoptosis sites leading to osteoclastogenesis and bone remodeling. Dying osteocytes or apoptotic bodies of osteocytes can directly control osteoclastogenesis and bone remodeling by secreting RANKL. The consequence of osteocyte apoptosis contributes to the secretion of several inflammatory cytokines, such as IL - 6, resulting in increased RANKL expression in osteocytes. Apoptotic osteocytes also release adenosine triphosphate (ATP) via the activated pannexin 1 channel, which acts as the bone lineage cells through ATP receptor gated (P2) channels. This interaction upregulates RANKL expression from nearby surface bone lineage cells to aggregate macrophages to differentiate themselves into osteoclasts.7 Moreover, apoptotic bodies of osteocytes interact with specific markers on osteoclast precursor cells to promote TNF - α gene expression leading to osteoclastogenesis. The prolonged apoptotic bodies of osteocytes can proceed to secondary apoptosis allowing the cell to secrete various inflammatory cytokines and subsequently activate immune cells to upregulate RANKL expression leading to osteoclastogenesis

Role of IL - 1

IL - 1 is one of the cytokines which exert their effects on bone resorbing cells and is a potent bone resorbing cytokine. Apparently IL 1 has paradoxical effects on bone formation, it inhibits bone formation both invitro and inuitro. It stimulates proliferation and differentiation of osteoblasts but inhibits its functions. Whereas transient exposure to IL1 stimulates bone formation by osteoblasts.8

IL 1 has direct and indirect mechanisms through which it exerts its bone resorbing power. It increases the production and release of PGE2 and thereby has an indirect effect on bone resorption and has a direct effect on osteoclasts through the 80Kda receptor.9

Role of TNF α

Lymphotoxin and tumor necrosis factor α are produced by activated lymphocytes. Their major effect on bone is to stimulate osteoclastic bone resorption.

It has been suggested that part of the effect of tumor necrosis factor α is mediated by prostaglandin E2 as well as IL - 6. Tumor necrosis factor α also affects cells with osteoblast phenotypes, inhibits differentiated function and stimulates cell proliferation.[10]

Role of Interferon Gamma

Gamma interferon though it has similar effects to TNF alfa and IL1, it has an opposite effect on bone resorption. It is effective in inhibiting bone resorption induced by IL1 or TNF alfa. Further, it has been found in long - term marrow cell cultures in which interferon y inhibits the formation of cells with the osteoclast phenotype.1[1]

Role of Neutrophils

In periodontitis, neutrophils can cause tissue destruction. P. gingivalis and other keystone bacteria act through different mechanisms and subvert the action of neutrophils and macrophages and as a ramification of which leads to survival of the whole dysbiotic microorganism committee and increased inflammation.

RANKL can induce neutrophil degranulation and migration, suggesting a critical role of RANKL in neutrophil - mediated injury.1[2]

Role of T cells

T - cells, following the original concept of osteoimmunology, have been identified as being critically involved in the mediation of inflammation - induced bone loss.

It is the CD4 helper T - cell population that causes periodontitis - induced inflammatory bone loss. There are, however, many CD4+ subsets that could account for alveolar bone loss.1[3]

In the traditional concept naive CD4+ T cells, when exposed to IL12 and IFNγ, become Th1 cells; IL4 develop cells into the Th2 lineage. Th1 cells express IFNγ and TNFα, while Th2 cells release IL4, IL5 and IL13, both having a major impact on immunity.

However, other subsets of CD4+ T cells maintain the integrity of the alveolar bone and the corresponding soft tissues – the Th17 and Treg cells. The development of Th17 requires TGF - β and IL6/IL23 while Treg cells depend on TGF - β and retinoic acid.1[4]

Either due to environmental factors, their own susceptibility or both, the stable lesion changes to a Bcell/ plasma cell response with the production of high levels of IL1 and IL6 and subsequently connective tissue breakdown and loss of bone. Immunoregulation depends on the balance between these two T cell subsets.

Roles of Th17 and exFoxp3Th17 Cells

Immune cells in arthritis - autoimmune disease have a subset of Treg cells that transform into interleukin - 17 (IL - 17) - expressing Foxp3 T cells (or exFoxp3Th17 cells) and exhibit Th17 cell - like functions following inflammatory stimuli. In addition, exFoxp3Th17 cells activate the osteoclastogenic activity more strongly than the conventional Th17 cells. Consequently, exFoxp3Th17 cells are critical for osteoclastogenesis.

These two T cell subsets are related to periodontitis and occur in periodontitis lesions. Mice lacking Th17, exFoxp3Th17 cells, and IL - 17 show a subtle inflammatory condition during periodontitis with less alveolar bone loss. Moreover, human T cells expressing IL - 17 have more periodontitis sites. Foxp3+ IL - 17+ T cells are significantly observed in severe periodontitis lesions and are suggested as the cells in transition from Treg cells to exFoxp3Th17 cells. In summary, both Th17 cells and exFoxp3Th17 cells are strongly implicated in periodontitis.1[5]

Role of gingival fibroblasts

Gingival fibroblasts are complex, in that they produce OPG in response to LPS and IL - 1, suggesting a protective role to suppress osteoclast formation, however, they may also amplify chronic inflammatory processes through IL - 6 and IFN production.

The periodontopathic bacteria such as Aggregatibacteractinomycetemcomitans (Aa) and Porphyromonasgingivalis (Pg) have unique mechanisms to induce RANKL in osteoblasts and gingival fibroblasts via LPS or IL - 1.1[6]

2. Conclusion

Understanding the biological mechanisms that control the immunopathogenesis of the remodeling and resorptive processes will clarify not only the local control of bone cell function but also the pathophysiology of accelerated bone loss, as seen in periodontal disease.

Bone resorption via osteoclasts and bone formation via osteoblasts are coupled, and their dysregulation is associated with numerous diseases of the skeletal system. A wide range of host and microbial factors contribute to alveolar bone loss in periodontitis. RANKL/ opg ratio is increased in periodontitis.

Yet, much remains to be understood about the complex mechanisms whereby these factors regulate bone resorption in periodontitis. Recent developments in the area of biological processes and mediators of osteoclast differentiation and activity have expanded our knowledge of resorption processes and set the stage for new diagnostic and therapeutic modalities to treat situations of localized bone loss as seen in periodontal disease.

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