ISSN: 0976-3031

Available Online at http://www.recentscientific.com

International Journal of Recent Scientific Research
Vol. 8, Issue, 1, pp. 15439-15442, January, 2017

International Journal of Recent Scientific Research

Review Article

BASIS OF OSTEOIMMUNOLOGY IN PERIODONTICS

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ARTICLE INFO

Article History:

Received 18th October, 2016
Received in revised form 10th November, 2016
Accepted 06th December, 2016
Published online 28th January, 2017

Key Words:

Osteoimmunology, periodontitis, immune complex, RANK, RANKL, OPG

ABSTRACT

Osteoimmunology is a collaboration of two fields namely osteology and immunology. During inflammatory conditions like periodontitis, alveolar bone resorption takes place as a result of the release of certain immune-regulatory cytokines or mediators like receptor activator of nuclear factor κ B (RANK) and receptor activator of nuclear factor κ B ligand (RANKL) etc., that are present on bone cells namely osteoclasts and osteoblasts respectively. These cytokines play a pivotal role in the process of periodontal tissue breakdown. The interrelationship between bone cells and immune cells that take part in the progression of periodontal disease has unfolded this versatile interdisciplinary speciality called osteoimmunology that has provided a substructure to study the mechanisms that are involved in periodontal destruction. This review emphasizes on the foundation of osteoimmunology and its role in periodontics.

INTRODUCTION

The periodontium is a consolidation of tissues that are in contiguity with an amalgamated biofilm harboring varied bacterial species. Due to chronic exposure to bacteria or their products, the immune responses are persistently activated in the gingival connective tissue. The alarming identification of microbial components by host cells, followed by the production of inflammatory mediators, is a crucial step in the pathogenesis of periodontitis. Veritably, periodontitis is differentiated from gingivitis by the irreversible nature of attachment loss.

A family of receptors called the toll-like receptors (TLRs) trigger the innate immune response and bind to various microbial components. The impact of some of these receptors like TLR-2 and TLR-4, range from expressing inflammatory cytokines to causing osteoclastogenesis and ultimately, alveolar bone loss. (Gelani V *et al*, 2009; Lima HR *et al*, 2010). Apart from TLRs, the nucleotide-binding oligomerization domain (NOD) receptors and the inflammasome system (a component of the innate immune system) have been indicated as prospective accessory molecules that instigate the host response against periodontal pathogens. (Uehara *et al*, 2007).

The key molecules like RANK (receptor activator of nuclear factor k B), RANKL (receptor activator of nuclear factor k B ligand) and its decoy receptor– OPG (osteoprotegerin) etc., that regulate osteoclast differentiation, play a major role in bone resorption. RANKL is an osteoclastogenic cytokine of the TNF (tumour necrosis factor) family that links the bone and the immune system. Similarly, pro-inflammatory cytokines like IL-1 (interleukin-1), IL-6, TNF-α, etc., also contribute to the destruction of periodontal tissues. Thus, the recollection that periodontitis comprises of an immuno-inflammatory component that causes an alteration in the bone metabolism, has contributed to a new outlook on the etiology of the disease. Scrutinizing the pathogenesis of periodontal disease that involves both bone cells as well as immune cells has lead to the evolution of the field of "Osteoimmunology" in periodontics.

History

At the outset, Horton *et al* in 1972, in an *in vitro* study, found a new soluble factor in the supernatant fluid from cultured human peripheral blood leukocytes that was effective in stimulating bone resorption. Few years later in 1981, Rodan and Martin propounded a hypothesis wherein the osteoblasts played a predominant role in mediating the hormonal control of osteoclastogenesis and bone resorption. Many studies supported this hypothesis but the factors expressed by osteoblasts or other cells remained indefinite until they were discovered independently by four groups using distinct approaches. (Boyle *et al*, 1997; Yasuda *et al*, 1998; Wong *et al*, 1997; Anderson *et al*, 1997).

Several years later, one specific cDNA was found to be over-expressive in mice and the protein encoded by the gene was

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named osteoprotegerin (OPG) because it appeared to protect the skeleton from bone resorption. (Boyle *et al*, 1997). Simultaneously another group of researchers at Japan, discovered a similar molecule that inhibited osteoclastogenesis, and called it the "osteoclastogenesis inhibitory factor". (Yasuda *et al*, 1998). Soon enough, both the groups determined its ligand, namely OPG ligand and osteoclast differentiation factor, respectively. This ligand appeared to be identical to a member of the TNF ligand family, which was discovered in the previous year as RANKL/TRANCE (TNF-related activation induced cytokine). (Wong *et al*, 1997). A similar cellular response as that of OPG ligand was found in RANK, which participated in the activation of T-cells in the immune system. (Anderson *et al*, 1997).

Soon after these successive findings, the term "osteoimmunology" was first meticulously suggested in the year 2000 by Joseph R. Arron and Yongwon Choi who enlightened that both fields namely osteology and immunology, could be studied together as a cohesive entity in order to prevent or treat many common diseases that involve both the skeletal and immune system.

Bone

It is a well-known fact that bone is a living mineralized connective tissue that is composed of cells, fibers and ground substance. The three types of bone cells that are of prime importance are: (i) Bone forming osteoblasts (ii) Bone resorbing osteoclasts (iii) Osteocytes that modulate bone-remodeling activity. Bone remodeling involves a continuous sequence of events wherein the osteoclasts perpetually remove mature bone, while the osteoblasts simultaneously form new bone, all of which facilitate constant repair and homeostasis.

The Immune Complex and Periodontitis

Periodontitis is a pathological disorder that involves inflammation of the periodontium and this occurs as a response to various pathogens. The immune complex or the host defense system comprises of host responses that aim at blocking the invading pathogens that cause periodontal diseases. Cells of the immune system that play a vital role in inflammation and host defense are neutrophils, monocytes/macrophages, dendritic cells, mast cells and lymphocytes that include T-cells and B-cells. The main features of these cells with regard to their role in osteoimmunology are listed below.

- Activated neutrophils express RANKL and OPG, thereby inducing osteoclastogenesis.
- Monocytes / macrophages have the ability to differentiate into osteoclasts in response to TNF-α in the presence of RANKL.
- RANK expressed on the surface of dendritic cells can interact with RANKL exhibited by T-cells that consequently influences bone resorption.
- Mast cellsare known to play a pivotal role in immediate inflammation. Besides macrophages and dendritic cells, mast cellsalso express TLRs that activate osteoclastic bone resorption.
- B-cells are regarded as the primary source of RANKL in periodontal diseases. (Kawai T *et al*, 2006).

Stimulated T-cells are known to produce certain activation products called cytokines that regulate inflammation in accordance with immune and reparative responses. Some of the important cytokines produced by T-cells and their primary role in forming a key link between the immune system and bone resorption are presented below.

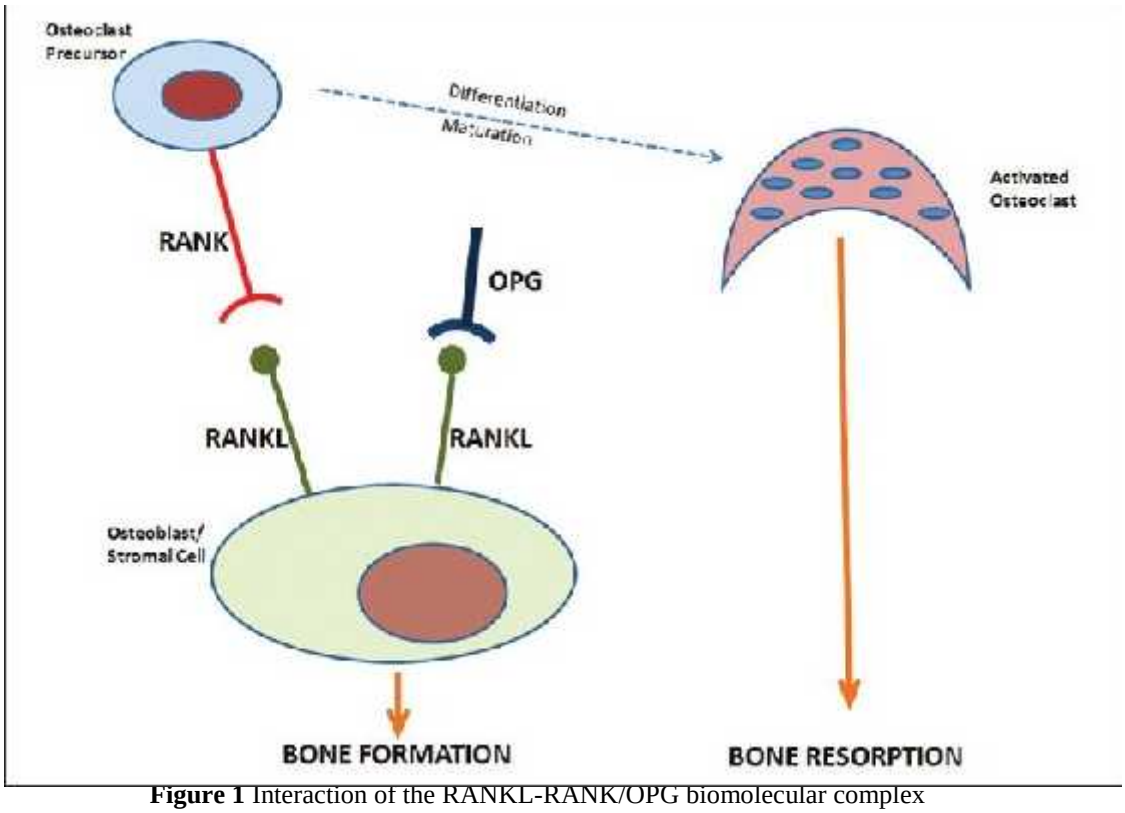

Figure 1 Interaction of the RANKL-RANK/OPG biomolecular complex

(Courtesy: Kohli SS and Kohli VS, 2011)

(i) IL-1 and IL-17 increase prostaglandin synthesis in addition to enhancing RANKL production and therefore may account for bone resorptive activity. (Wei *et al*, 2005).
(ii) IL-6 stimulates both RANKL and OPG production in bone thereby inducing osteoclastogenesis. (Roodman GD, 1992).
(iii) INF-γ inhibits osteoblast proliferation and enhances bone resorption via elevated RANKL and TNF-α production by T-cells.
(iv) TNF-αand TNF-βare potent stimulators of bone resorption. There is an increased expression of TNF-α during periodontal tissue breakdown as it inhibits osteoblast differentiation as well as collagen synthesis and furthermore stimulates osteoclast formation. (Wei *et al*, 2005).
(v) RANK, RANKL and OPG are cytokines that belong to the TNF-α family. RANK is a receptor that is found on the surface of osteoclast precursors whereas RANKL is found on the surface of osteoblasts / stromal cells. OPG is considered as a decoy receptor for RANKL. It is also known as osteoclastogenesis inhibitory factor (OCIF) as it inhibits RANK-mediated activation by binding to RANKL.

RANK-RANKL-OPG interactions

During inflammatory conditions, RANK binds to its ligand RANKL that is followed by stimulation of differentiation of the precursor cells into mature osteoclasts, which resorb bone. OPG comes into play when it binds to RANK without stimulating any differentiation, thereby exerting a protective effect on bone (Figure 1). Hence, the interaction between RANKL-OPG and RANKL-RANK determines osteoclast differentiation, that ultimately influences bone turnover and homeostasis.

Immune Mediators

The immune mediators in osteoimmunology include (i) Transcription factors (ii) Immune receptors and costimulation. (Bhanu MM, 2011)

Transcription factors are a group of proteins that bind to DNA and aid in genetic transcription. The predominant transcription factors in osteoimmunology are listed as follows:

(a) AP-1 (activator protein-1)
(b) NFAT (nuclear factor of activated T-cells)
(c) NF-κB (nuclear factor κB)
(d) ID2 (inhibitor of DNA binding protein-2)
(e) SHN-3 (schnurri-3)
(f) STAT-1 (signal transducer and activator of transcription-1)
(i) **Immune receptors:** Apart from the significant RANK, other essential immune receptors include:
  (a) c-fms (colony stimulating factor receptor)
  (b) DC-STAMP (Dendritic cell-specific transmembrane protein)
  (c) Ephrin and Semaphorin receptors
  (d) OSCAR (osteoclast-associated receptor)

The **co-stimulatory molecule** is B7-H3 (CD276).

Osteoimmunology In Periodontitis

Gram-negative bacteria such as *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* invade the connective tissue and alveolar bone that causes a host response leading to periodontitis. Net bone loss occurs when the amount of bone that is lost, is not compensated by the formation of new bone. Therefore, an interference with the coupling process is deemed as the trademark of periodontitis. Concomitantly, RANK, RANKL and OPG form an integral part in the regulation of bone metabolism wherein an increase in RANKL expression or decrease in OPG, can cause an imbalance that favours osteoclastogenesis followed by cumulative bone resorption.

During the same year when osteoimmunology came into existence, the two forms of RANKL namely mRANKL (membrane-bound) and sRANKL (soluble cytokine) were ascertained in an *in vitro* study. (Nakashima *et al*, 2000). Subsequently, in another study, RANKL mRNA levels were examined to be highest in deep periodontal pockets. (Nagasawa *et al*, 2002). Consecutively, in one study, the expression of RANKL mRNA was demonstrated in inflammatory cells, especially lymphocytes and macrophages (Liu *et al*, 2003) and in another study, high levels of RANKL and low levels of OPG were expressed in tissues with periodontitis. (Crotti *et al*, 2003). According to Han *et al* in 2006, in the absence of T-cells, B-cells have the ability to contribute to alveolar bone loss through RANKL production. Furthermore, it has been unambiguously proved that exaggerated immune responses release several pro-inflammatory cytokines and mediators that may lead to osteoclastogenesis as a result of RANKL stimulation. (Jin *et al*, 2007; Leiwiecki, 2009). Therefore, collective evidence stipulates the interrelationship between the bone and immune system in the emerging field of osteoimmunology.

CONCLUSION

The complex interaction between the skeletal and immune system has given rise to the interdisciplinary field of osteoimmunology. Extensive research in the form of longitudinal human clinical trials will provide better understanding of the periodontal disease in terms of its pathogenesis as well as potential therapeutic modalities to treat the same.

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How to cite this article:

Nashra Kareem *et al*.2017, Basis of Osteoimmunology In Periodontics. *Int J Recent Sci Res.* 8(1), pp. 15439-15442.