

The Role of Inflammatory Cytokines and the RANKL-RANK-OPG Molecular Triad in Periodontal Bone Loss-A Review

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Abstract

Periodontal diseases are chronic inflammatory disorders involving the supporting structures of the teeth. Connective tissue destruction and loss of bone support of the dentition are key features of this disease. Early studies have revealed that biofilm plaque accumulation in the dentogingival area is the primary etiological factor of periodontal diseases. Recent research has not only reinforced the bacterial etiology of periodontal disease, but has also emphasized the role of inflammation in this pathologic process. The host mounts an immune-inflammatory response to combat the bacterial attack. The host response is like a double-edged sword. It eliminates the offending pathogens, but overstimulation and amplification of the same leads to tissue destruction and bone loss. In the mid-1990s, extensive research in the field of bone biology led to the discovery of the RANKL-RANK-OPG molecular triad. This article explores the mechanisms by which inflammatory host response leads to alveolar bone loss-the role of cytokines, factors that stimulate osteoclastogenesis via the RANKL-RANK-OPG pathway and how inflammation interferes with the uncoupling of bone formation and bone resorption. In addition to the conventional therapeutic modalities aimed at eliminating the microbes, additional therapeutic strategies that interfere with the RANKL-RANK-OPG axis may have a protective effect on the bone loss.

Keywords: Inflammation; RANKL; OPG; RANK; Osteoclastogenesis; Cytokines; Periodontal disease; IL-1; TNF; Alveolar bone loss

Introduction

Periodontal diseases, which are chronic inflammatory disorders localized to the attachment structures of the teeth, are considered to be the major cause of tooth loss in adults and the most prevalent form of bone pathology in humans [1]. The term periodontal disease refers to both gingivitis and periodontitis. Gingivitis is an inflammatory condition of the soft tissues surrounding the teeth [2]. If unchecked, gingivitis progresses to periodontitis, an inflammation of the supporting structures of the teeth [3]. Specific gram-negative anaerobic bacteria species such as Porphyromonas gingivalis and Tannerella forsythia have been associated with periodontitis [4].

The initial host response to bacterial infection is a local inflammatory reaction that activates the innate immune system [5]. An imbalance between the plaque biofilm and the host immune system results in the overexpression of an array of proinflammatory cytokines, propagation of inflammation through the gingival tissues and the subsequent destruction of alveolar bone [6].

Thus the inflammatory process results in destruction of connective tissue and alveolar bone, the hallmarks of periodontal disease.

The Role of Inflammation in Alveolar Bone Loss

There are two critical factors, which dictate whether bone loss occurs in response to inflammatory reaction.

1. The concentration of pro-inflammatory cytokines and mediators present in the gingival tissue must be sufficient to activate the pathways leading to bone resorption.

2. The inflammatory mediators must penetrate the gingival tissue to reach within a critical distance to alveolar bone [5].

Page and Schroeder showed that bone resorption ceases when a 2.5 mm zone is created between the site of bacteria and bone [7].

Inflammatory Mediators

There are several classes of molecules that activate a host response which in turn stimulates osteoclastogenesis either directly or indirectly [8]. These include lipid-based molecules such as prostaglandins, leukotrienes [8], pro-inflammatory cytokines such as IL-1, IL-6, IL-11 and IL-17, tumor necrosis factor-alpha, leukemia inhibitory factor, and oncostatin M. The kinins such as bradykinin, kallidin and thrombin and various chemokines can also lead to bone resorption [9].

Chemokines are chemotactic cytokines that stimulate recruitment of inflammatory cells. Based on the structure of their ligand, they are divided into two major families-CC and CXC. Their receptors are referred to as CC chemokine receptor (CCR) and CXC chemokine receptor (CXCR). CXCR2 receptor binds several chemokines that are neutrophil chemoattractants [10]. Neutrophil recruitment is important to protect against bacterial attack. Yu JJ et al. conducted a study in which oral gavage of Porphyromonas gingivalis was administered to CXCR2 and IL-17 deficient mice. The results revealed increased periodontal bone loss in these mice compared to wild-type mice, suggesting that chemokines and IL-17 are important in protecting host against pathogen-initiated bone loss. IL-17 is a key cytokine produced by a newly identified subset of T helper cells (Th) called the "Th17" lymphocytes and it is important in stimulating chemokine production to recruit neutrophils. The enhanced bone loss observed in this study is the result of a defective ability to stimulate neutrophil migration to the inflamed bone, which requires IL-17 receptor dependant signals,

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thus underscoring the importance of IL-17 in the defense against oral pathogens [11]. From their study Zhang et al. concluded that IL-17A produced by Th17 cells stimulate the development of osteoclasts (osteoclastogenesis) in the presence of osteoblasts [12] and Cardoso et al. observed expression of IL-17 in gingiva from patients with periodontitis [13].

The role of pro-inflammatory cytokines, interleukin-1 (IL-1) and tumor necrosis factor (TNF) in bacteria-induced bone loss was demonstrated in an animal model study by Assuma et al. Porphyromonas gingivalis (Pg)-soaked silk ligatures were applied to the posterior mandibular teeth of Macaca fascicularis primates to induce experimental periodontitis. The primates received local injections, over a period of 6 weeks, of antagonists to TNF-alpha and IL-1 (soluble TNF-alpha and IL-1 receptors) or vehicle control. The gingival connective tissue sections in close proximity to bone demonstrated significant inflammatory cell recruitment and osteoclast formation surrounding bone in the control primates. Thus, infection with Pg in these animals was associated with expansion of the inflammatory front to alveolar bone. The antagonists to cytokines reduced the appearance of inflammatory cells in this region and the formation of bone resorbing osteoclasts. Thus, inhibition of inflammatory mediators can prevent the "inflammatory front" from reaching the alveolar bone leading to a reduction in bone loss as observed in this animal model [14]. In a follow-up study with the same model Delima et al. in 2001, stated that IL-1 and TNF blockers inhibited the loss of connective tissue attachment [15].

In their study, Graves DT et al. concluded that *P. gingivalis* induced osteoclastogenesis was reduced in TNF receptor-deficient mice compared to wild-type controls, thus indicating that osteoclast formation resulted from stimulation of the host response rather than from the direct effect of bacterial products [16]. Gaspersic et al in rat ligature model study concluded that the administration of recombinant human TNF-alpha (rhTNF-alpha) accelerated the progression of periodontitis [17]. In a study by Garlet et al. TNF-alpha receptor-1-knockout mice developed significantly less inflammation and alveolar bone loss in response to Aggregatibacter actinomycetemcomitans oral gavage. The levels of the pathogen as quantified by real-time PCR was higher in the TNF receptor ablated mice, compared to the wild-type controls. The quantitative mRNA expression of inflammatory cytokines IL-1 beta, interferon-gamma, and receptor activator of nuclear factor-kappa B ligand (RANKL) was significantly lower in the TNF receptor ablated mice. Thus, the absence of TNFR-1 resulted in lower production of cytokines in response to the pathogen. Decrease in TNF-alpha seemed to reduce the host response, thereby leading to higher levels of bacteria. However, there was reduced expression of cytokines that stimulate bone resorption, which resulted in less net bone loss [18]. In response to *P. gingivalis* oral gavage, mice with genetically deleted IL-6 had decreased bone loss compared to wild-type mice, thus indicating the pro-inflammatory effects of IL-6 leading to bone resorption. (Baker PJ et al.) [19]. Li et al. examined the role of B and CD4 T cells in adaptive immunity of rats infected with Aggregatibacter actinomycetemcomitans (*Aa*). Sprague-Dawley male rats were fed *Aa*-containing mash or control-mash for 2 weeks. B and CD4 T cells were obtained from draining lymph nodes at 2, 4 and 12 weeks, post inoculation. Quantitative polymerase chain reaction-based messenger RNA expression was conducted for 89 cytokine family genes. B and CD4 T cells of *Aa*-infected rats increased and were activated, resulting in enhanced isotype-switched serum immunoglobulin G by 2 weeks post inoculation. Bone resorption was evident 12 weeks after *Aa*-feeding. In B cells, interleukin-2 (IL-2), macrophage-inhibiting factor, IL-19, IL-

21, tumor necrosis factor (TNF), CD40 ligand (CD40L), CD70, bone morphogenetic protein 2 (BMP2), BMP3, and BMP10 were upregulated early; while IL-7, Fas ligand (FasL), small inducible cytokine subfamily E1, and growth differentiation factor 11 (GDF11; BMP11) were upregulated late (12 weeks). BMP10 was sustained throughout. In CD4 T cells, IL-10, IL-16, TNF, lymphotoxin-beta (LT β), APRIL, CD40L, FasL, RANKL and osteoprotegerin were upregulated early, whereas IL-1 β , IL-1RN, IL-1F8, IL-24, interferon- α 1, GDF11 (BMP11), and GDF15 were upregulated late (12 weeks). There was upregulation in mRNA for a number of cytokines not normally ascribed to periodontal disease. IL-16 was upregulated in CD4 T cells in the early phase of the response [20]. IL-16 has been shown to be involved in the selective migration of CD4 T cells, and participates in inflammatory diseases [21]. IL-19, a novel cytokine of the IL-10 family, was also upregulated in CD4 T cells in response to *Aa* [20]. IL-19 produced by synovial cell in Rheumatoid arthritis (RA) patients promotes joint inflammation (Sakurai et al.) [22]. IL-21, which has recently been shown to induce receptor activator of nuclear factor kappaB ligand (RANKL) and was implicated in arthritis (Jang et al.) [23] was upregulated in B cells responding to *Aa* [20]. By 12 weeks, there was also an induction of IL-24 in CD4 T cells responding to *Aa* [20]. IL-24 was increased in the synovium of patients with rheumatoid arthritis, and this cytokine was implicated in recruitment of neutrophil granulocytes (Kragstrup et al.) [24]. B cell-activating-factor (BAFF, or TNFSF13B) and a proliferation-inducing ligand (APRIL), members of the TNF family, were upregulated in B cells and CD4 T cells, respectively, in response to *Aa* infection [20]. IL-23, a proinflammatory cytokine composed of IL-23p19 and IL-12/23p40 subunits, is known to promote the differentiation of Th17 cells. Studies showed that IL-23 and IL-12 were expressed at significantly higher levels in periodontal lesions than in control sites, suggesting that IL-23-induced Th17 pathway is stimulated in inflammatory periodontal lesions (Ohyama et al.) [25]. IL-33 is a new member of the IL-1 family, which plays a role in inflammatory response. Injecting IL-33 or IL-33R agonistic antibody into TNF transgenic mice overexpressing human TNF inhibited the development of spontaneous joint inflammation and cartilage destruction. *In vitro*, IL-33 directly inhibits mouse and human M-CSF/receptor activator for NF- κ B ligand-driven osteoclast differentiation, suggesting an important role for IL-33 as a bone-protecting cytokine with potential for treating bone resorption (Zaiss et al.) [26]. The bone resorption protein RANKL and its soluble decoy receptor OPG was also induced in the CD4 T cells of *Aa*-fed rats [20].

The role of bone morphogenetic proteins (BMPs) and growth differentiation factors (GDFs) in periodontal disease

Bone morphogenic proteins (BMPs) and growth differentiation factors (GDFs) are members of the transforming growth factor- β (TGF- β) superfamily. They play important roles during development and organogenesis in delivering positional information in both vertebrates and invertebrates, and are involved in the development of hard as well as soft tissue (Herpin, Lelong and Favrel) [27]. BMP2 was induced in B cells early (week 4) of the inflammatory process, at the same time that RANKL was induced in CD4 T cells (Li et al.). This suggests that bone repair mechanisms were induced early, well ahead of impending bone resorption. However, by 12 weeks of infection by *Aa*, BMP2 was shut down, as bone resorption proceeded. BMP3 was also upregulated at week 4 in B cells responding to *Aa* [20]. BMP3 has been shown to be a negative regulator in the skeleton, as mice lacking BMP3 have increased bone mass. Transgenic mice over-expressing BMP3 had altered endochondral bone formation resulting in spontaneous rib fractures [28]. Both BMP2 and BMP3 were upregulated in B cells at the

same time (4 weeks post infection), and were shut down at 12 weeks, at which time bone resorption was evident [20]. B cells responding to Aa upregulated BMP10 at all time points [20]. BMP10 has been shown to regulate myocardial hypertrophic growth (Chen et al. 2006) [29]. BMP-10 may function as a tumor suppressor and apoptosis regulator for prostate cancer [30]. Thus the expression of BMP 10 in the Aa rat model at all points suggests its role in inflammation and bone resorption [20]. Also the involvement of BMP10 in cardiac hypertrophy [29] and in prostate cancer [30] suggests a possible link between periodontal disease and systemic diseases.

Growth differentiation factor 11 (GDF11) or BMP11, plays an important role in establishing embryonic axial skeletal patterns [31]. In the GDF11 was upregulated at 12 weeks post infection, in both B and CD4 T cells, at the time of bone resorption. This suggests that GDF11 may have a novel role in bone resorption [20].

The Aa-induced rat model, the Pg-induced mouse model and several other animal studies discussed above strongly support the role of pro-inflammatory cytokines in bone loss. The role of novel cytokines not previously ascribed to periodontal disease has been extensively discussed and these studies also suggest a possible link between periodontal disease and systemic diseases.

Osteoimmunology

Extensive research in the fields of immunology and osteology has revealed an intimate relationship between inflammation/the immune system and the skeletal system [32]. The immunoskeletal interface involves centralization of the immune and skeletal functions around common cells types and cytokine effectors that control the physiological bone mass. Prolonged immune activation can lead to skeletal deterioration. This interconnection of the skeletal and the immune systems has spawned the emergence of a new field of science termed "osteoimmunology" [33]. The field of osteoimmunology offers better insights into the understanding of pathogenesis of periodontal disease by explaining the role of inflammation in alveolar bone loss.

Osteoclasts and the Receptor Activator of NF-Kappa B (RANK)/RANK Ligand (RANKL)/Osteoprotegerin (OPG) System

Osteoclasts are unique cells of the human body tasked with resorbing bone. These multinucleated giant cells bind down onto the bone surfaces creating a sealing zone and a ruffled-membrane border into which apical proton pumps accumulate hydrogen ions that combine with chloride ions to form hydrochloric acid, which degrades bone mineral. The exposed collagen matrix is attacked by acid resistant endosomal and lysosomal enzymes that cleave collagen fibers effectively removing small quantities of bone [34].

How osteoclasts form, what regulates their differentiation and activity was an enigma. Research has revealed that osteoclast precursors circulate amid the monocyte/macrophage population and differentiate into preosteoclasts that fuse and form giant bone resorbing mature osteoclasts [35]. Inflammatory processes such as rheumatoid arthritis and periodontal infection predispose to osteoclastic bone resorption by production of pro-inflammatory cytokines such as IL-1 and TNF-alpha [36]. The osteoclast however, does not possess receptors for the cytokines or hormones. So, for years the biologists were perplexed as to how they resorbed bone. This conundrum was solved with the discovery of the osteoprotegerin (OPG), receptor activator of nuclear factor-kappa B ligand (RANKL) and receptor activator of nuclear factor kappa-B (RANK).

Discovery of OPG/RANKL/RANK Molecular Triad - The Solving of the Puzzle

In 1981, Rodan and Martin proposed a novel hypothesis wherein the osteoblast played a central role in mediating the hormonal control of osteoclastogenesis and bone resorption [37]. But, the factors expressed by the osteoblast/stromal cells remained undetermined until they were discovered independently by four groups using different approaches. Boyle and coworkers at the Amgen Inc (Thousand Oaks, CA, USA) discovered OPG serendipitously when they were attempting to identify tumor necrosis factor receptor-related molecules with possible therapeutic utility by generating transgenic mice that over-express various TNF receptor related cDNAs. Mice over-expressing one particular cDNA developed marked osteopetrosis because they did not have osteoclasts in their bones. The protein encoded by the gene was termed osteoprotegerin-OPG (the bone protector) [38].

Using the standard approach to test the Rodan-Martin hypothesis of purifying a factor from human embryonic fibroblasts that inhibited osteoclastogenesis, researchers at Snow Brand Milk Products Co. (Sapporo, Hokkaido, Japan) reported their discovery of an identical molecule. They obtained a partial protein sequence and subsequently cloned the cDNA for OPG [39].

The discovery of OPG became the key to identify the long-sought osteoclast differentiation factor expressed on osteoblastic/stromal cell that was essential for osteoclast development. Using expression cloning and OPG as a probe, both the groups quickly identified its ligand, which they termed OPG ligand [40] and osteoclast differentiation factor [41] respectively. This ligand turned out to be identical to a member of the TNF ligand family, which had been identified in the preceding year as RANKL [42] and TNF-related activation induced cytokine (TRANCE) [43]. The cellular receptor was identified as being identical to previously identified RANK, which Anderson and coworkers at Immunex (Seattle, WA, USA) had discovered while they were sequencing cDNAs from a human bone marrow derived myeloid dendritic cell cDNA library. [42]. Both the groups found that RANK had partial homology to a portion of the extracellular domain of human CD40, a member of the TNF receptor superfamily, and it was involved in the activation of T cells in the immune system. The groups then isolated RANKL by direct expression screening and found, like Wong and coworkers [43] did, that it increased dendritic cell stimulated naïve T cell proliferation and survival of RANK-expressing T cells. These discoveries led to the conclusion that RANKL is involved in osteoclastogenesis and T cell activation.

Osteoclast Formation/Osteoclastogenesis

Osteoclastogenesis is coordinated by the interaction of the three members of the TNF superfamily-OPG/RANKL/RANK [44] RANKL is expressed predominantly as a membrane-bound ligand on osteoblasts, fibroblasts, and activated T and B cells and its osteoclastogenic action can be blocked by its soluble decoy receptor osteoprotegerin (OPG) [9,35]. Together with Macrophage-colony stimulating factor (mCSF), RANKL is a key cytokine in the induction of osteoclastogenesis both *in vitro* and *in vivo* [45]. It binds directly to RANK on the surface of preosteoclasts and osteoclasts, stimulating both the differentiation of osteoclast progenitors and the activity of mature osteoclasts [40,46,47].

Regulation of Bone Remodeling - The Role of the RANKL-RANK-OPG System

Systemic factors and local stimuli in the bone microenvironment

target the molecular interplay of RANKL-RANK-OPG cytokine system, thus regulating the remodeling of alveolar bone. (Lerner 2; Boyle et al. Mundy et al. Horowitz et al.) [48-51]. Systemic modulators include calcitonin, parathyroid hormone, thyroid hormone, gonadal steroids, vitamin D, glucocorticoids and growth hormone. Local mediators include pro-inflammatory cytokines as well as prostanoids (Lerner) [48]. Bacterial products may interfere with bone remodeling balance by regulating RANKL expression (Lerner, Henderson and Nair) [48,52]. Gram-negative bacteria such as *A. actinomycetemcomitans*, (Teng et al. Kikuchi et al. Teng et al.) [53-55], *P. gingivalis* (Okahashi et al.) [56], *Treponema denticola* (Choi et al.) [57] and *Streptococcus pyogenes* (Okahashi et al. Sakurai et al.) [58,59] have been shown to upregulate RANKL expression in a variety of cells.

RANKL-RANK-OPG in Periodontal Disease

Studies have revealed that during inflammatory response, cytokines, chemokines and other mediators stimulate periosteal osteoblasts, altering the expression levels of receptor activator of nuclear factor-kappa B ligand (RANKL) on the osteoblast surface [9,49]. RANKL is expressed by osteoblasts in the form of a membrane-bound protein (mRANKL) or cleaved into a soluble form (sRANKL) [60,61]. IL-1 stimulates osteoclastogenesis and bone resorption, largely through up-regulation of RANKL, while TNF can stimulate osteoclastogenesis directly or indirectly through RANKL [62]. Inhibition of RANK ligand caused a decrease in alveolar bone loss in several models of periodontal disease (Teng et al. Han et al. Jin et al.) [55,63,64].

Teng et al. in their study demonstrated the role of CD4⁺ T cells in mediating periodontal bone loss. Also, they found that administration of RANK ligand inhibitor; osteoprotegerin reduced osteoclastogenesis and inhibited alveolar bone destruction [55]. Han et al. in 2006 demonstrated that B cells contribute to periodontal bone loss in the absence of T cells through production of RANKL [63].

Bone resorption and formation are regulated by the relative concentrations of RANKL, RANKL receptor RANK on osteoclast

precursor cells and the soluble decoy receptor OPG. When RANKL expression is enhanced relative to OPG, RANKL is available to bind to RANK on osteoclast precursors, tipping the balance to favor activation of osteoclast formation and bone resorption [49]. The binding of RANKL to osteoclast precursors occurs at a stage when hematopoietic stem cells have differentiated from the colony forming unit for granulocytes and macrophages to the colony forming unit for macrophages (CFU-M). Binding of RANKL to RANK on CFU-M in the presence of macrophage colony stimulating factor induces differentiation of preosteoclast into a multinucleated cell that becomes a mature osteoclast, which then resorbs bone [65]. When OPG concentrations are high relative to RANKL expression, OPG binds RANKL, inhibiting it to bind to RANK. Preventing the binding of RANKL to RANK leads to reduced formation of osteoclasts and apoptosis of preexisting osteoclasts [49]. Jin et al. in 2007 conducted a study in which rats were administered subcutaneously an OPG-Fc fusion protein to block RANK ligand. Compared to the controls, reduced osteoclastogenesis and significant preservation of the alveolar bone volume was observed in among the OPG-Fc treated rats [64]. Leiwiecki in 2009 demonstrated that treatment with Denosumab, a human monoclonal antibody specific for RANKL reduces the risk for fractures and increases the bone mineral density in post-menopausal women. It also inhibits osteoclast-mediated damage caused by rheumatoid arthritis [66].

The studies discussed above have provided valuable insights into the role of inflammation or host response in the pathogenesis of periodontal disease. The studies have unequivocally demonstrated that over amplification of the immune system releases a host of pro-inflammatory cytokines and mediators that can lead to osteoclastogenesis. Also, these inflammatory mediators can stimulate the release of RANK ligand and thereby lead to bone resorption.

The Assessment of RANKL/OPG Ratio in the Severity of Periodontitis

A number of clinical studies have investigated the concentrations

Study	Healthy subjects (n)	Gingivitis subjects (n)	Mild perio subjects (n)	Moderate perio subjects (n)	Chronic perio subjects (n)	Generalized aggressive severe subjects (n)	Chronic with immunosuppressant subjects (n)	Conclusion
Bostanci et al. (GCF) [68]	21	22			28	25	11	GCF RANKL & OPG were oppositely regulated in periodontitis groups.
Bostanci et al. Gingival tissue [69]	9	8			11	12	10	RANKL/OPG ratio increased in all periodontitis groups.
Lu et al. (GCF and gingiva) [6]	4				20			GCF RANKL, but not OPG was elevated in periodontitis groups.
Mogi et al. (GCF) [70]	28		27	58		47		RANKL/OPG ratio was significantly elevated in periodontitis groups.
Liu et al. (Gingival tissue) [71]	6			27		25		RANKL/OPG was elevated in periodontitis groups.
Kawai et al. (gingiva and blood) [72]	12				32			sRANKL, but not OPG was significantly higher in periodontitis groups.
Wara-aswapati et al. (gingiva and plaque) [73]	15				15			RANKL/OPG ratio was significantly higher in periodontitis groups.
Garlet et al. (gingival tissue) [74]	10	7			20	16		RANKL/OPG and MMP/TIMP expression determined disease progression/severity
Nagasawa et al. (gingival tissue) [75]	2				30			OPG is induced by LPS-stimulated gingival fibroblast.

sRANKL: Soluble Receptor Activator of Nuclear Factor-Kappa B Ligand; TIMP: Tissue Inhibitors of Metalloproteinases; LPS: Lipopolysaccharides; perio: Periodontitis

Table 1: Summary of human studies evaluating the RANKL and OPG in Periodontal Disease.

of RANKL and OPG in the gingival crevicular fluid of individuals with periodontitis to determine the RANKL/OPG ratio. Table 1 summarizes the human studies evaluating the RANKL and OPG levels in periodontal disease [67].

With a net increase in the ratio of RANKL/OPG in gingiva and crevicular fluid associated with bone loss and with the severity of periodontal disease, the possibility of interference with the RANK/RANKL/OPG axis may offer novel therapeutic outcomes. The desired outcome would be an increase in OPG or a decrease in RANKL that brings the OPG/RANKL ratio to a balance where bone formation is equal to bone resorption. A summary of animal studies in which osteoprotegerin fusion protein (OPG-Fc) and other inhibitors of RANK-mediated osteoclastogenesis are presented in Table 2 [67].

Thus the inference from the above mentioned animal studies is, therapeutic modalities which interfere with the RANK-RANKL-OPG axis will have a protective effect on osteoclastogenesis and periodontal bone loss.

Role of Cytokines in Bone Uncoupling

Bone is resorbed by osteoclasts, following which new bone is laid down by osteoblasts in the resorption lacunae. Under physiologic conditions, the two activities are coupled, i.e., the amount of bone formed by osteoblasts is equal to that resorbed by osteoclasts. In pathologic processes like periodontal disease and osteoporosis the two processes are uncoupled i.e., there is deficient bone formation following resorption [80].

The inflammatory process that leads to osteoclastogenesis and bone resorption may also be responsible for the failure to form adequate amount of new bone i.e., inflammation causes uncoupling of bone formation following bone resorption [8]. Al-Masahat et al. in 2006 and Liu et al. in 2006 stated that prolonged inflammation in diabetic animals interferes with bone formation in the periodontium following an episode of bone resorption. The prolonged inflammation may stimulate the death of the osteoblasts [81,82]. Application of cytokines like IL-1 beta and TNF-alpha *in vivo* not only stimulates bone resorption but limits bone formation by inhibiting the coupling process (Bertolini et al. Nyugen et al.) [83,84]. Osteoblast survival is a key factor in bone formation. A study by Diarra and colleagues reported that TNF-alpha stimulates production of Dickkopf-1 (DKK-1), which suppresses bone formation by inhibiting the WNT (wingless WNT/beta catenin) pathway. DKK-1, a negative regulator of WNT pathway is up-regulated by TNF stimulation through TNF-1 receptor and P38 MAPK (mitogen-activating protein kinase) signaling. The up-regulated DKK-1 not only promotes bone resorption but also blocks bone

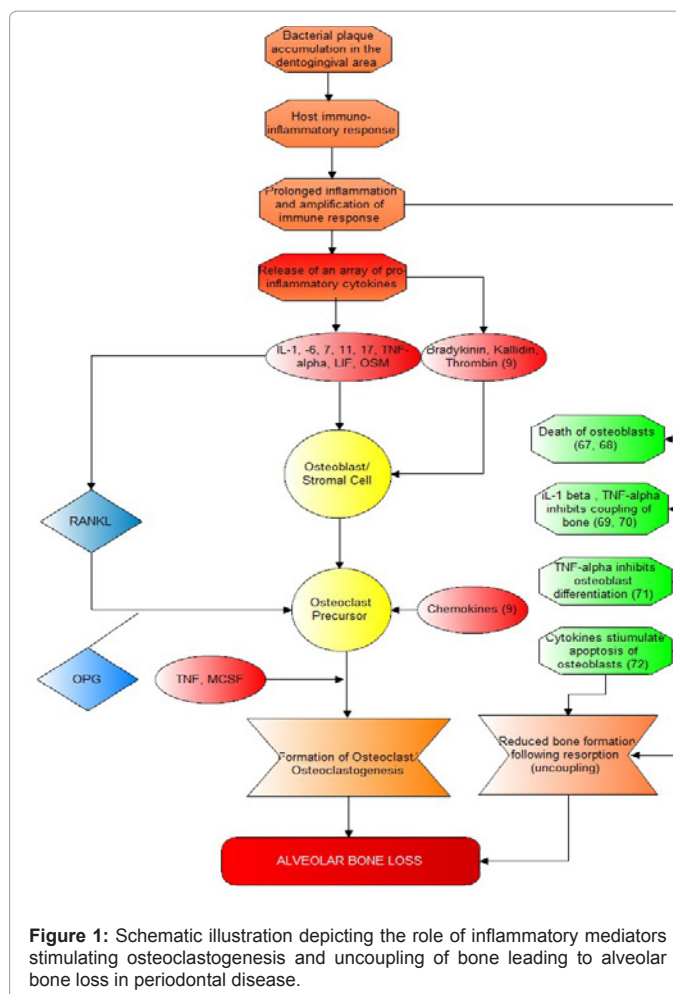


Figure 1: Schematic illustration depicting the role of inflammatory mediators stimulating osteoclastogenesis and uncoupling of bone leading to alveolar bone loss in periodontal disease.

formation and repair in the diseased joint [85]. Thus, inflammatory cytokines like TNF-alpha can limit bone formation by inhibiting osteoblast differentiation. In addition, the pro-inflammatory cytokines may directly stimulate osteoblast or osteoblast precursor apoptosis or indirectly affect it by stimulating expression of Fas, a potent apoptotic mediator [86]. Periodontal ligament cells are an important source of osteoblast precursors. TNF-alpha induced apoptosis of periodontal ligament cells may affect the pool of osteoblast precursors [87]. Another mechanism for uncoupling is the reduced function of osteoblasts mediated by diminished production of bone matrix proteins. A study by Centrella et al. in 1988 showed that TNF-alpha reduces collagen production and alkaline phosphatase activity in cells obtained from fetal rat parietal bone [88]. TNF-alpha and TNF-beta induce a two-fold to three-fold reduction in synthesis of non-collagen bone matrix proteins like osteocalcin by osteoblasts [89]. Eguchi et al. stated that TNF specific inhibitor, etanercept, promotes BMP-2 induced ectopic bone formation when applied systemically or locally *in vivo*, thereby improving the coupling process [90].

Thus evidence from the literature has unequivocally established the negative impact of the inflammatory process on bone coupling. The net bone loss observed in periodontitis is due to the cumulative effect of inflammation-induced bone loss and the uncoupling of bone resorption and bone formation (Figure 1).

Study Method	Study Method
Jin et al. [64]	Systemic delivery of rhOPG-Fc
Teng et al. [55]	Intraperitoneal injection of srOPG-Fc
Valverde et al. [76]	Subcutaneous kaliotoxin, K+-channel blocker T cells.
Kawai et al. [77]	Intraperitoneal injection of OPG-Fc
Mahamed et al. [78]	Intraperitoneal injection of hu-OPG-Fc
Rogers et al. [79]	Oral gavage of SD282, a p38 MAPK inhibitor
Assuma et al. [14]	Intrapapillary injection of TNF-alpha and IL-1 antagonists.

rhOPG-Fc: Human recombinant osteoprotegerin fusion protein; MAPK: Mitogen-Activated Protein Kinase; SFRP1: Secreted Frizzled-related Protein 1; hOPG-Fc: Human Osteoprotegerin fusion protein; srOPG-Fc: soluble recombinant Osteoprotegerin fusion protein; huOPG-Fc: human osteoprotegerin fusion protein; SD282: an indole 5-carboxamide selective p38* MAPK inhibitor (Scois, Fremont, CA). (David L Cochran)

Table 2: Summary of animal interventional trials of periodontal disease.

Conclusion

Periodontal diseases are chronic inflammatory disorders that afflict the supporting structures of the teeth. It is widely recognized that bacteria initiate periodontal diseases. The host responds to this bacterial attack by mounting an immuno-inflammatory response. The host response is essential to ward off the bacterial attack and prevent the systemic dissemination of infection. But in the process, the inflammatory response can also cause tissue destruction and alveolar bone loss. Prolonged inflammation and amplification of the inflammatory response releases a wide spectrum of pro-inflammatory cytokines and mediators. The cytokines and pro-inflammatory mediators propagate the inflammatory process and the “inflammatory front” advances to the alveolar bone. Alveolar bone loss is the cardinal sign of periodontitis. Experimental periodontitis studies have shown that cytokines like IL-1 and TNF-alpha can lead to alveolar bone loss. These cytokines can also induce osteoclastogenesis via the RANKL-RANK-OPG pathway. IL-1 and TNF-alpha also have a negative impact on bone coupling. The net bone loss seen in periodontitis is due to the cumulative effect of inflammation-induced bone loss and the uncoupling of bone formation and bone resorption. This intricate relationship between inflammation and bone metabolism has led to a new field of science termed “osteimmunology.” Extensive research in field of bone biology has provided valuable insights into pathogenesis of periodontal disease. Inflammation is now recognized as the central component of periodontal disease. Better understanding of the disease process will pave the way for adopting novel treatment approaches and thereby improve clinical outcomes. Therapeutic agents antagonistic to the inflammatory mediators or agents which block RANK ligand may be useful adjuncts to the conventional periodontal treatment procedures. We are still at the tip of the iceberg and longitudinal human clinical trials are required to prove the benefits of these therapeutic procedures.

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