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RANK-RANKL-OPG: A current trends in orthodontic tooth movement and its role in accelerated orthodontics

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Abstract

RANKL is a type II membrane protein bearing close homology to TNFSF members TRAIL, FasL, and TNF- α . RANKL has been definite for its key characteristic role in bone metabolism and the immune system. It is an apoptosis regulator gene, a binding partner of osteoprotegerin OPG, a ligand for the receptor RANK, and it controls cell proliferation by modifying protein levels. Osteoblasts and stromal stem cells receptor activator of NF κ -B ligand (RANKL), binds to receptor and RANK, is apparent on the surface of osteoclasts and their predecessors. Osteoprotegerin (OPG) secreted by osteoblasts and osteogenic stromal stem cells keep the skeleton from extreme bone resorption by binding to RANKL and averting it from interacting with RANK osteocytes. The critical cause of RANKL in alveolar bone remodelling during orthodontic tooth movement. The RANKL/OPG proportion in bone marrow is thus a significant element of bone mass in normal and disease conditions. This article reviews the role of the RANKL/RANK/OPG system in bone and other tissues in Orthodontic tooth movement.

Keywords: RANKL/RANK/OPG, osteoblast, osteoclast, osteoprotegerin, resorption, OTM

Introduction

The bone is embraced by four key components: cells, the extracellular matrix of collagen fibres, mucopolysaccharides and calcium salts. Bone is dynamic, and frequently remodels and mineralizes. Bone remodelling can be physiological, and pathological. In physiological bone remodelling, a balance should preserve osteoblastic synthesis and osteoclastic resorption. Pathological bone remodelling arises naturally once the balance is disturbed, which leads to destructive bone arthropathies Alida *et al.* 2020 [1]. Orthodontic forces are applied to a tooth and transmitted through the periodontal ligament and alveolar bone. The forces ignite the sequence of signal transduction events which leads to a shift in the osteoblastic and osteoclastic ratio. During orthodontic force tender to the areas of compression and tension. An atmosphere forms where osteoblastic activity overcomes, and new bone forms on the side of the tooth by stretching the PDL fibres. The areas where PDL fibres are under compression and increased osteoclastogenesis, producing bone resorption (Masella and Meister 2006) [2]. The events leading to orthodontic tooth movement (OTM) are complex and include the interface between the alveolar bone cells, PDL cells, and intercellular actions. The sequence of events at the tissue and cellular levels during OTM has been systematically recognized as the culmination of biochemical events at the molecular level in response to a mechanical or orthodontic force (Krishnan and Davidovitch 2006) [3]. Orthodontic tooth movement is a disease-free inflammatory reaction reliant on bone modelling and remodelling. The rate of tooth movement depends on the resorption of bone approved by osteoclasts on the compression side of tooth movement at the bone and periodontal ligament border. The stimulation of osteoclasts rests on stromal and osteoblast-derived factors. Receptor activator of nuclear factor kappa-B ligand (RANKL), is concealed by osteoblasts to allow binding to RANK on the surface of developed osteoclast cells, permitting for activation and survival of osteoclasts; (Boyce & Xing, n.d) [4]. The movement of RANKL is disputed by osteoprotegerin (OPG), secreted by osteoblasts to turn into a distraction receptor of RANKL (Nishijima and Yamaguchi, 2006) [5]. The RANKL/OPG ratio and RANK manifestation by osteoclasts control the variation of osteoclasts vital for the early phase of bone remodelling.

The RANKL/RANK/OPG pathway is vital in defining bone mass as it discharges osteoclast progenitors into circulation. RANKL-induced osteoclast activation is vital to homeostasis over progenitor recruitment connecting bone remodelling with haematopoiesis regulation. During tooth movement, RANKL expression rises in the gingival crevicular fluid with compression force in juvenile patients (Kanzaki and Chiba, 2006) [6]. Confined transfer of RANKL rises osteoclast assembly on the compression side of tooth movement associated to control, a parallel increase in tooth movement. RANKL is an acute acceleration aspect in OTM that induce continuous bone resorption on the compression side of tooth movement. The approaches and identification of RANKL, RANK and OPG. The four groups of the factors expressed by osteoblasts and stromal stem cells that regulate osteoclastogenesis (Kim and Handa, 2007) [7]. OPG was revealed unpredictably by researchers designed to identify tumour necrosis factor receptor (TNFR)-related molecules that might have therapeutic value. These researchers prepared transgenic mice overstating various TNFR-related cDNAs and found that mice overstating one particular cDNA developed marked osteopetrosis because they had no osteoclasts. They named the protein encoded by the gene osteoprotegerin the bone protector because it protects the skeleton from low bone mass and High fracture risk by restraining bone resorption. The researchers from Japan discovered the same molecule by releasing human embryonic fibroblasts that held in reserve osteoclastogenesis. Both the groups were quickly familiar with the ligand of this protein. They termed it OPG ligand (OPGL) and osteoclast differentiation factor (ODF), correspondingly (Brendan and Lianping, 2008) [8]. Brodetska *et al.* proposed that tooth impaction is associated with blocked NF- κ B signalling, turbulences in cascade activation of caspase-3, and the disproportion in the ratio of components of the RANKL/RANK/OPG signalling alliance. Accordingly, the partially obstructed or delayed process of bone resorption [9].

Materials and methods

The electronic databases PubMed, Google Scholar, Science Direct, and Cochrane Library beside with a courtesy manual search of all journals till the year 2021. No confines and language restrictions were useful during the electronic search to comprise all the relevant articles about the topic of interest. The search in PubMed yielded 208 articles which were separated based on the relevance of the title and abstract to the topic of interest. 104 articles were excluded based on this criteria. The full texts of the 52 articles were analysed of which 26 were excluded based on the exclusion criteria of this systematic review. Only one relevant article could be extracted through hand search and no articles were retrieved from other databases. The inclusion criteria include Vitro and Vivo studies.

RANKL, RANK, and OPG Pathway

Rank

Rank was originally discovered on dendritic cells (DCs), and RANKL mediates the survival of DCs. The interaction between activated T cell-derived RANKL and RANK expressed on DCs increases the antigen-presenting capabilities of the latter, thus augmenting the number and cell cycle of antigen-specific T cells as well as enhancing the immune response of memory T cells. RANK is expressed extensively in normal cells and mammary glands and some cancer cells. Tumours with a high possibility of metastasis of

bone. Activation of RANK mutations in exon 1 of RANK in humans, growing RANK-mediated NF- κ B signalling and osteoclast development and activity. Such mutation clarification for the osteolysis in patients with familial Paget's disease has the prominence of this system in humans¹⁴. The prospective role of RANK in tumour cell proliferation and its recognition could be a future advancement in antitumor therapy. However, still, it is not identified with inactivating mutations of RANK. (Fig 1).

RANKL

RANKL is a type II homotrimeric transmembrane protein stated as a membrane-assured and a secreted protein derivative from the membrane due to proteolytic cleavage. The factors excite the osteoclast formation and stimulate expression in osteoblasts and stromal cells. RANKL is decidedly articulated in lymph nodes, spleen and bone marrow. The activated T cells in synovial cells are inflamed in the joints of the patients suffering from rheumatoid arthritis. RANKL seem to be in control, at the slightest amount, with arbitrating the damaged joint in patients [10]. T-cell production of RANKL also persuades the manifestation of interferon by osteoclasts. T-cell develops to yield interferon, RANK-TRAF6 signal in osteoclast progenitor cells promotes osteoclastogenesis. In bone tissue, upon binding of RANKL expressed in osteoblasts to RANK on osteoclast precursor cells, TRAF6 is recruited to the cytoplasmic tail of RANK, leading to the activation of NF- κ B and AP-1. In assistance with the signal from the immunoreceptor tyrosine-based activation motif (ITAM)-harbouring adaptors to activate calcineurin, TRAF6 signal activates NFATc1, the main transcription factor of osteoclastogenesis, which induces the formation of multinucleated osteoclasts. The osteoclasts and osteoblasts are in a straight line and affect one another over ephrinB2-EphB4 bidirectional signalling, ephrinB2 ligand reverse signals to suppress osteoclast variation by constraining the c-Fos-nuclear factor of activated T cell c (NFATc) 1, however, EphB4-receptor forward signalling develops osteoblast differentiation [11]. RANKL rouses the release of undeveloped osteoclast into the movement. Though, it does not persuade utilization in protein tyrosine phosphatase in mice with osteoclast with bone defect bond and resorption [12]. RANKL-induced osteoclast activation controls the predecessor conscription as part of homeostasis and host defence, which involves bone remodelling with the hematopoiesis parameter. RANKL was identified in mammary epithelial cells during pregnancy [13]. In mice, its communication for lactational hyperplasia of mammary epithelial cells and production of milk. The expression by malignant tumour cells also directs RANK which induces the proliferation of tumour cells.

Osteoprotegerin

Osteoprotegerin (OPG) is seen in many tissues with osteoblasts, including the heart, bone marrow, spleen, liver, and kidney. It defends against bone loss by the support of homozygous mutation in juvenile patients with Paget's disease which is an autosomal recessive disorder pigeon-holed by increasing bone remodelling and fractures [15]. In a recent article, an incapacitating mutation in exon 3 of OPG materialized to be in three siblings with idiopathic hypophosphatasia, an autosomal recessive bone disorder categorized by augmented bone remodelling related to kyphosis, defects of long bones, and protrusion in children. RANKL expression by osteoblasts also controls OPG

manifestation. Overall, the Up - regulation of RANK expression by cytokines and factors of growth is connected with the down-regulation of OPG. The proportion of RANKL to OPG variations in osteoclastogenesis. Even though the

unreliable data and many journals emphasize the proportion of RANKL/OPG. It also is a substantial determinant of bone mass [16].

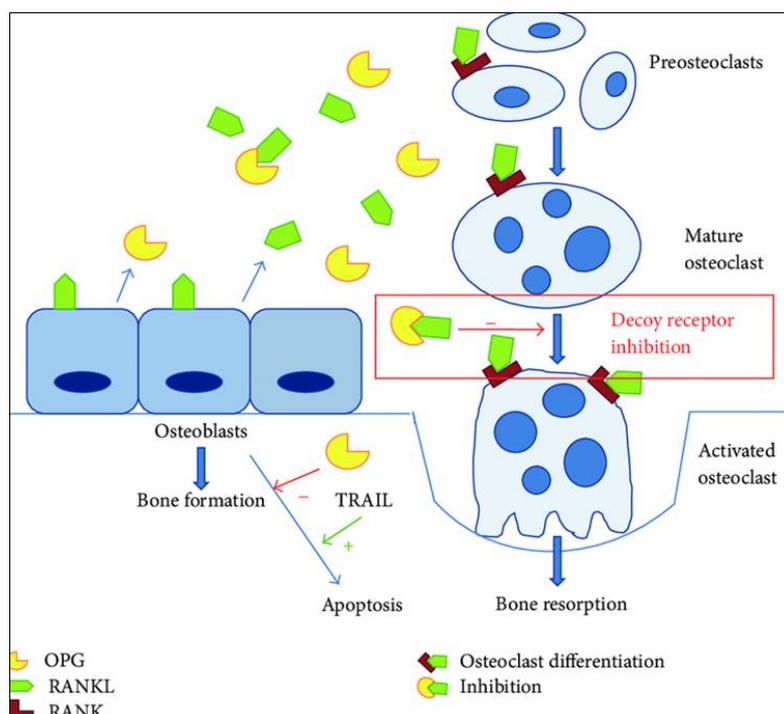


Fig 1: OPG/RANK/RANKL pathway

Differentiation of RANK/RANKL/Osteoprotegerin

Different approaches have been discovered, factors communicated by osteoblasts and stromal stem cells that control osteoclastogenesis. The unexpected discovery of OPG in studies designed to identify tumour necrosis factor receptor (TNFR)-related molecules that have therapeutic utility [17]. Researchers made transgenic mice overexpressing various TNFR-related cDNAs and found that mice overexpressing one particular cDNA developed marked osteopetrosis because they had no osteoclasts. They termed the protein programmed by the gene osteoprotegerin since it looked to protect the skeleton from low bone mass and increased fracture risk by restraining osteoclastic bone resorption. Researchers in Japan discovered an identical molecule by purifying human embryonic fibroblasts that inhibited osteoclastogenesis [18]. Both groups quickly identified the ligand of this protein, using it as a probe for expression. They called it OPG ligand and osteoclast differentiation factor. It is identical to a member of the TNF ligand family, which had been recognized the year before as RANKL and TNF-related activation-induced cytokine. Afterwards, identifying OPG as a ligand for OPG, the cellular receptor was matching to the RANK. The researchers at Immunex had revealed the sequencing of cDNAs from human bone marrow-derived myeloid dendritic-cell cDNA library [19]. RANK had partial homology to a share of the extracellular domain of human CD40. It is involved in activating T cells in the immune system and insulates the RANKL by direct appearance. Wong *et al.* [20], found the

survival of increased RANK-expressing T cells and propagation of dendritic cell-stimulated T cells. American Society for Bone and Mineral Research (ASBMR) suggested that RANKL and OPG by the approved names for these proteins. RANKL has been involved in osteoclast and T-cell biology has reproduced the now growing field of osteoimmunology [21].

Role of RANKL/RANK/OPG in orthodontic tooth movement

Orthodontic treatment time and current enterprises in orthodontic research. Orthodontic treatment time means around 1-2 years, depending on the severity of malocclusion, orthodontic treatment mechanics, patient compliance, and biology. Orthodontic tooth movement is a disease-free inflammatory reaction reliant on bone modelling and remodelling [22]. The defining factor of tooth movement is bone resorption conceded out by osteoclasts on the compression side of orthodontic tooth movement at the bone and border of the periodontal ligament. The stimulation of osteoclasts is contingent on stromal and osteoblast-derived factors. RANKL is concealed by osteoblasts which aid RANK on the surface of osteoclast cells, permitting to activate variation and existence of osteoclasts. The contrasted movement of RANKL is by osteoprotegerin (OPG), concealed by osteoblasts. The RANKL/OPG ratio and RANK manifestation by osteoclasts control the variation of osteoclasts essential for the initial phase of bone remodelling.

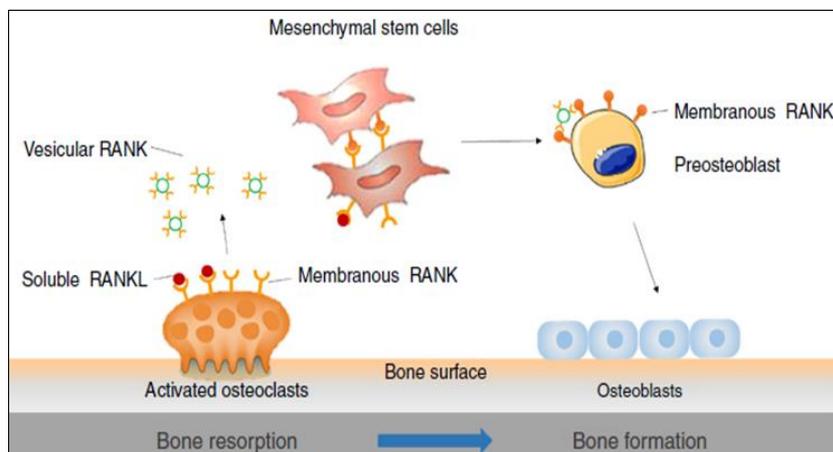


Fig 2: RANKL signalling in osteoblast differentiation and signalling initiatives osteoclastogenesis. In BMSCs, RANKL binding activates signalling, which impedes osteoblast variation

RANKL-RANK signalling controls osteoblast differentiation and bone formation. Chen *et al.* established that RANK in bone marrow mesenchymal stem cells (BMSCs) decreased during osteogenic differentiation. RANK significantly promotes, while overexpression suppresses, the osteoblast differentiation of BMSCs *in vitro* [23]. Mice with a RANK in MSCs suggestively flow osteoblast differentiation and bone formation (Fig 2). Stimulatingly, in a mouse model, RANK mice exhibit bone loss compared to sham-operated mice. The study reveals that RANKL signalling in BMSCs functions as a negative regulator in osteoblast differentiation and formation of bone. Chang *et al.* In this study developed an innovative RANKL-loaded formulation, which controls the release of RANKL biologically and effectively accelerates OTM. To use RANKL as a possible clinical therapeutic and developed a RANKL-loaded injectable therapeutics that continuously accelerate OTM. We can definite that our

formulation consisting of RANKL adsorbed on PLGA (Poly Lactic-co-Glycolic Acid) microspheres embedded in HEC gel (Hydroxyethylcellulose) is a suitable system for RANKL delivery. They achieved a linear release over 28 days and minimized spurt release. The dynamic release mechanism showed a quasi-Fickian release mechanism through distribution and formulation and also maintained the bioactivity of RANKL by enabling osteoclast differentiation of (RAW 264.7) murine preosteoclast cells, similar to control²⁴. (Fuji and Yamaguchi) established that Low-level laser irradiation (LLLI) aided osteoclast ogenesis on the compression side by stimulating the RANK/RANKL, and (M-CSF) through experimental tooth movement. In reaction to orthodontic force, RANK, RANKL, and OPG enable the direction of bone remodelling. An increase in the absorption of RANKLin gingival crevicular fluid (GCF) during OTM.

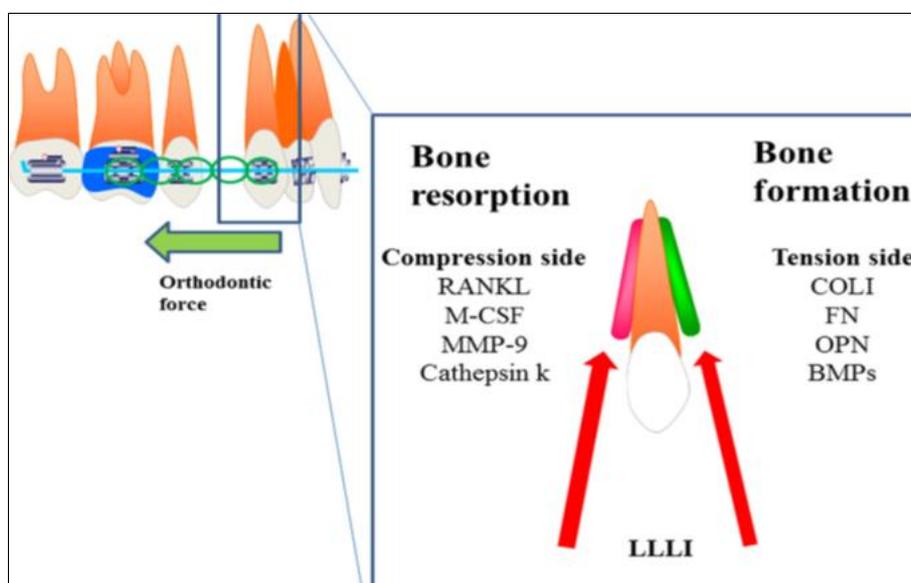


Fig 3: The schematic figure shows the molecular effects of LLLT on accelerated tooth movement. Low-level laser irradiation (LLLI) has been recommended to accelerate tooth movement.

On the tension side, LLLI stimulates bone formation and has been related to the improved expression of soft Type I collagen (COL1), fibronectin (FN), and osteopontin (OPN) during investigational tooth movement. Type I collagen is ample in the periodontal ligament, and fibronectin is seen throughout the mesenchyme. Fibronectins bind to collagen fibres and proliferation. The schematic Figure (Fig 3) shows

the molecular effects of LLLT on accelerated tooth movement. Low-level laser irradiation (LLLI) has been suggested to accelerate tooth movement by stimulating osteoclastogenesis on the compression side stimulating the RANK/RANKL and the c-FMS/macrophage-colony-stimulating factor R (M-CSF) during OTM. On the tension side, LLLI also stimulates bone formation and increases the

expression of COL1, FN, and OPN. ALP, alkaline phosphatase; BMP, bone morphogenic protein; RANKL, RANK ligand; M-CSF, the c-FMS/macrophage colony-stimulating factor; COL1, type I collagen; FN, fibronectin; OPN, osteopontin; MMP-9, matrix metalloproteinase-9. Chemotaxis is of the fibroblasts in the periodontal ligament [25].

Severe ORR has been detected in the resorbed cementum and periodontal (PDL) tissues to excessive orthodontic force subsequent in RANKL expression and causing an increase in osteoclastogenesis. The excessive orthodontic forces stimulated the process of ORR via RANKL and IL-6 expression in hPDL cells. Consequently, PDL cells are exposed to compressive forces that lead to inflammatory cytokines, which strengthen the development of ORR. Current studies have established that both PDL cells and cementoblasts rapid to RANKL. The IL-1 β and excessive forces induced significant RANKL expression in cementoblasts. ORR could be due to both PDL cells and cementoblasts, probably via RANKL expression in these cells.

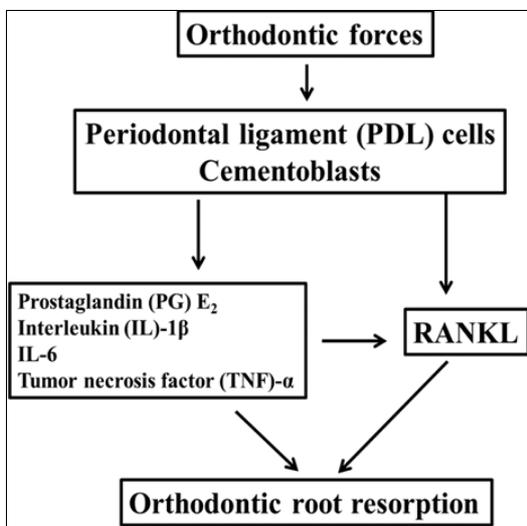


Fig 4: Role of RANKL in Orthodontic root resorption

In addition, these forces can increase RANKL and decrease OPG secretion in human PDL cells *in vitro*. Animal studies have proved the communication of RANKL in periodontal tissues during rat experimental tooth movement, and that the extent of experimental tooth movement in rats was accelerated by the transfer of the RANKL genes, and repressed by the transmission of the OPG gene, to the periodontal tissue. RANKL and OPG levels in GCF are increased and decreased, correspondingly, during OTM [26].

Clinical Significance

Latest studies demonstrated that orthodontic force transforms the levels of OPG, RANK, and RANKL in GCF during OTM. The rate of orthodontic tooth movement is significantly increased by the transfer of the RANKL gene. It has also been reported that the compressed PDL cells in cases of severe EARR may produce a large amount of RANKL, and regulate osteoclastogenesis. Consequently, the RANK/ RANKL /OPG system may offer an important link between bone remodelling, OTM, and root resorption.

Conclusion

RANKL/RANK/OPG system signifies the most important advances in osteoclast biology in the previous decade. This

system helps maintain skeletal homeostasis and is disturbed in most diseases that affect the skeleton by different levels of RANKL, and OPG, which are expressed by osteoblasts and stromal cells other cells. Osteoclasts not only respond to signals from osteoblasts and other cell types involved in immune responses, but they also regulate osteoblast functions. The multifunctional roles of RANK, OPG, and RANKL may provide an important link between bone remodelling, orthodontic tooth movement, and root resorption to other local and systemic conditions

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