REVIEW ARTICLE

An insight into the regulatory mechanisms of cells involved in resorption of dental hard tissues

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ABSTRACT
Dental resorptions constitute a challenge to dentistry due to the complexity of cellular and molecular biology. The various cells involved in resorption, collectively orchestrate the interplay between various cytokines, hormones, enzymes, and hard tissues influencing the progression of resorption. The concern and curiosity on this subject are not new. This paper attempts to review the various regulatory mechanisms of cells involved in resorption of mineralized dental tissues.

Key words: Alveolar bone, cytokines, osteoprotegerin, resorption, receptor activator of nuclear factor-κB, receptor activator of nuclear factor-κB ligand, teeth

INTRODUCTION

The skeleton is a metabolically active organ system, comprising of tissue-specific cells and extracellular matrix (ECM) that undergoes continuous remodeling throughout life. The remodeling of ECM is necessary to establish and maintain the hard tissue mass and architecture. Any disturbances in these events may lead to both structural and metabolic pathologies.[1]

Resorption of dental hard structures was first described in the 16th century in an early dental text, "Artzney Buchlein" (Hopewell-Smith, 1930).[2] Resorption with reference to dental tissues is a condition associated with either a physiological or a pathological process resulting in loss of dentin, cementum, or alveolar bone.[3]

Exfoliation of human deciduous teeth is a classic example of physiologic resorption. Although normally, the permanent teeth are protected from being resorbed, pathological resorption may occur in association with several local and systemic conditions.[4] Bone resorption is a complex process involving highly coordinated interactions between osteoblasts and osteoclasts that are modulated by receptor activator of nuclear factor-κB (RANK), receptor activator of nuclear factor-κB ligand (RANKL) and osteoprotegerin (OPG) system.[5]

Almost every day, dentists diagnose and treat pathological resorptive process in the alveolar bone and teeth. Resorption of mineralized tissues in the oral region offers the possibility of making comparative studies of general biological interest on the resorption of different mineralized tissues. In addition, the teeth and surrounding alveolar bone provide an excellent experimental model for studies on the local effects of mechanical forces, drugs and other substances which are considered to influence the resorptive process and their regulation.[6]

It has long been documented that resorption involves an elaborate interaction among inflammatory cells, resorbing cells and hard tissue structures. Injuries to and irritation of bone, dentin, and cementum add to chemical changes within these tissues with resultant formation of multinucleated giant cells referred to as clast cells. These clast cells are responsible for all hard tissue resorptive processes.[3] Over the years, considerable research has been carried out on bone and tooth resorption with respect to molecular biologic events. The purpose of this review is to integrate new knowledge regarding regulatory mechanisms of cells involved in resorptive process.

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KEY CELLS IN RESORPTION

Monocytes and macrophages

Monocytes are recruited to the site of irritation by the release of many proinflammatory cytokines and thus differentiate into macrophages. The migration and recruitment of macrophages

are regulated by macrophagic chemotactic factors that are derived from bone and tissue breakdown products.[3]

Clastic cells

The cells involved in resorption other than monocytes and macrophages are osteoclasts, odontoclasts, dentinoclasts, and cementoclasts. Osteoclasts are tissue-specific polykaryon bone-resorbing multinucleated giant cells, characterized by specialized membrane structure, clear zone, and ruffled borders.[3] Osteoclasts are differentiated from hemopoietic cells of the monocyte/macrophage lineage originating from either a unique primordial stem cell or an early osteoclast-specific derivative of the pluripotential hematopoietic stem cell.[7-9] Odontoclasts are generally smaller in size, having fewer nuclei and form smaller resorption lacunae than the osteoclasts.[3,6,10]

Odontoclasts probably have the same origin as osteoclasts. Odontoclasts are derived from tartarate-resistant acid phosphatase (TRAP) positive circulating monocytes. Dentinoclasts are similar to odontoclasts in origin, but they specifically resorb dentin.[11,12]

REGULATION OF RESORPTION

Mineralized tissues are protected from resorption by their surface layer of blast cells.[13] The resistance of the dental tissues to resorption depends on the structure and composition of mineralized tissues and of the surrounding cell.[6] Hence alveolar bone, dentine, and cementum differ in their susceptibility to resorption.[13] The alveolar bone is under a constant process of remodeling and the presence of teeth makes this more complex. The alveolar bone therefore adapting to the functional demands, is considered to be a structural element that is never stable.[14]

The complex process of bone resorption occurring during both physiologic and pathologic instances involves highly coordinated interaction between osteoblasts and osteoclasts that are modulated by enzymes, hormones, and RANK/RANKL/OPG system [Figure 1].[5,8,15] It is suggested that the OPG/RANKL/RANK system is instrumental for interactions between bone, vascular and immune cells. These protein ligands function as paracrine regulators of osteoclastogenesis and bone metabolism and share homologies with members of the tumor necrosis factor (TNF) receptor super family.[16-18]

OPG represents a mature protein of 380 amino acids. In contrast to all other TNF receptor super family members, OPG lacks transmembrane and cytoplasmic domains and is secreted as a soluble protein.[17] OPG mRNA has been detected in bone, cartilage, aorta, skin, lungs, heart, kidney, liver, brain and in several other tissues. At the cellular level, OPG is expressed in osteoblasts, stromal cells, endothelial cells, aortic smooth-muscle cells, fibroblasts, dendritic

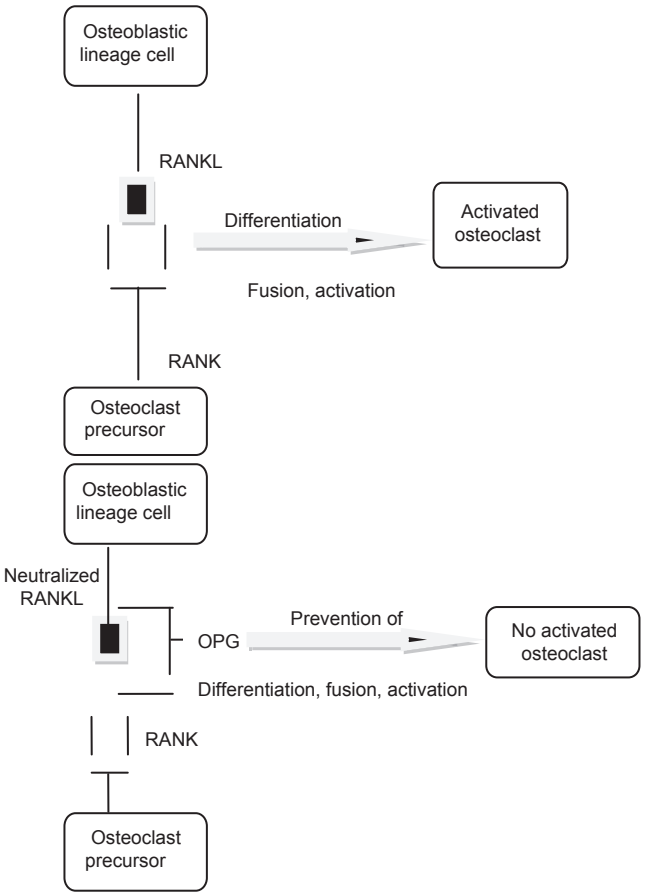

Figure 1: Flowchart depicting interrelationship between RANK, RANKL, and OPG molecules. RANK: receptor activator of nuclear factor-κB, RANKL: receptor activator of nuclear factor-κB ligand, OPG: osteoprotegerin

cells and lymphoid cell lines.[17,18] It is apparent that osteoclast formation and activation is critically regulated by the RANKL/RANK/OPG system and that the relative expression of these molecules will determine the number of osteoclasts formed and consequently the bone mineral density of the skeleton.[18] Various cytokines, peptides, hormones and drugs influence the expression of OPG. TNF-α, interleukin-1α, interleukin-18, transforming growth factor-β, bone morphogenetic protein, and steroid hormones such as 17β-estradiol are different cytokines, which upregulate the expression of OPG. Glucocorticoids and immunosuppressant cyclosporine A, parathyroid hormone, prostaglandin E_2, and basic fibroblast growth factor suppress the expression of OPG.[5,8,17] OPG functions mainly as a soluble decoy receptor for RANKL. The major biological action of OPG is inhibition of osteoclast differentiation, inhibition of osteoclast resorptive function and stimulation of osteoclast apoptosis.[8,15-17] The presence of OPG in serum is an absolute requirement for maintenance of bone mass by making unavailable sufficient quantities of RANKL. Several studies have investigated the clinical use of OPG as an anti-resorptive agent for treating a variety of bone disorders characterized by increased osteoclast activity.[18]

RANK is a 616-amino acid peptide on the cell surface of osteoclast precursors. RANK can be demonstrated at the mRNA level in many organs and tissues, but at the cellular level it is mainly expressed in osteoclast progenitor cells, osteoclasts, B- and T-lymphocytes, and in dendritic cells.[8,18] Regulation of RANK expression has been less extensively studied as compared to RANKL.[18] It has been stated that transforming growth factor-β (TGF-β) and vitamin D3 (D3), increases RANK mRNA. Recently, it has also been found that dexamethasone also enhances the mRNA expression of RANK. Interleukin-4 (IL-4) as well as activation of glycoprotein (gp) 130 by IL-6, decrease RANK mRNA. The decreased RANK expression caused by gp 130 stimulation is critical considering the stimulatory effect on bone resorption by IL-6 (+ sIL-6R). The neuropeptides like vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase activating peptide-38 (PACAP-38) have also been shown to decrease D3-stimulated RANK mRNA, which might, at least partly, explain the inhibitory effects of these neuropeptides on osteoclastogenesis. The literature has revealed that neither TNF nor RANKL affects expression of RANK, but co-stimulation with both these cytokines results in a substantial upregulation of RANK mRNA, which is likely a mechanism by which TNF synergistically potentiates the osteoclastogenic effect of RANKL.[18]

RANKL is a 317-amino acid peptide produced by osteoblastic lineage cells and activated T cells. When RANKL is expressed by cells of osteoblastic lineage, it is cell-bound and when expressed by T-lymphocytes it is known as soluble (s-RANKL).[5,17,18] The role of RANKL, together with another very important protein ligand, macrophage colony stimulating factor (M-CSF) which binds to its receptor c-forms, is to promote osteoclast formation, fusion, differentiation, activation, and survival, thus favouring bone resorption.[17,18] The biological effects of RANKL are produced when it binds to RANK.[17] Bone, bone marrow and lymphoid tissue including fetal liver, lymph nodes, spleen and thymus express high levels of mRNA for RANKL. Lower levels can be detected in heart, lung, thyroid, and placenta.[17,18] The soluble form of RANKL with M-CSF induces osteoclast formation even in the absence of cellular presentation. A possible explanatory mechanism for this is the differentiation of peripheral blood mononuclear cells and macrophage-like cells. RANKL is produced by activated T cells as a soluble protein, and therefore bone resorption is regulated by the immune system, where T-cell expression of RANKL may contribute to pathological conditions such as periodontitis and autoimmune arthritis. OPG and the soluble form of RANKL (s-RANKL) are present in the bloodstream, and measurement of their concentrations offers insights into the regulatory mechanisms of this system.[17,18]

Bone resorption can be physiologic or pathologic. Physiologic resorption of dental hard tissues occurs during tooth eruption and shedding. Pathologic resorption of bone has been documented in many of the lesions of oral and maxillofacial skeleton. The mechanism of resorption remains same for different lesions, but what triggers the event of resorption differs. Conditions that result in bone and tooth resorption include impaction, trauma, peri-radicular and periodontal diseases, infections, odontogenic cysts and tumors, benign and malignant tumors, metastatic tumors and radiation therapy.[19]

OPG is expressed by odontoblasts, ameloblasts, and dental pulp cells,[20,21] whereas RANK by multinucleated odontoclasts, localized near the dentine surface in resorption lacunae, or by mononucleated precursors.[16,22] RANKL is expressed by odontoblasts, pulp, periodontal ligament (PDL) fibroblasts, and cementoblasts.[16,23,24] As in osteoclasts, RANKL is also expressed in odontoclasts, suggesting an autocrine or paracrine effect of this regulator on these cells.[22]

The dental enamel is normally not exposed to any resorbing cells, especially prior to eruption it is protected by the enamel epithelium. However, multinucleated giant cells may be seen at the resorbing surface of the enamel in cases of profound root resorption and resorption of impacted teeth. It has also been noted that odontoclasts resorbing enamel, phagocytose crystals that have been liberated from partially demineralized enamel matrix by acids and subsequently dissolve them intracellularly.[6,11] Internal resorption is an unusual form of tooth resorption, that begins centrally within the tooth. Histologically internal resorption shows a variable degree of resorption of the inner or pulpal surface of the dentin and proliferation of the pulp tissue. Resorption of enamel is evident only if the lesion is situated in the coronal portion of the tooth.[19]

During initiation (epithelial thickening) of tooth development, OPG is weakly expressed in thickened tooth epithelium. OPG is also expressed in the outer edges of the invaginated tooth epithelium of the bud stage. A strong expression of OPG in both internal and external enamel epithelium is observed during cap stage and in the internal enamel epithelium during early bell stage. Weak expression of OPG was observed in pre-ameloblasts.[25]

Studies have also shown that teeth from explants treated with OPG, showed a distinct reduction in mineralization of enamel and resulted in thinner enamel.[25,26] These above-mentioned features suggest that OPG may not be responsible for resorption of protein matrix at the time of amelogenesis.

The resorbing activity of odontoclasts is related to the expression of the OPG/RANKL/RANK system by PDL cells. It has been shown that PDL cells, isolated from either non-resorbing deciduous teeth or permanent teeth, express OPG, but not RANKL. In contrast, PDL cells derived from resorbing deciduous teeth predominantly express RANKL and less OPG. RANKL regulates odontoclast differentiation and dose-dependently increases odontoclast resorbing activity. OPG suppresses the RANKL-induced activation of resorbing activity in odontoclasts.[23,27-30]

In the dental follicle environment, the ratio of OPG to RANKL supports, rather than inhibits, osteoclastogenesis.[16,31,32] During permanent tooth eruption, cytotrophic factors released from the dental follicle and/or the stellate reticulum, such as parathyroid hormone-related peptide (PTHrP), interleukin-1α, and TGF-β1, stimulate the expression of RANKL. Out of these factors, PTHrP controls the regulation of relative expression levels of RANKL/OPG on dental follicle cells, as well as in human PDL cells. PTHrP increases RANKL and down regulates OPG expression via a cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) -independent pathway, consequently leading to physiological root resorption of deciduous teeth and successful eruption of permanent teeth.[11,31,32] The differentiation and activation of localized preodontoclasts is also influenced by M-CSF. It is expressed by odontoblasts, ameloblasts, and dental pulp cells and its mechanism of action appears to involve upregulation of RANK and downregulation of OPG gene expression.[21,33] Recent studies have suggested that the cells of dental pulp may have some cytokine-producing cells, which mediate monocyte-macrophage lineage to form osteoclasts/odontoclasts.[34]

The exact mechanism includes the mediation of T-cells, odontoblasts, and fibroblasts. T-cells can be activated to express RANKL, thereby inducing differentiation and activation of preodontoclast cells under the influence of locally produced cytokines.[16,35] The odontoblasts and fibroblasts, which express RANKL, interact with mononuclear progenitors and produce active odontoclasts. A same sequence of events leads to physiological root resorption even in the absence of permanent successor. Cytokines, IL-β, prostaglandin E_2, TNF-α, or hormones such as dexamethasone and 1, 25 dihydroxycolecalciferol $(OH)_2$ D3, induced by the weakened PDL, stimulate expression of RANKL by PDL fibroblasts, leading to the recruitment of active odontoclasts and thus begin the resorption process.[16,17]

Recent studies, have corroborated that cementoblasts also express RANKL and OPG, which is modulated by PTHrP.[36] Cementoblasts secrete large quantities of OPG under non-resorbing conditions, which could be the reason why cementum is more protected than bone from resorption.[37]

Tartarate resistant acid phosphatase (TRAP) is an active enzyme, which plays a role in bone resorption inside and outside the osteoclast cell. TRAP can remove phosphate groups from osteopontin, an event that subsequently disrupts adhesion of osteoclasts to the bone. This suggests that the enzyme regulates osteoclast adhesion to bone and also enable migration of osteoclast to adjacent sites of resorption. The ability of TRAP to degrade phosphoproteins in bone by dephosphorylation illustrates a preliminary stage in the degradation of bone matrix, which is an inhibitor of resorption. Intracellularly TRAP has been localized in the transcytotic vesicles of osteoclasts. These TRAP-containing vesicles fuse with transcytotic vesicles transporting matrix degradation products. Later TRAP is secreted out of the cell together with matrix degradation products. Odontoclasts also possess many vesicles within which TRAP activity occurs and controls resorption in a similar process.[11]

Literature states that root resorption is related to complex combination of mechanical factors and biological activity, which comprehends the role of immunologic structures, including specialized cells.[10] During the dentinogenesis, the coronal dentin is protected by the recently formed enamel as well as the external dental epithelium, stellate reticulum, stratum intermedium, and by the ameloblasts. The root dentin is protected by Hertwig's epithelial root sheath, intermediate cementum, and after the fragmentation of the sheath, by the cementoblasts and cementum. Such structures keep the dentin protected against the immunologic system during the development of the natural tolerance, and in case the dentinary proteins are exposed, they may cause an immunologic response against the "self" components of the organism, known as an autoimmune reaction.[38,39]

Once exposed to the immunologic system, a cascade of events takes place for the lymphocytes to recognize and activate other cell types to differentiate in order to eliminate the "nonself" components. In the case of dentin, osteoclasts are the primary cells involved in root resorption, and they come from the lineage of macrophage– phagocytic cells located in the tissues derived from the monocytes playing an important role in the immune response. One of the ways for macrophages to be activated is by microbial products such as endotoxins and cytokines from T cells such as interferon-γ (IFN-γ). When activated, they kill microorganisms, secrete pro-inflammatory cytokines and present the antigens to T-auxiliary cells.[40]

The process of root resorption in humans is an essential step to attain immunological maturation. In some occasions, the immunologic system attacks the dentition in an unknown immune response that tries to destroy their roots, –a process named idiopathic root resorption.[41] This complex process would involve the main cells of a developed organisms' organic defense.[42]

Cytokines and chemokines are substances used by the immunological cells to communicate. Only IL-1α has a potent capacity to increase root resorption. As the studies concerning root resorption continue, some researchers have tried to associate its origin with a specific antigen present in the dentin that would trigger the immunologic system.[43]

CONCLUSION

Healthy jaw bone structures are critical for tooth retention, good oral health as well as for esthetic reasons. Knowledge on the mechanisms involved in physiologic root resorption process may enable us to delay or even inhibit exfoliation of

primary teeth in those cases where the permanent teeth are not present. The discovery of RANK/RANKL/OPG signaling pathway and the identification of its role in the pathogenesis of bone loss, have provided the rationale for development of therapeutic drugs, in early detection of pressure-producing agents in cysts, tumors and in timely treatment of impacted teeth to minimize the resorptive destruction.

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