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**Key Messages:** The immunology of root resorption is a theme still quite discussed in Endodontics. This literature review aims to analyze the immunological events that culminate in root resorption.

Review Article

# The Immunologic Relationship between Root Resorptions and Osteoclastic Activity - Literature Review

**Abstract**

Current literature indicates the close relationship between root resorptions and the role of clasts responsible for hard tissue destruction. The process is complex and involves mechanical factors and intense biological activity. Immunological interactions stimulate the recruitment and migration of clasts into a specific area, in order to destroy bone, cementum and dentin. Nevertheless, understanding the whole process will bring light to other questions concerning the role of the immunologic system in other parts of the human body. The aim of this review was to describe the development of the process, from mineralization to the destruction of hard tissues and the possible relationship between root resorption and cellular immune system.

## Introduction

Dental resorptions have been a challenge for odontology since Michael Blum first described it in 1530 in the city of Leipzig in Germany. Nevertheless, due to its complexity and the integration of the immunologic system, its scientific comprehension is considered recent, embracing nearly two decades. In a search to better understand this process, it is fundamental to study the formation of hard tissues, in order to have notions of how they are degraded, and how the most common cells of the immunologic system work together to interact with more sophisticated competent cells to recognize and finally destroy dental roots [1].

## Literature Review

Root resorption can be described as the destructions of the dental roots by competent cells from the immunologic system. The teeth are amazing specialized sensory organs with special characteristics: possessing some of the hardest tissues is the human body. The enamel, located in their crown, protects the dentin beneath from the outer environment. The roots of the teeth however, are protected by cementum. The pulp lies in the middle of the tooth and is responsible for nutrition, dentin formation and sensorial purposes, responding basically with pain to stimulus.

Enamel, cementum and dentin are located only in the teeth and show similarities in their formation. Cementum is an avascular mineralized tissue that covers and protects the root surfaces of the teeth as a whole, occupying the interface between dentin and the periodontal ligament (PDL). Not only does the cementum help anchor the tooth to its alveolar bone, it also plays a crucial role to protect the integrity of the root surfaces. Although enamel is not a connective tissue and has no collagen involved in its makeup, its formation follows many of the principals involved in the formation of hard connective tissue [1,2].

Hard tissue formation demands good blood supply enriched with nutrients for the production of an organic matrix capable of accepting mineral (hydroxyapatite). For all the hard tissues in the human body, except enamel, such matrix consists of collagen and ground substance and the mineral is located around and within the collagen fibrils. In enamel most of the organic matrix is lost once mineralization has been initiated, to accommodate more minerals [3].

The process of mineralization in the connective hard tissues entails an initial nucleation mechanism involving a cell - derived matrix vesicle. In enamel, the mechanism of initial mineralization is thought to be an extension from the apatite crystals of dentin, with further crystal growth dictated by the enamel matrix [4].

### The role of the clasts

The teeth are in constant movement due to mastication and stress applied directly over them caused by diverse situations, such as oral habits. Therefore it´s only expected that the periodontum transfers such impacts to the dental roots that, depending on the kind and duration, may cause significant hard tissue degradation. This could be described as a cellular event that involves many cell types, from the first defense line, such as lymphocytes, to giant multinucleated cells which are formed through asynchronous fusion of mononuclear cells. Such cells belong to the macrophage lineage and come from the hematopoietic system. They are named clasts, and are didactically subdivided in osteoclasts, dentinoclasts and odontoclasts, whose main characteristics is being relatively easy to identify under the light microscope because of their size (50 to 100μm) and their typical multinucleation. The structural, organizational and functional differences between dentinoclasts and osteoclasts are insignificant. Dentinoclasts are somewhat smaller. In general, clasts, during active root resorption, occupy shallow depressions, designated as Howship's lacunae, where their potential acidic production takes place. Bone turnover is a normal and necessary event in the maxillaries and

therefore clasts must be activated so that their production and recruitment be necessary to destroy calcified tissues for a number of different reasons, being inflammation the most common of them. However; hormones do play an important role in bone turnover but do not seem to be able to reach the cells alone. Specifically, Parathyroid Hormone (PTH) is not capable of entering the cells alone, and so it produces a secondary response in bone cells consisting of activation of adenyl cyclase with production of increased concentration of cAMP [5]. The authors conclude that this effect on cAMP is rapid and represents the second messenger by which PTH causes subsequent cell transformation for resorption. This concept was supported by the observations that the dibutyryl derivative of cAMP is able to stimulate bone resorption *in vivo* and *in vitro* [6]. Thereafter, clasts lay over the bone mineralized surface, where their cell membrane is thrown into deep folds which form a kind of brush border, designated as ruffled border. At the periphery of the brush border the plasma membrane is closely opposed to the mineralized surface and the adjacent cytoplasm, filled with fibrilar contractile proteins. Not only does this sealing zone attach the cells to the mineralized surface as it also isolates a microenvironment between them and the mineralized surface. Clasts are rich in acid phosphatases as well as other lysosomal enzymes; however and surprisingly, they do not function with lysosomal structures as in most other traditional cells. A recognized feature of the clasts is the presence of a proton pump associated with the ruffled border, pumping hydrogen ions into the sealed compartment and thus intensifying the acid environment [7,8].

Clasts are easily characterized by their morphology, which generally shows 2 to 10 nuclei/cell, their ability to form bone matrix, as well as the capacity for calcification of bone matrix and high alkaline phosphatases activity on the outer surface of the cell. A possible other property is the increased intracellular cyclic adenosine monophosphate (cAMP) production in the presence of parathormone (PTH), and some studies have found high cAMP responses to PTH in Isolated bone-cell populations possibly harboring clasts within them [9-12].

The effects of hormones on cells are important for recruitment and for their stimulation for diversified functions. cAMP, for instance, is regarded as a second messenger and is used for intracellular signal transduction, transferring into cells the effects of hormones which cannot pass through the plasma membrane. cAMP is synthesized from ATP by adenylate cyclase located on the inner side of the plasma membrane and anchored at various locations in the interior of the cell [13].

Internal signaling systems translate external stimuli to a narrow range of internal signals or second messengers [14]. Not only cAMP, but also cyclic guanosine monophosphatase (cGMP) which is also a two second messenger associated with bone remodeling [15]. Therefore hormones may change bone turnover in normal conditions as well as in pathologic processes.

According to some studies, it´s an open question whether clasts could degrade both organic and inorganic phases of bone. In order to bring more information to these questions, developed systems have brought light to peculiar osteoclastic biology [16]. Some studies have also shown that osteoclasts are of myeloid ontogeny, and are able to generate resorptive cells in culture from pure populations of mononuclear phagocytes [17]. When it concerns the clastic cells, more specifically about their origins, the macrophage lineage is indirectly being mentioned as well. Macrophages are antigen presenting cells (APC) that work together with T lymphocytes to activate more sophisticated immune cell types with the aid of the cytokine family to enhance their production and recruitment. The cytokine family is large and plays important roles in cellular recruitment and stimulations. It includes the Interleukins (IL), Interferon (IFN), Tumor Necrosis Factor (TNF), Coloning-stimulating Factor (CSF), Chemokines (CKs), and Growth Factor (GF) [18].

Immunocompetent response comes mainly with the integrated action of four cellular types: T cells (fundamental for the recognition of antigens exposed by APC cells), B cells (for antibody production), Natural Killer Cells (NK) that represent a subset of positive cytotoxic lymphocytes CD56, and Denditric Cells (DC) which in spite of belonging to the group of APC cells have also the ability of differentiate into different cell types [19,20]. Not only is the inflammatory bone destruction governed by local cytokine production but also the normal bone remodeling throughout the lifetime of an individual. Some of the factors which regulate physiologic bone remodeling are also the prostaglandins (PGs), IL-1, TNF-α and possibly IL-6 [21].

There are works that claim that collagens and proteoglycans are considered the two major classes of extracellular matrix macromolecules in skeletal, as well as in dental tissues. An analysis of changes in these matrix constituents during cell differentiation and morphogenesis may lead to a better understanding of the biological role of these macromolecules in development. Transplantation of demineralized bone matrix from the rat diaphysis to subcutaneous sites in allogeneic recipients results in new endochondral bone formation accompanied by hematopoietic bone marrow differentiation in the newly formed ossible [22,23].

The main features that distinguish the osteoclasts are the expression of calcitonin receptors, their capacity to degrade bone by producing a resorption lacunae; the synthesis of tartrate resistant acid phosphatase and distinctive polarization. They form the ruffled membrane at the osteoclast-bone interface. The process of resorption demands a lot of energy from these cells, so they have adapted by expressing many nuclei, surrounded by multiple Golgi complexes, an array of mitochondria and free polysomes, a rough endoplasmic reticulum for synthesizing proteins, as well as many coated transport vesicles, and also numerous vacuolar structures. Altogether such characteristics are typical of high energy expanding cells whose metabolisms are intense and urgent. Microscopic investigations suggest that not only the osteoclasts, but also fibroblasts, along with foreign body giant cells and macrophages cells are involved in the phagocytosis of collagen during resorption [24].

Some classic works describes the remarkable increase of hydrolytic enzymes during tissue remodeling, indicating the use of such enzymes in the degrading bone process by the osteoclasts [25,26], as well as the prostaglandins which seem to play a distinct role in the activation of the clasts as suggested by a study [27], who believed in their being a mediator of mechanical stress, in association with the opinion of Yamasaki et al., after experiments with rodents. Still in the role of prostaglandins, other studies carried

out in animals have identified the role of prostaglandins (PGE1 and PGE2) in stimulating bone resorption [28,29]. They believed that the hyperalgesia and hyperpyretic effects of prostaglandins had a direct action on osteoclasts in increasing their numbers and their capacity to form the ruffled border and effect bone resorption. To corroborate their results in associating prostaglandins with osteoclasts, another study assessed this relationship by testing dental movement after the administration of indomethocin, an anti-inflammatory agent and a specific inhibitor of prostaglandin synthesis [30] and concluded that like other bone resorbing agents, PGE2 seems to stimulate osteoblastic cell differentiation and new bone formation, coupling bone resorption *in vitro*.

A great variety of chemically different substances seem to play distinct roles in bone turnover. Growth factors (platelet-derived growth factors), hormones (PTH), and interleukins as well as other cytokines with the capacity to induce PGE2 production, are able to alter bone remodeling [31]. Another study evaluated the effects of prostacyclin and thromboxane A2 in orthodontic tooth movement and osteoclastic activity on rats. They concluded that that there is analogue increase in the number of multinuclear osteoclasts, osteoclastic bone resorption, as well as in the rate of orthodontic tooth movement [32].

## Immunologic considerations

Root resorption is a phenomenon which can be classified as physiologic and pathologic. The former is clearly observed in dental exfoliation and during dental movement due to mastication and the latter is usually divided in external (involving the outer part of the tooth–cementum and dentin) or internal (involving the walls corresponding to pulpal space) resorptions [33]. These conditions involve the first type of immunologic defense, denominated innate or cellular immunologic system which is unspecific in its phagocytic function, while is able to stimulate the second lineage of more sophisticated T cells through chemotactic substances representative of the adaptive or humoral immune response, which is characterized by the B and T lymphocytes; the former being responsible for the protection of the organism against extracellular antigens through the production of antibodies; and the latter for the organic protection against intracellular antigens [34]. When an antigen is detected in the human body, both kinds of immunities work together to detect the nonself structures, to attack, to destroy, and to keep, in the cell membranes, part of their structures so that they can be recognized in case they invade the organism again. More interestingly yet is the fact that some structures and some cellular types of the organism, since the very beginning of the intra-uterine life, must be hidden from the immunologic system not to be recognized as antigens, and consequently be attacked by the immunologic system. There are evidence that dentin is immunogenic, and once the dentinary proteins are exposed, an immunologic reaction may be triggered causing root resorption [35,36]. If dentinary antigens are liberated, macrophages will be recruited as one of the main cells recruited in the first line of immune defense. One of the ways for macrophages to be activated is by microbial products, such as endotoxins and cytokines from T cells, such as IFN-γ. Macrophages can also acquire different morphology in the varied tissues of the body, such as Kupffer cells in the liver and osteoclasts in the bone, or even odontoclasts or dentinoclasts to destroy dental structures [37-39].

Replanted teeth with severe damage in the periodontal ligament and absence of infection will lead to replacement resorption, which can be synthesized by the approximation and consequent replacement of the dental structures by osseous tissue [40,41]. This process may progress and lead to dental loss and that´s the normal outcome of replanted teeth depending on the time elapsed between the trauma and the dental assistance.

An important study was carried out by King and Courts [42]. They showed that the drop in autoantibody titers to tooth root antigens was shown to coincide with active root resorption in dogs. They had planned to establish a quantitative mouse model for root resorption and to observe if a similar drop in tooth root autoantibodies coincided with active root resorption in the mentioned animals. For that, they accomplished uniform spots of necrosis in the periodontal ligaments of the lower incisors of 36 male Swiss albino mice with the insertion of a cryoprobe through skin incisions. Contralateral incisors were used as controls. Six mice were then killed at 0, 3, 5, 7, 10, 14, and 21 days. The blood, as well as the incisors, were collected. The serum autoantibody titers were determined with the aid of an enzyme-linked immune sorbent assay (ELISA) antigen prepared with the extract of the incisor roots which had been harvested in the mice. There was no evidence of root resorption on the control teeth.

On the other hand, the localized lesions located on the treated teeth were considered as being of a significant size between 7 and 14 days. However, most of them erupted into the mouth around 21 days. The autoantibody titers dropped by 3 days, remained depressed until 14 days; r0eturning to pretreatment levels by 21 days. With all these results, they concluded that the mouse, like the dog, harbors a serum autoantibody to tooth root antigens which is suppressed during active root resorption.

Another study was designed to assess the response to traumatic root resorption in mice after their being hyperimmunized with crude dentin extract. Their hypothesis was that the elevated dentin antibody titers would correlate with root resorption. They immunized the mice with mouse dentin and the controls were then sham immunized. They boosted all mice again four weeks later with and without mouse dentin. All mice were reboosted two more times at weekly intervals with mouse dentin and afterwards twice, at weekly intervals, also with rat dentin; this was accomplished to increase mouse serum antibody titers to dentin. The animals were killed ten days later; the serum was tested for antibody to dentin antigen. They were able to observe root resorption on the incisors in the sham-immunized mice but not in the dentin-immunized mice. They found that only the serum antibody titers to dentin from preimmune mice and bleed five were statistically significant. The authors' data conclude that antibodies do not mediate the traumatic root resorption process as were originally hypothesized. They suggested that hyperimmunization with dentin may, surprisingly as it may seem, protect the animals against traumatic root resorption [42].

Another interesting work has featured that replacement dental resorption might be a consequence of trauma and cause transplant

and reimplants to fail. Hidalgo, Itano and Consolaro [35,43] showed the participation of the immuno-pathological responses in inflammatory dental resorption. They claimed that the mechanisms of the two most common types of dental resorption were different. They aimed to study the immuno responses of patients who suffered dental trauma with subsequent replacement dental resorption. The ELISA results demonstrated that the serum from the patients with replacement root resorption contained larger amounts of IgG and smaller amounts of IgM anti-total human-dentin extract and anti-fractions of extract than did the serum from control individuals. They concluded that dentin has antigens and therefore is immunogenic; and the serological profile of patients with replacement dental resorption may be identified through biochemical analysis of their blood and added that their method may allow the early diagnosis of the dental resorptions before they become radiographically visible.

## Conclusions

Root resorption continues to be a difficult and complex subject for odontology, although relatively common in the dental practice. The processes involved in their establishment, although connected, still bring more questions than answers concerning the recruitment, differentiation and interactions of the cell types and both immunity defense systems. Despite all the investigations and new immunologic approaches, the etiologic factors and predictability of this phenomenon still remain obscure.

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