

SYLWIA MAJEWSKA-BEŚKA^{1, D-F}, JOANNA SZCZEPAŃSKA^{2, A, D}

Genetic and Molecular Mechanisms of Root Resorption – a Literature-Based Study

Genetyczne i molekularne mechanizmy resorpcji korzeni zębów – na podstawie piśmiennictwa

¹ Postgraduate studies, Department of Pediatric Dentistry, Medical University of Lodz, Poland

² Department of Pediatric Dentistry, Medical University of Lodz, Poland

A – koncepcja i projekt badania; B – gromadzenie i/lub zestawianie danych; C – opracowanie statystyczne;
D – interpretacja danych; E – przygotowanie tekstu; F – zebranie piśmiennictwa

Abstract

Resorption is a common condition in dentistry. The etiology of this process is multifactorial, and not completely examined. It is known that factors such as inflammatory conditions, individual predispositions, such as root morphology and external conditions, the forces used during orthodontic treatment, influence the origin of this process. Current research puts particular emphasis on cellular and molecular mechanisms and the role of genetic factors in the evaluation of resorption. The aim of the study was to review the literature concerning the molecular and genetic factors underlying the resorption process of bone and mineralized tissues of teeth, in the context of physiological deciduous teeth resorption, and pathological resorption as a consequence of orthodontic treatment. Based on current knowledge, although it is not possible to precisely predict whether mineralized dental tissue influenced by pathological conditions is prone to resorption, it is possible to assume that such an eventuality is a risk factor to be taken into consideration. The mechanism of dental hard tissue resorption is similar to that which occurs in bone tissue. Research into molecular and genetic resorption mechanisms may be useful in the future prevention or treatment of the ongoing resorption process (*Dent. Med. Probl.* 2012, 49, 3, 329–335).

Key words: root resorption, bone resorption, genetic factors, osteoclasts, odontoclasts.

Streszczenie

Resorpcja jest zjawiskiem powszechnie spotykanym w stomatologii. Etiologia tego procesu jest wieloczynnikowa i nie do końca poznana. Wiadomo, że wpływ na jej powstawanie mają czynniki zapalne, predyspozycje osobnicze, takie jak np. morfologia korzeni i czynniki zewnętrzne, np. siły użyte podczas leczenia ortodontycznego. Obecnie coraz częściej zwraca się uwagę na komórkowe i molekularne mechanizmy oraz rolę czynników genetycznych w procesie rozwoju resorpcji. Celem pracy było omówienie mechanizmów molekularnych i genetycznych leżących u podstaw procesów resorpcji tkanki kostnej i tkanek zmineralizowanych zębów w aspekcie fizjologicznej resorpcji zębów mlecznych oraz resorpcji patologicznej będącej wynikiem leczenia ortodontycznego – na podstawie piśmiennictwa. Opierając się na obecnej wiedzy, nie można dokładnie przewidzieć, czy tkanki zmineralizowane zębów pod wpływem procesów nefizjologicznych zostaną dotknięte resorpcją. Biorąc jednak pod uwagę czynniki ryzyka, można określić takie prawdopodobieństwo. Mechanizm resorpcji twardych tkanek zęba jest podobny do procesu występującego w tkance kostnej. Badania nad molekularnymi i genetycznymi mechanizmami resorpcji mogą pomóc w przyszłości w jej zapobieganiu lub ustaleniu skutecznej terapii już istniejącego procesu patologicznego (*Dent. Med. Probl.* 2012, 49, 3, 329–335).

Słowa kluczowe: resorpcja korzenia, resorpcja kości, czynniki genetyczne, osteoklasty, odontoklasty.

Resorption is a process resulting in the loss of mineralized tissue. It is a phenomenon that has a multifactorial etiology, influenced by both environmental and individual predispositions. Resorption may concern the bone, as well as the hard tissues of the tooth. The process of resorption commonly occurs in the bone and, under normal physiological conditions, is necessary for the proper process of remodeling. In the case of teeth, physiological resorption occurs only in primary dentition [1–3].

Pathological resorption occurs, among other reasons, because of the action of non-physiological forces and inflammatory factors, and may occur in both the bone and tissue of the tooth. While dissolution of bone occurs under the influence of osteoclasts, the tooth structure is broken down by the action of both osteoclasts and odontoclasts. There are many ways in which these two cell types are similar in terms of structure, function and mechanism of action; however, more is known about osteoclasts. As for odontoclasts, it is not certain how their precursors arise, what mechanisms govern their differentiation and then causes them to merge into multinucleated cells, or why they are activated in some cases but not in others [2, 4, 5].

It has not yet been explained why resorption is specific to the root of the deciduous tooth and not the tooth next to or lying under the permanent tooth. The tissue where resorption takes place is located between the root of the primary and the crown of the fixed tooth. In the case of physiological resorption, it is assumed that the process is initiated by the underlying developing permanent tooth, which provokes the resorption of the bone and the root lying above it; however, the pulp of the deciduous tooth also participates in this process [5–7].

In permanent dentition, external or internal resorption may occur as a result of inflammatory conditions of the pulp, mechanical damage to the tooth, especially after partial or complete dislocation, and fracture of the tooth root. Also, improperly performed bleaching and prosthetic restorations can induce resorption. Another example is root resorption caused by pressure resulting from orthodontic treatment; its scope and course depends on the forces exerted on the tooth and root morphology. In recent years, more attention has been paid to the genetic factors concerned with these processes, particularly since root resorption is observed in some systemic diseases. However, the genes directly linked with the resorption process have not yet been identified. This process can also be modified by environmental factors [1, 2, 8, 9].

The aim of this study is to review the molecular and genetic mechanisms underlying the resorption processes of bone and mineralized tooth tissues as well as presentation of the role of osteoclasts, odontoclasts, odontoblasts and the mechanisms of physiological and pathological external resorption in the course of orthodontic treatment, on the basis of the literature.

Mechanism of Bone Resorption

Mature, large, multinucleated clastic cells are formed by the fusion of mononuclear precursors under the influence of monocyte growth factors and other factors secreted by osteoblasts and osteogenic cells. The mechanisms that govern the fusion are not fully understood [10]. The cells then migrate to those regions of mineralized tissue, which are subject to resorption. After reaching its target, the clastic cell adheres to the mineralized tissue: for example, bone. Full maturity of the osteoclasts and their ability to resorb is achieved after contact with the tissue designated for resorption.

The mechanism of clastic cell adhesion involves integrins: transmembrane glycoprotein receptors located on the cell surface of osteoclasts, which also play a role in the changes occurring in the cell after it adheres to mineralized tissue. The adhesion process forms the so-called *free zones* or *clear zones*, facilitates the transmission of chemical signals between the cell and its environment and reforms the cell membrane into a folded edge, called a ruffled border [4], demarcated from the surroundings by the free zone. In the membrane of the cellular ruffled border there are, among other things, an H⁺ ATPase pump responsible for reducing the pH of the environment in the resorbing zone, which in turn facilitates further enzymatic activity. Osteoclasts have the ability to resorb organic and inorganic components of bone tissue as well as manufacture chlorine and hydrogen ions, hydrolytic enzymes, metalloproteinases (MMP-9) and cathepsin K, which are of particular importance in the processes of bone remodeling [5].

Regulation of Osteoclast Function

In bone tissue, osteoblasts regulate osteoclast activity by, among other things, M-CSF – monocyte – macrophage colony stimulating factor and OPG – osteoprotegerin, which competes for the RANK receptor located on the osteoclasts with the cytokine – ligand RANKL – receptor activa-

tor of nuclear factor kappa B ligand, and makes the connection of membrane receptor RANK with RANKL impossible, preventing the activation of osteoclasts. RANKL is also known as ODF – osteoclast differentiation factor and is a key cytokine for the formation and activation of osteoclasts. A strong inhibitory effect on the production of RANKL in osteoblasts is expressed by TGF- β – transforming growth factor β , which stimulates the production of OPG [7, 10, 11].

Other cytokines that regulate osteoclast formation are TGF- α – transforming growth factor α , interleukin 1 β and interleukin 6; they have a pro-inflammatory effect and increase the concentration of RANKL [12]. Interferon gamma, produced by activated T-lymphocytes, inhibits osteoclastogenesis, probably at the stage of osteoclast precursor differentiation. CSF-1 – colony stimulating factor or M-CSF – monocyte stimulating factor are involved in the proliferation and differentiation of mononuclear osteoclast precursor cells [13].

In vivo immunohistochemical studies on developing mouse teeth show the presence of RANKL and OPG in odontoblast, ameloblast and pulp cells [14]. Other sources report that cytokine RANKL is also produced by cementoblast, periodontium and pulp fibroblasts, while OPG and M-CSF are produced by odontoblasts, ameloblasts and dental pulp cells [5]. So the above mentioned cytokines secreted by the tooth cells might also have an impact on osteoclastogenesis.

Odontoclasts Morphology and Mechanism of Action

The origin of odontoclasts is not exactly explained, but there are indications that they arise in a similar manner as osteoclasts [15]. It is known that the cells are multinucleated, and have an osteoclast-like structure characterized by their ability to dissolve hard tissue, such as cementum and dentine. As with osteoclasts they produce a ruffled border in contact with the resorbed surface. However, they are smaller, have fewer nuclei and produce smaller resorption lacunae [7]. Odontoclasts, as with osteoclasts, also produce the RANK receptor, and probably the RANKL cytokine, which can suggest autocrine or paracrine activity [5, 11].

Odontoclasts produce hydrolytic enzymes that are secreted into resorption lacunae. The action of the proton pump (H⁺-ATPase) acidifies the environment outside the cell and causes the dissolution of mineralized apatite, while the organic portion is dissolved by matrix metalloproteinases (MMP-9) and cathepsin K [5]. MMP-9 is regarded as the main proteinase that dissolves the protein

of the dentine of deciduous teeth during physiological resorption. This enzyme is located in vacuoles, lysosomes, in the spaces between the ridges of the odontoclast cell membrane and in areas directly related to resorbed dentin. According to Linsuwanont et al. [3] cathepsin K also is synthesized and secreted by odontoclasts during physiological resorption of teeth. However, investigations conducted by Domon et al. [16] confirm its expression in both odontoclasts and osteoclasts during induced tooth movement in rats, implying that Cathepsin K takes part also in the pathological processes of bone resorption.

Physiological Resorption of Deciduous Teeth

It is commonly believed that the force exerted by a permanent tooth initiates the resorption of bone and the roots of the overlying milk teeth. However, it seems that this pressure has less impact than that of the dental follicle and the stellate reticulum of the permanent tooth. Stellate cells produce, among other things, PTH-rP (a parathyroid hormone called PTH-related protein), which connects to the appropriate cell receptor on the dental follicle. Stimulation of the latter causes the secretion of CSF-1, MCP-1 – monocyte chemotactic protein-1, and vascular endothelial growth factor. These factors promote the recruitment of monocytes from a rich network of blood vessels, as well as their diversification and fusion, and the formation of osteoclast or odontoclast precursors.

As the presence of the RANKL cytokine is necessary in the next stage, it is desirable to have cells with the ability to produce it. Fortunately, the dental follicle cells are just such an example and hence, can also affect the development of clastic cells. PTH-rP secretion also causes an increase in RANKL and decreases OPG production by the periodontium of the tooth undergoing resorption. However, prior to physiological resorption, cytokine is released in different proportions with the opposite effect, that is, protecting the root [5]. The process of root resorption does not proceed continuously; it is interrupted by rest periods and deposition of cement on resorbed surfaces.

A study by Domon [17], based on an analysis of TRAP activity (tartare resistant acid phosphatase), identified three types of resorbing surface on deciduous teeth. The first type possessed many TRAP-positive cells, where the root surface was actively being resorbed by odontoclasts. However, a second, TRAP-negative, area demonstrated no active odontoclasts, suggesting a period of

interruption or repair. Finally the third area was populated by small TRAP-positive cells defined as mononuclear preodontoclasts, that is, odontoclasts with small resorption lacunae, and was considered to be occupying a preparatory phase to the process of resorption. The TRAP enzyme is also characteristic of osteoclasts during their period of activity.

Role of Pulp in the Process of Resorption

The pulp seems not to participate in the initial stages of deciduous tooth root resorption. Odontoclasts usually occur in the pulp when the resorption process has advanced roughly one millimeter into the cemento-enamel junction. At this time, inflammatory cells such as T and B lymphocytes occur and are involved in breaking down the pulp. Thereafter, root dentine is resorbed by odontoclasts [5].

Both RANKL and CSF-1 or M-CSF can be found in higher concentrations in the pulp cells of primary, rather than permanent, teeth. The large amount of RANKL and CSF-1, and decreased expression of OPG, seen in the pulp of deciduous teeth with ongoing resorption may indicate that, as in the case of osteoclasts, RANKL and CSF-1 stimulate odontoclast differentiation and OPG inhibits this process. In addition, in the pulp tissue of primary tooth being resorbed, three other factors were identified: MCP-1 – monocyte chemoattractant protein, TGF- β – transforming growth factor and Cbfa1 – core binding factor a1 (a transcription factor). Cbfa1 is necessary for proper differentiation of osteoblasts and correct bone function. Therefore, while RANKL, CSF-1 and MCP-1 favor resorption, TGF- β , OPG and Cbfa1 inhibit it.

Elsewhere than the pulp, these factors are also produced by the cells of the peridontium, odontoblasts and follicle cells of the permanent tooth lying below the resorbed milk tooth [7]. This does not mean that the process of resorption is controlled only by the pulp cells of the deciduous tooth and the germ of the permanent tooth. Endodontically treated primary teeth, those with necrotic pulp or without a regular successor, are also subjected to resorption, although sometimes with a delay.

Expected Impact of Extracellular Proteins on the Resorption of Teeth

BSP – bone sialoprotein and OPD – osteopontin are extracellular proteins found in the fibers of the periodontium of deciduous and permanent teeth. However, their expression and location dif-

fers between fixed and primary teeth; while they are located not characteristically around the roots in permanent teeth, they are present mainly in the area of the odontoclast resorption lacunae around the roots in deciduous teeth. Lee et al. [6] suggest that these proteins may be important for the adhesion of odontoclasts to the roots in the process of physiological resorption. It is not known for sure whether these proteins appear around the roots during its development, or later, and under what circumstances. It seems that the BSP and the OPD can act as signals for selective adhesion of odontoclasts. Recent *in vitro* studies have indicated that the addition of OPD and BSP to osteoclasts stimulates the cells to resorb bone [6].

Influence of Orthodontic Treatment on the Increased Risk of Resorption

Orthodontic tooth movement always causes root micro resorption to some extent, but it is not noticeable on radiographs and the prognosis is not poor, unless there is a tendency towards deterioration. The degree of root destruction depends on many factors: the distance that the root must traverse from the initial point to the destination and, hence, the type of defect, the duration of treatment, the force used [2, 8], root morphology (short, thin, tapered roots are prone to greater resorption), trauma, parafunctions and so on [8]. The type of braces used to treat malocclusion seems to be important; permanent braces will more often cause resorption than removable devices [8, 18].

The influence of the orthodontic tooth movement on the bone also plays a significant role in this process. The more efficient the remodeling process which occurs in this tissue, the lower the risk of root resorption. So, to effectively move the tooth, the bone should be susceptible to changes and the root should be resistant, which will result in minor damage. Why the bone is resorbed to a greater extent than the root is not entirely clear, since the latter, when subjected to a force moves it to the bone substrate. One possible explanation is that cement is more mineralized and harder than bone. It also seems that the root is better protected against resorption thanks to the periodontium, which provides a cover made of fibroblasts, cementoblasts and collagen fibers, which are also densely arranged, making this tissue more elastic than bone [8]. When the periodontium is damaged, for example, as a result of trauma, inflammation, or occlusal overload, the cover disappears, increasing the risk of resorption [5]. Advanced resorption occurs in approximately 3% to 5% of patients [8].

External Apical Root Resorption

External apical root resorption (EARR) relates mainly to maxillary incisors. It is visible on radiographic images, and although it is a relatively common consequence of orthodontic treatment, it may not have anything in common with it. It occurs in 7–13% of patients not undergoing orthodontic treatment [1]. In patients treated for malocclusion, while more than one third of the root resorption observed is above 3 mm, severe cases of resorption of more than 5 mm are present in 2–5% of patients [19]. Factors that increase the risk of EARR are earlier trauma, status after reimplantation and periapical inflammation, as well as parafunctions and absence of adjacent teeth, indicating the associated occlusal overload.

For people undergoing orthodontic treatment the risk of root resorption is also increased due to the large forces applied by braces, and the tooth being subjected to a greater range of movement. Since orthodontic tooth displacement is never perfectly parallel, the tension caused by the forces during treatment are mainly concentrated at the apex, which may also be due to the periodontal fibers running in different directions around the tip. Views concerning the effect of the length of the root prior to orthodontic treatment on possible resorption, have evolved over time. Until recently it was thought that short roots are more susceptible to resorption. However, recent reports have suggested that longer roots are more predisposed to resorption since their displacement requires greater force.

Part of the apical cementum contains cells, while part of the crown is acellular. As the correct function of the cells depends on the degree of cement vascularity, the concentration of stress causes damage and circulatory problems in the region, leading to destruction of cells and higher susceptibility to resorption [1, 12]. Circulatory disorders can contribute to the formation of necrosis, and its removal by immune cells may lead to damage to the structure of the tooth root [19]. Even after the orthodontic force is not longer applied, the tooth resorption process continues until the periodontal fibers are stabilized.

Impact of Genes on Increased Predisposition for External Apical Root Resorption

The occurrence and severity of EARR is influenced by many genes, and so it does not describe a Mendelian pattern of inheritance. Although

a family history of susceptibility to resorption seems to have been confirmed, there is no clear pattern of inheritance. According to monozygotic twin studies, EARR demonstrates less than 100% compatibility in twins, which suggests the influence of factors other than just genetic ones [9]. Harris et al. [20] after assessing the genetic predisposition to EARR in central incisors and the mesial and distal roots of the mandibular first permanent molars, found that siblings are characterized by a similar degree of root damage in effect of orthodontic treatment as compared to other members of the family.

Al-Qawasmi et al. [9, 12, 21] highlight a correlation between external root resorption of maxillary central incisors and the nature of polymorphic marker D18S64, located close to the TNFRSF11A gene. This close proximity may influence susceptibility to EARR as the RANK receptor is encoded by TNFRSF11A. The gene encoding TNAP/TNS-ALP (tissue non-specific alkaline phosphatase) may also possess great importance in the etiology of EARR, as the enzyme it encodes is involved in the development and mineralization of cementum. As Breertsen et al. [22] have shown, mice with a malfunctioning gene produced defective, acellular root cementum. Tissue of abnormal hardness is more susceptible to damage and resorption.

Association of the External Apical Root Resorption with Interleukin-1 β Gene Polymorphism

A study examining Brazilian patients receiving orthodontic treatment found a relationship between polymorphism in the gene encoding interleukin-1 β and increased susceptibility to EARR. Individuals with a 1st allele proved to be more susceptible to resorption than patients who possessed a 2nd allele. *In vitro* studies on monocytes have shown that those derived from patients homozygous for allele 2 produce four times more interleukin-1 β than those from patients homozygous for allele 1, and two times more than heterozygous patients [19]. The above information is consistent with the results of Al-Qawasmi et al. [23] whose study addressed a group of related Caucasian Americans. It has been shown that IL-1 β polymorphism is responsible for about 15% of the cases with resorption of the central incisor apex [1, 23]. Individuals who are homozygous for the 1st variant allele have an increased risk of about 2 mm of bone resorption, compared with those who are not. Occurrence of the first variant

allele tends to contribute to decreased levels of interleukin 1- β , which in turn significantly increases the risk of root resorption. It is also believed that interleukin 1- β stimulates bone resorbing osteoclasts, so a low concentration would result in less alveolar bone resorption, thus preventing tooth movement, which has the knock on effect of causing root tension, circulatory disorders and necrosis of, among others, the periodontal fibers, leading to root resorption.

Patients orthodontically treated and with an advanced periodontal disease have increased levels of IL-1 (interleukin 1) in the gingival fluid and periodontal tissues. The genes encoding interleukin-1 are located on chromosome 2q13. Two genes, IL-1A and IL-1B, encode the proinflammatory cytokines IL-1 α and IL-1- β and a third gene IL-1RN encodes the IL-1ra protein, which acts as a receptor antagonist. It can be concluded that the development of periapical lesions is affected by the balance between IL-1- β and IL-1ra [19, 23]. However, this does not mean that genes uniquely responsible for resorption have been already discovered. It is known that the etiology of root resorption is multifactorial and the phenotype is influenced by both genes and environmental factors.

Al-Qawasmi et al. [23] found a significant risk of root apex resorption in Caucasian patients with IL-1 β polymorphism. By contrast, Tomoyasu et al. [24] found no correlation between IL-1 β polymorphism and an increased risk of resorption in a group of 54 Japanese patients receiving orthodontic treatment. Perhaps the IL-1 β polymorphism does not equally affect all populations.

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Conclusions

The etiology of root resorption is multifactorial, and its phenotype is influenced by both genes and environmental factors. The mechanism of hard dental tissue resorption is similar to that which occurs in bone tissue. Clastic cells are also morphologically and functionally similar, and the process of their formation, the factors causing maturation and regulating their activity are almost the same.

The physiological process of tooth resorption is not controlled only by the cells of the primary tooth pulp and permanent teeth germs. Primary teeth which are endodontically treated and without permanent successors also undergo the processes of resorption, while the adjacent permanent tooth remains intact. It seems that extracellular proteins such as OPD and BSP may affect the selective resorption.

Based on current knowledge, it is impossible to precisely predict whether mineralized dental tissues under the influence of orthodontic treatment will be affected by resorption. However, family and other risk factors should be taken into consideration.

Studies on the genetic and molecular mechanisms of resorption including those involving cytokines, enzymes and other proteins involved in the metabolism of bone and dental hard tissue (resorption promoting factors such as RANKL, CSF-1, MCP-1, and TGF- β , OPG, Cbfa1, inhibit this process) can be useful in the future prevention or treatment of this ongoing pathological process.

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Address for correspondence:

Joanna Szczepańska
Department of Pediatric Dentistry
Medical University of Lodz
Pomorska 251
92-213 Łódź
Poland
Tel. +48 42 675 75 16
E-mail: joanna.szczepanska@umed.lodz.pl

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