Osteoclastic Activity in Orthodontic Tooth Movement- A Review

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Abstract

It is a well-known concept that bone remodeling occurs during orthodontic tooth movement. The orthodontic literature is vastly full of information about the changes occurring on the periodontal ligament level. However, changes occurring in the alveolar bone are being elucidated. What we know about bone resorption has changed a lot in the last few decades. The osteoclast is the only cell to nibble and breakdown the bone, and also aids in formation and resorption of bone tissue. In this review, we briefly describe the phases and theories of tooth movement and also the changes involved during orthodontic tooth movement.

Keywords: *osteoclast, tooth movement, osteoclastogenesis, prostaglandins, RANKL, bisphosphonates, M-CSF*.

Introduction

Bone is the hardest organ in the body. Its function is moving, supporting and protecting the body and storing minerals. What we know about bone resorption has changed a lot in the last few decades. The osteoclast is the only cell, breaking down the bone, and in the formation and resorption of bone tissue, osteoclast play an important role.[1]

The success of orthodontic treatment is influenced by a number of factors, including balance of bone remodeling, bone resorption, periodontal health, oral hygiene, and orthodontic forces.[4]

The osteoclast is essential for the two basic processes of bone biology, the first is bone modeling, which forms bone elements and ensures the correct shape and density of the bone.

The second process is bone remodeling, and the mechanism of bone remodeling ensures bone tissue renewal and adapting to the environment. The balance of bone remodeling and resorption is essential for health.[1]

A lot of research has been done on the mechanical forces and tooth movement compared to the focus on cellular biology. The principle of tooth movement in which applied pressure results in remodeling is a microscopic fact.[2]These processes are mediated by complex interactions of various cell signaling pathways that act to regulate cell proliferation and maturation in the PDL.[6]

The need to understand the specific remodeling pathways is essential to target those cells and achieve an impeccable prognosis. The other advantage of knowing these cells can also help us to stimulate the body directly or indirectly to produce or activate these cells.

This review will focus at the theories of tooth movement, biological role of osteoclast and age-related

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effects on activities of osteoclast. [2]

PHASES OF TOOTH MOVEMENT:

There are three phases of tooth movement:

4. Initial phase
5. Lag phase
6. Post lag phase

Initial phase occurs immediately after the application of force to tooth. The movement is rapid due to the displacement of tooth in periodontal space. The time frame of the initial phase usually occurs between twenty-four hours to two days. Due to the force applied on the tooth there is a compression and stretching of periodontal ligament which in turns causes extravasation of vessels, chemo-attraction of inflammatory cells and recruitment of osteoblast and osteoclast progenitors.[2]

In lag phase the movement is minimal or sometimes no movement at all. The reason for this phase is the hyalinization of compressed periodontal ligament. The movement will not take place until the necrosed tissue is removed by the cells.The tooth movement stops for twenty to thirty days and during this time frame all the necrotic tissue is removed along with the resorption of adjacent bone marrow.

The third phase is the post lag phase in which the movement of tooth gradually or suddenly increases and is usually seen after forty days after the initial force application.[2]

THEORIES OF TOOTH MOVEMENT:

There are three possible theories:

4. Bone-Bending theory
5. Biological Electricity theory
6. Pressure-Tension theory

Bone-bending theory:

This theory was proposed by Farrar in 1888. According to him when an orthodontic force is applied to the tooth, it is transmitted to all tissues near the area of force application. These forces bend bone, tooth and the solid structures of periodontal ligament. Since the bone is more elastic than the other structures it bends effortlessly and the process of tooth movement gets accelerated.

Biological electricity theory:

Basset and Becker in 1962 stated that whenever the alveolar bone flexes or bends it releases electric signals (piezo-electric signals) and to some extent is responsible for tooth movement.

The characteristic of these signals is:

(a) They have a quick decay rate which means it is initiated when the force is applied and at the same time it disappears quickly even with the force maintained.

(b) They produce equal signal on the opposite side when the force is released

A small voltage is observed called as ‘‘streaming potential”. They are different from piezoelectric signals and they even can be generated by external electric field another type of signal present in bone that is not being stressed called as ‘‘bioelectric potential”.

The bone which is metabolically active shows electronegative changes that are proportional to its activity.[2]

It was concluded that the area with electronegative charge is characterized by elevated level of osteoclastic activity and the area of electropositive charge is characterized by elevated level of osteoblastic activity.

Pressure-tension theory:

Sandstedt and Schwarz hypothesized that a tooth moves in the periodontal space by creating a pressure and tension side. The alteration of blood flow in periodontal ligament results in less oxygen levels on the pressure side due to compression of the periodontal ligament and vice versa. That low oxygen tension cause’s decreased Adenosine triphosphate (ATP) activity. These changes can directly or indirectly act on cellular activity and

differentiation. If the force exceeds the pressure (20–25 g/cm2 of root surface), tissue necrosis can occur due to the strangulated periodontium.[2]

OSTEOCLAST: A HIGHLY SPECIALIZED POLAR CELL

The osteoclast is a member of the monocytes/ macrophage family that differentiates under the aegis of two critical cytokines, namely RANK ligand and M-CSF. The osteoclast, which is the sole bone-resorbing cell, is a unique polykaryon whose activity, in the context of the osteoblast, dictates skeletal mass.[3, 5]

ROLE OF PROSTAGLANDINS IN TOOTH MOVEMENT

Clinical and animal studies by various authors have identified the role of prostaglandins (PGE1 and PGE2) in stimulating bone resorption.They have reported a direct action of prostaglandins on osteoclasts in increasing their numbers and their capacity to form a ruffled border and effect bone resorption. A recent study evaluated the effects of prostacyclin and thromboxane A2 in orthodontic tooth movement and osteoclastic activity on rats.

It was found that these analogues increase the number of multinuclear osteoclasts, osteoclastic bone resorption, and the rateof orthodontic tooth movement.[11]

DIFFERENTIATION OF OSTEOCLAST:

Osteoclasts are derived from the hematopoietic system. In bone marrow, hematopoietic stem cell experiences several differentiations. Each subtype of cell has a specific marker.

Stages in osteoclast differentiation:

5. Hematopoietic stem cells differentiate into multipotential progenitor cells in presence of regulatory cytokines such as c-Kit^{+}, c-Fms^{-}, Mac-1^{dull}.

6. Multipotential progenitor cells differentiate into early stage precursor by c-Kit^{+}, c-Fms^{-}, Mac-1^{dull}, and RANK^{-}.

7. Precursors differentiates into mononuclear osteoclast

8. Mononuclear osteoclast differentiates into multinuclear osteoclast.

The differentiation of osteoclast is mainly regulated by two critical cytokines; RANKL and macrophage-colony stimulating factor (M-CSF). PU.1 is a domain transcription factor of myeloid, B-lymphoid cells also regulates the transcription of c-Fms and CD11b/CD18 which controls the osteoclast phenotype.

Mature osteoclasts are large whose size is up to 100 μm, multinucleated and polarized, firmly adhering to the surface of the bone.

In the process of bone resorption, there are four different cell structures of osteoclast:

1. Sealing zone isolates the resorptive area from the extracellular environment;

2. Ruffled board, facing the bone matrix, is composed of the plasma membrane to absorb the bone matrix;

3. Basolateral membrane, facing the vascular compartment, is participating in bone resorption, which contributes to transporting the bone degradation products;

4. Functional secreted domain.[1]

OSTEOCLASTOGENESIS:

Application of force during orthodontic tooth movement leads to the initiation of osteoclastogenesis. First, tissue damage occurs with inflammatory processes in the PDL. Second, alveolar process deformation takes place.

A few days after force application, the first osteoclast progenitor cells appear at the compression sites in the alveolar crest vasculature and marrow spaces, and the PDL space widens. Osteoclast appears in higher quantity at the compression sites compared to tension sites. In addition, pro-inflammatory cytokines such as IL- 6, IL-8 and

TNF-α are produced.

RANKL stimulates and inhibits osteoprotegrin during tooth movement. RANKL is up regulated in response to compressive forces through a prostaglandin endogenous 2 pathway supporting the role of osteoclastogenesis. RANKL-mediated osteoclastogenesis and tooth movement are both inhibited by local osteoprotegrin gene transfer.[7]

It has been shown that an increase in RANKL and a decrease in osteoprotegrin have a negative impact on tooth movement therapy in terms of causing severe root resorption. During the period of 5–7 days following force activation, osteoclasts are cleared from compression sites. This may be due to osteoclast apoptosis followed by secondary necrosis.

A second pathway for osteoclast death occurs through integrins, focal adhesion proteins and cytoskeleton, by force activation. This pathway causes osteoclast apoptosis by amplifying the signal and activating caspases. The type of force stimulus and cell phenotype determines whether the osteoclast undergoes apoptosis followed by secondary necrosis or just apoptosis.

The role of osteocytes, the predominant bone cell in alveolar bone during orthodontic movement, has not been well studied in the orthodontic literature. Osteocytes are well-equipped to facilitate bone adaptation to loading.

The physiological changes in periodontal tissue during orthodontic tooth movement affect the activity, metabolism, and communication of osteocytes. Nitric oxide is an important regulator of bone response to mechanical loading. [7]

It is produced by endothelial nitric oxide synthase or inducible nitric oxide synthase and has been shown to: mediate adaptive bone formation and osteoclast activity and prevents osteocytes apoptosis. Several authors have shown that inhibition of NO production increases osteoclastogenesis. Orthodontic force results in strain within the bone giving rise to fluid flow leading to production of NO by osteocytes. Additionally, it has been suggested that iNOS mediates inflammation-induced bone resorption in the compression area. It has been shown that osteocytes and osteoclast undergo apoptosis at orthodontic compression sites.[7]

AGE RELATED EFFECTS ON OSTEOCLASTIC ACTIVITY UNDERGOING ORTHODONTIC TOOTH MOVEMENT:

Remodeling of the alveolar bone and periodontal tissue in adults is much slower than in adolescents because of the reduced cellular activities and alveolar vascularity, altered bone composition and richer collagen in the tissue.

Furthermore, it was recently demonstrated that the levels of mediators such as RANKL in gingival crevicular fluid (GCF) were different in adults and adolescents undergoing orthodontic treatment.

X.Li et al conducted a study with Sprague-Dawley rats in 2016. They stated that the expression of RANKL on the compression side did not show significant difference between the young and the adult groups after seven-day force application ($p > 0.05$), while it was significantly higher in the adult group than in the young group after seven-day post-orthodontic retention ($p < 0.05$).

The bone-resorptive activity in the young rats was more dynamic than that in the adult rats. The expression of RANKL and the number of osteoclasts in adult rats did not drop to the control level during the post-orthodontic retention period while RANKL expression and the number of osteoclasts in young rats had returned to the baseline.[8]

DRUG RELATED EFFECTS ON OSTEOCLASTIC ACTIVITY UNDERGOING ORTHODONTIC TOOTH MOVEMENT:

Bisphosphonates are a group of medicines that slow down or prevent bone loss, strengthening bones. Bisphosphonates inhibit osteoclasts which are responsible for breaking down and reabsorbing minerals such as calcium from bone (the process is known as bone resorption). Bisphosphonates allow osteoblasts (bone building cells) to work more effectively, improving bone mass.

Cathepsin K, which is specifically expressed and secreted by activated osteoclasts during bone resorption, is a key enzyme in the degradation of critical proteins in the bone matrix, including type I collagens. Bone resorption can be inhibited by the removal of cathepsin K from osteoclasts. Unlike other anti-resorptive drugs, cathepsin K inhibitors do not affect osteoclast activity, and osteogenic activity is maintained by the cross-coupling of osteoblasts to osteoclasts

A pseudo-receptor of RANKL, OPG can also inhibit osteoclast formation and accelerates apoptosis by binding to RANKL, which inhibits the interaction between RANKL and RANK. [10]

RANKL is therefore treated as an ideal target for inhibiting osteoclast formation based on the information obtained so far regarding the RANKL/RANK/OPG system. Denosumab, a synthetic IgG2 monoclonal antibody, can also specifically bind to and inactivate RANKL using the same action mechanism as OPG.[10]

Conclusion

Adaptive biochemical response to applied orthodontic force is a highly sophisticated process.[9]In this review,as a key cell in the bone metabolism system, studies on the mechanisms of osteoclast activation have further deepened our understanding of osteoclast.With further research, especially in bone immunology and the RANK/RANKL pathway, it is expected to provide new ideas for the biological mechanism of osteoclast and new directions orthodontic tooth movement and for drug development for bone diseases.[1]

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