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A New Cyte in Orthodontics: Osteocytes in Tooth Movement

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Abstract

Objectives—Orthodontic tooth movement (OTM) relies on the orchestration of clinical and biologic events that include the application of clinical force followed by a cascade of cellular and molecular responses. Our understanding about OTM today has evolved from, and is largely based on historic studies. However, the advances in bone biology and clinical orthodontics today continue to pave the pathway toward an improved knowledge base, and state of the art therapeutics in OTM. Osteoblasts and osteoclasts have been the primary cells analyzed in OTM. However, the role of osteocytes, a cell previously thought to be static, should be considered in light of new findings in molecular biological research. Osteocytes are now known to be significant in controlling responses to mechanical forces and therefore may be central to both OTM and normal tooth eruption. In this review we explore the biology of OTM by focusing specifically on the potential role of osteocytes.

Conclusion—Evidence from recent studies reveal that osteocytes have a role in controlling the response to mechanical forces and OTM. We therefore propose that these findings and further research endeavors may shape the future of clinical applications – specifically enhanced outcomes in OTM.

Introduction

The biologic and mechanical underpinnings of orthodontic tooth movement (OTM) are central to the understanding of how to correct dental and/or skeletal malocclusion with orthodontic appliances. The past orthodontic scientific literature has provided a substantial foundation toward dissecting the mechanisms that control and/or facilitate OTM. Central to this process are several cell types; among them are the osteoclasts, known to resorb bone, and osteoblasts, which build bone. The classic cascade of bone remodeling is that 1) osteoclast precursors are attracted from the blood stream; 2) the precursors form osteoclasts; 3) localized bone resorption occurs; 4) coupling – whereby, osteoclastic resorption occurs in parallel to the generation of osteoblasts and 5) bone formation occurs (1). In OTM, mechanical forces, which can be intermittent or continuous, can stimulate this bone

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remodeling cascade in alveolar bone. This occurs differently depending on whether the perspective is from the pressure or tension side of the tooth involved in OTM. The pressure side of OTM is characterized by bone resorption, while on the tension side bone formation occurs when forces are within a healthy biological range.

This biologic response to force is governed by two predominant control mechanisms; biologic electricity and the pressure-tension theory. The bioelectric theory is based on the fact that changes in the bone metabolism stem from electric signals that occur when alveolar bone bends. Researchers have endorsed that changes occurring in alveolar bone during OTM are likely due to a piezoelectric effect; mechanically induced deformation of collagen crystals produces a stress-generated potential (SGP) (2). However, while the presence of piezoelectricity is thought to explain the electric signals that in turn lead to maintenance of the bony skeleton, the correlation with OTM is less clear since orthodontic movement occurs as a result of a sustained force versus the intermittent type of forces that cause SGPs. Alternatively, the pressure-tension theory posits that chemical messengers are responsible for cellular changes. Specifically, the tooth is displaced in the socket in response to orthodontic force propagated through the periodontal ligament (PDL). As the blood flow within the PDL is decreased where the PDL is compressed and increased where the PDL is stretched, the chemical environment is concomitantly altered to stimulate second messengers such as cyclic AMP (cAMP), and the activation of the cells responsible for OTM. Briefly, the cAMP elevation that results activates the cellular differentiation and proliferations through kinase activity in the nucleus of each cell. In addition to cAMP, inositol phosphates, and intracellular calcium respond to mechanical forces by elevating their biologic levels. The resultant effect is the entry of calcium to the cell may come from G-protein controlled ion channels or release of calcium from internal cellular stores (1). The pressure-tension theory is generally accepted as the classic theory of OTM although biologic electricity is still noted for its importance in bone homeostasis.

As we consider the mechanisms governing OTM, it is important that we think of it from the perspective of how it impacts orthodontic treatment approaches and outcomes. In other words, how rapidly can an orthodontist accomplish effective OTM while remaining biologically safe? Herein, we look at the biologic factors of OTM from a unique perspective – that is, how the osteocyte may be involved in OTM beyond the typical role in maintaining the bony architecture. The possibility of an expanded hypothesis that includes the osteocyte as an active cell in OTM is explored within the framework of canonical theories of bone remodeling and OTM.

Recent discoveries suggest that osteocytes are critical in OTM in addition to osteoblasts and osteoclasts (3). Osteocytes, formerly thought to be inactive cells, are now viewed as active regulators in bone remodeling (4). This scientific construct is nicely illustrated in murine studies, both for somatic bone remodeling and also in OTM (3–5). In order to appreciate the paradigm shift, it is critical to establish the fundamental role of osteocytes in bone remodeling. Through evaluation of the recent molecular biological literature, we postulate that a direct osteocyte mechanism may exist that can improve orthodontic clinical outcomes. The current literature is viewed through the lens of how an unsuspecting cell, the osteocyte, may provide opportunities to improve clinical care.

Orthodontics and the Osteocyte role in bone remodeling

A fundamental understanding of bone biology is critical to deciphering the interrelationship between bone remodeling and OTM. The cellular and molecular basics of bone biology related to OTM rely on several precepts. Among them, that in order for OTM to be effective 1) it is necessary that the duration and magnitude of force be optimal and based on the type of movement; and that the 2) forces are light and continuous. The prevailing thought surrounding the fundamental tenet above is based on studies in humans and dogs (6). Taken together, we understand these clinical scenarios based on osteoclast and second messengers as the predominant effectors that facilitate OTM. When force levels are excessive, on the pressure side, blood flow in the compressed PDL is completely blocked. Subsequently the compressed PDL undergoes necrosis and an ensuing undermining resorption, where osteoclasts are recruited from the bone adjacent to the compressed PDL instead of from the bloodstream through the PDL (7). The sequela associated with this scenario is an increase in the time required to move the tooth in the bone (from 2 days under normal circumstances to 7–14 days) (7). While the predicted outcome of heavy forces (i.e. a lag phase) may be in extreme scenarios, the clinical observation can be associated with extreme tooth mobility.

In the above scenario OTM is characterized by a rate and type of bone remodeling that is distinct from other clinical situations. Indeed the rate of turnover of bone varies by site and clinical situation. Cortical bone turnover rate is 2–10% per year and trabecular bone turnover rate is 30–35% per year, while alveolar bone turnover rate is believed to be approximately 15–30% per year when not under OTM forces (2).

Osteocytes have been shown to be an active member of bone remodeling and not just a static cell as previously thought. Osteocytes are now considered the main mechanosensing cell, making up 90–95% of cells in bone. Without osteocytes, bone is completely insensitive to unloading (8). Osteocytes can exert control on osteoblasts and osteoclasts through multiple signaling pathways, such as receptor activator of nuclear factor kappa-B ligand (RANKL), osteoprotegerin (OPG), and nitric oxide (NO) (4). Osteocytes, which differentiate and embed themselves into cortical and trabecular bone, can build and resorb bone (4, 9, 10). Dentin matrix protein 1 (Dmp1) is known to be a key molecule in regulating osteocyte formation, maturation, phosphate regulation, and regulating mineralization (4). Additionally, osteocytes are ideally positioned for regulatory activities through communication by dendritic processes within canniculi to send and receive signals to send throughout the bone (4). The number and location of osteocytes and their interactions with the surrounding cells and tissue, makes them logical biologic candidates to participate in OTM.

The Osteocyte in Tooth Movement – What is in Cyte?

The literature surrounding osteocytes and their importance in OTM has emerged through recent studies from the cellular and molecular perspective. On the cellular level, changes in osteocytes are observed well before the osteoclasts appear during OTM (Fig. 1). For example, osteocyte apoptosis is known to peak 24 hours after initiating OTM, well before the osteoclasts formation starts at 72 hours (3). When osteocytes are ablated prior to OTM, mice showed significantly impeded OTM when compared to control mice and a concomitant

decrease in osteoclast number and activity (5). These studies show the importance of osteocytes in OTM, but whether this is due to a lack of mechanosensing or due to the by-products associated with osteocyte apoptosis is still unclear. Further research is needed to address these questions and to identify how this information could inform clinical practice.

The past decade has witnessed a significant increase in the number of studies interrogating the role of the osteocyte during OTM. For instance, NO, matrix extracellular phosphoglycoprotein (MEPE), connective tissue growth factor (CTGF) and osteopontin (OPN) specific to osteocytes have been shown to play a significant role in OTM (11–14) (Fig. 1). Specifically, NO is known to rapidly increase in osteocytes after mechanical stress, such as pulsating fluid flow or intermittent hydrostatic compression (15, 16). The increase in NO is recognized to protect osteocytes against apoptosis, increase bone formation, and decrease bone resorption (17). Endothelial nitric oxide synthase (eNOS) is believed to be the main source of NO from osteocytes (4). eNOS is expressed at its highest level at 24 hours on the compression and tension sides during OTM (11). Inducible nitric oxide synthase (iNOS) is increased to its highest level at 6 hours after the OTM (4, 11). Overall there are increased levels of NO when OTM is initiated (11).

MEPE is predominantly expressed in osteocytes and involved in mineralization and phosphate homeostasis in bone (4). In alveolar bone, MEPE is seen only in osteocytes and more specifically localized to their dendritic processes (12). Mepe-null mice are characterized by increases in trabecular bone mass and mineral apposition rate with aging. Alveolar osteocytes have a high basal level of MEPE, but during OTM it decreases dramatically on the first day and then reaches maximum expression on day three, which differed from DMP1 expression in osteocytes (12). Furthermore, MEPE can accelerate or inhibit mineralization depending on cleavage of the mature protein, suggesting that MEPE might have dual functions depending on its proteolytic processing. These studies also contend that MEPE could have dramatic effect on pressure and fluid dynamics within the canaliculi to modify how it receives and responds to mechanical stimulation (12).

With a greater understanding of the role of osteocytes during OTM, questions may be asked about how to impact osteocytes to uniquely direct OTM. Knowledge gained from further investigation of osteocytes could identify new genetic mechanisms of OTM and help to direct cell-based therapies to enhance OTM, potentially by NO, DMP1, or MEPE. Osteocytes are uniquely positioned to sense the earliest changes in forces applied during OTM and may play a primary role in recruiting osteoclasts to the site of OTM. Hypothetically, a method could be identified in alveolar bone to utilize the lacunae-cannicular system to help prepare alveolar bone for OTM. These theories among others will need to be interrogated to identify what, if any, potential clinical benefits exist through an expanded knowledge of osteocyte biology to impact OTM.

How to Move Teeth, or How Teeth Move

A clinical scenario where the molecular events that facilitate OTM can be investigated is found in Primary Failure of Eruption (PFE) (18). PFE is defined as the failure of a tooth to erupt fully in the absence of a mechanical obstruction. The term “primary” denotes that the

defect is inherent to the eruption mechanism of the tooth itself. And for the purposes of this review, although PFE clearly refers to the inability of teeth to erupt fully into functional occlusion, it is also by extension (and definition) a reference to teeth that will not respond to orthodontic forces as is defined above. This condition provides an interesting model to not only understand “how to move teeth” - but “how teeth move.” More specifically, PFE-affected teeth are partially erupted into the oral cavity, but have been shown anecdotally to be mobile in the socket when they are surgically luxated (19). Thus, the teeth are not ankylosed but instead somehow unable to respond to forces due to a molecular defect.

It seems intuitive that the same defect responsible for PFE is a critical element in normal OTM. This begs the question of which molecular or cellular event is most central to a defect common to tooth eruption and orthodontic movement. The likely culprit of PFE is often cited as a defect within the PDL. The PDL is known to be involved in post-emergent tooth eruption (20), which is consistent with the rubric that defines PFE, that is, the eruption pathway is clear and the tooth that has “failed to erupt” is also partially erupted (or supracrestal). Hence, the connection between the PDL and eruption failure is as follows: the PDL arises from the dental follicle, which has been shown to be essential for eruption (21). Subsequently, the PDL becomes a source for progenitor cells that can form bone and cementum and produce growth factors that facilitate homeostasis (22). While it is rational to conclude that the PDL is implicated as the effector of eruption and therefore eruption failure, it is imperative to vet the other cellular and molecular possibilities. The *PTH1R* gene (OMIM 168468) has been established as causative for many cases of PFE (23, 24). What is unknown, however, is the pathogenesis of the *PTH1R* mutation that leads to PFE. While the PDL seems to be a likely target of a defect causing PFE, the role of the osteocyte has not been considered or discussed. Interestingly, *PTH1R* is known to be important in osteocytes through their mechanosensing transduction pathway and in promoting osteocyte survival during mechanical stimulation (25). The osteocyte, as discussed in this review, provides another possible pathway of PFE pathogenesis through its mechanosensing capabilities.

Conclusion

The plausibility of the osteocyte, a mechanosensing cell, is gaining momentum to become a key player in OTM. One possibility is that if the mechanosensing function of the osteocyte is impaired that this may lead to the sequence of events resulting in PFE versus normal tooth eruption and optimal OTM.

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References

1. Norton LA, Burstone CJ. The Biology of tooth movement. Boca Raton, Fla.: CRC Press; 1989.
2. Graber LW, Vanarsdall RL, Vig KWL. Orthodontics: current principles and techniques. 5th ed. Philadelphia, PA: Elsevier/Mosby; 2012.
3. Moin S, Kalajzic Z, Utreja A, Nihara J, Wadhwa S, Uribe F, et al. Osteocyte death during orthodontic tooth movement in mice. *Angle Orthod*. 2014;84(6):1086–92. [PubMed: 24694014]

4. Dallas SL, Prideaux M, Bonewald LF. The osteocyte: an endocrine cell... and more. *Endocr Rev.* 2013;34(5):658–90. [PubMed: 23612223]
5. Matsumoto T, Iimura T, Ogura K, Moriyama K, Yamaguchi A. The role of osteocytes in bone resorption during orthodontic tooth movement. *J Dent Res.* 2013;92(4):340–5. [PubMed: 23358677]
6. Reitan K, Kvam E. Comparative behavior of human and animal tissue during experimental tooth movement. *Angle Orthod.* 1971;41(1):1–14. [PubMed: 4992550]
7. Proffit WR. *Contemporary orthodontics.* 5th ed. St. Louis, Mo.: Elsevier/Mosby; 2013.
8. Tatsumi S, Ishii K, Amizuka N, Li M, Kobayashi T, Kohno K, et al. Targeted ablation of osteocytes induces osteoporosis with defective mechanotransduction. *Cell Metab.* 2007;5(6):464–75. [PubMed: 17550781]
9. Belanger LF. Osteocytic osteolysis. *Calcif Tissue Res.* 1969;4(1):1–12. [PubMed: 4310125]
10. Tang SY, Herber RP, Ho SP, Alliston T. Matrix metalloproteinase-13 is required for osteocytic perilacunar remodeling and maintains bone fracture resistance. *J Bone Miner Res.* 2012;27(9):1936–50. [PubMed: 22549931]
11. Tan SD, Xie R, Klein-Nulend J, van Rheden RE, Bronckers AL, Kuijpers-Jagtman AM, et al. Orthodontic force stimulates eNOS and iNOS in rat osteocytes. *J Dent Res.* 2009;88(3):255–60. [PubMed: 19329460]
12. Gluhak-Heinrich J, Pavlin D, Yang W, MacDougall M, Harris SE. MEPE expression in osteocytes during orthodontic tooth movement. *Arch Oral Biol.* 2007;52(7):684–90. [PubMed: 17270144]
13. Terai K, Takano-Yamamoto T, Ohba Y, Hiura K, Sugimoto M, Sato M, et al. Role of osteopontin in bone remodeling caused by mechanical stress. *J Bone Miner Res.* 1999;14(6):839–49. [PubMed: 10352091]
14. Sakai Y, Balam TA, Kuroda S, Tamamura N, Fukunaga T, Takigawa M, et al. CTGF and apoptosis in mouse osteocytes induced by tooth movement. *J Dent Res.* 2009;88(4):345–50. [PubMed: 19407155]
15. Klein-Nulend J, Semeins CM, Ajubi NE, Nijweide PJ, Burger EH. Pulsating fluid flow increases nitric oxide (NO) synthesis by osteocytes but not periosteal fibroblasts--correlation with prostaglandin upregulation. *Biochem Biophys Res Commun.* 1995;217(2):640–8. [PubMed: 7503746]
16. Klein-Nulend J, van der Plas A, Semeins CM, Ajubi NE, Frangos JA, Nijweide PJ, et al. Sensitivity of osteocytes to biomechanical stress in vitro. *FASEB J.* 1995;9(5):441–5. [PubMed: 7896017]
17. Tan SD, Bakker AD, Semeins CM, Kuijpers-Jagtman AM, Klein-Nulend J. Inhibition of osteocyte apoptosis by fluid flow is mediated by nitric oxide. *Biochem Biophys Res Commun.* 2008;369(4):1150–4. [PubMed: 18339304]
18. Proffit WR, Vig KW. Primary failure of eruption: a possible cause of posterior open-bite. *Am J Orthod.* 1981;80(2):173–90. [PubMed: 6943937]
19. Rhoads SG, Hendricks HM, Frazier-Bowers SA. Establishing the diagnostic criteria for eruption disorders based on genetic and clinical data. *Am J Orthod Dentofacial Orthop.* 2013;144(2):194–202. [PubMed: 23910200]
20. Wise GE, King GJ. Mechanisms of tooth eruption and orthodontic tooth movement. *J Dent Res.* 2008;87(5):414–34. [PubMed: 18434571]
21. Cahill DR, Marks SC Jr. Tooth eruption: evidence for the central role of the dental follicle. *J Oral Pathol.* 1980;9(4):189–200. [PubMed: 6777476]
22. Muthukuru M Bone morphogenic protein-2 induces apoptosis and cytotoxicity in periodontal ligament cells. *J Periodontol.* 2013;84(6):829–38. [PubMed: 22839695]
23. Frazier-Bowers SA, Hendricks HM, Wright JT, Lee J, Long K, Dibble CF, et al. Novel mutations in PTH1R associated with primary failure of eruption and osteoarthritis. *J Dent Res.* 2014;93(2):134–9. [PubMed: 24300310]
24. Frazier-Bowers SA, Simmons D, Wright JT, Proffit WR, Ackerman JL. Primary failure of eruption and PTH1R: the importance of a genetic diagnosis for orthodontic treatment planning. *Am J Orthod Dentofacial Orthop.* 2010;137(2):160. [PubMed: 20152661]

25. Maycas M, Ardura JA, de Castro LF, Bravo B, Gortazar AR, Esbrit P. Role of the Parathyroid Hormone Type 1 Receptor (PTH1R) as a Mechanosensor in Osteocyte Survival. *J Bone Miner Res.* 2015;30(7):1231–44. [PubMed: 25529820]

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Figure 1.

A simple cartoon of orthodontic tooth movement (OTM) illustrating the importance of osteocytes from Day 1 to Day 3. Black boxes describe the cellular and molecular changes. Blue boxes illustrate the cellular changes on the tension side. Green boxes illustrate the cellular changes on the compression side.