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Featured Review Article

Biphasic theory: breakthrough understanding of tooth movement

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ABSTRACT

Background: Research on the biology of orthodontic tooth movement has led to the prevailing compression-tension theory, which divides the response to orthodontic force into two opposing reactions spatially separated: on the compression side, osteoclasts resorb bone to create space for tooth movement, whereas on the tension side, osteoblasts form bone to restore the alveolar bone structure.
Methods: Here we take a critical look at the literature on how force-induced inflammation, the periodontal ligament, osteoclasts, and osteoblasts contribute to the biological reaction to orthodontic force. We introduce new evidence that supports a novel theory to explain the biology of tooth movement—the Biphasic Theory.
Results: The Biphasic Theory of Orthodontic Tooth Movement divides tooth movement into the initial Catabolic Phase, during which osteoclasts resorb bone at both compression and tension sites, and the Anabolic Phase, which occurs subsequently to restore alveolar bone to its pretreatment levels.
Conclusions: The Biphasic Theory of Tooth Movement successfully addresses shortfalls in the Compression-Tension Theory of Tooth Movement, provides clinicians with a better understanding of how orthodontic forces move teeth, and offers new targets for therapies aimed at accelerating tooth movement.

1. Introduction

Although studied for decades, the biology of orthodontic tooth movement remains the focus of intense investigation, as innovative technologies give us important insights into the molecular, cellular, and tissue responses to orthodontic force. This knowledge is important because it establishes the foundation of orthodontics, which relies on stimulating the movement of teeth through alveolar bone. Although the biological changes during tooth movement are the basis of any orthodontic treatment, optimizing this movement and reducing potential risk factors remain the main challenges for researchers and clinicians in this field. In this review, we introduce you to the Biphasic Theory of Orthodontic Tooth Movement and how we can better understand the effects of orthodontic forces on the teeth, the periodontal ligament (PDL), and the alveolar bone.

Although the tissue responses that enable orthodontic tooth movement are generally known, the mechanisms driving these responses remain unclear. Some of the unanswered questions include the following: How do orthodontic forces activate bone resorption and formation? Are the effects of orthodontic force direct or indirect? Does the PDL play a role in controlling the rate of tooth movement? To address these and other questions, we begin with an overview of how each type of bone cell functions.

2. Bone cells and their role in tooth movement

The key to understanding the Biphasic Theory is recognizing that alveolar bone is perhaps the most reactive skeletal tissue in the body. When orthodontic force is applied to a tooth, coordinated and calibrated signals travel from the tooth through the PDL to the alveolar bone. The bone cells that make tooth movement possible are the bone-forming osteoblasts, bone-resorbing osteoclasts, and mechanosensoring osteocytes.

Osteoclasts carry out the critical job of resorbing bone during orthodontic tooth movement. Formed through fusion of monocyte/macrophage precursor cells in the bone marrow, mature multinucleated osteocytes are distinctive cells. When mature, they

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express the calcitonin receptor [1], tartrate-resistant acid phosphatase (TRAP) [2], and cathepsin-K [3] and secrete an array of proteases to digest the extracellular matrix. Anatomically, mature osteoclasts are notable for the appearance of an elaborate ruffled border that is rich in proton pumps that acidify the bone surface causing bone resorption.

Osteoclasts are the main players in the initial Catabolic Phase. They control the rate of bone resorption during orthodontic treatment and, therefore, the rate of tooth movement [4]. However, the recruiting and activity of osteoclasts during orthodontic treatment require signals from several other cell types. Left unchecked, activated osteoclasts would resorb excessively the alveolar bone leading to pathology such as osteopenia and fractures. Because of the need for such tight regulation, osteoclasts cannot be the direct target of orthodontic forces. Instead, orthodontic forces must target the upstream regulators of osteoclastogenesis and osteoclast activation, such as inflammatory cytokines and chemokines [5]. These regulators are part of the osteoimmunology network that is active during normal physiological and pathological alveolar bone remodeling [6].

Osteoblasts are mesenchymal stem cell–derived mononuclear cells residing along bone surfaces. When mature, they synthesize osteoid, a mix of collagenous and noncollagenous proteins in the extracellular matrix. Of importance to the Biphasic Theory is the finding that inflammatory cytokines also trigger osteoblast proliferation and differentiation [7]. Inactive osteoblasts, known as bone-lining cells, are flat until growth factors or other anabolic stimuli induce activation and they become cuboidal. In the Biphasic Theory, osteoblasts are the main cells participating in the Anabolic Phase, and they have a limited role during the initial Catabolic Phase where they can activate osteoclasts through the RANKL (receptor activator of nuclear factor kappa-B ligand)-RANK pathway.

Osteocytes are mature osteoblasts immobilized within the mineralized bone matrix [8]. They contact each other and cells on the bone surface via a fine network of cellular processes housed in canaliculi. Their intricate three-dimensional network enables osteocytes to serve as mechanosensors to detect mechanical load and signal osteoclasts and osteoblasts to reshape bone to fit the mechanical demand.

Although it is clear that osteocytes are critical for normal bone remodeling, their precise role in the Biphasic Theory is unclear. They may play a role in the Catabolic Phase by activating osteoclasts. Evidence from transgenic mice with nonfunctional osteocytes have significantly fewer osteoclasts and less orthodontic tooth movement compared with normal mice, indicating that alveolar bone osteocytes are vital for cellular communication during tooth movement [9]. It is also probable that osteocytes function in the Anabolic Phase to coordinate osteoblast activation [10]. Interestingly, there is crosstalk between osteocytes and the PDL during tooth movement, suggesting another possible mechanism for osteocytes to influence tooth movement [11].

3. Biphasic theory of orthodontic tooth movement

Tooth movement results from tightly regulated responses of osteoclasts, osteocytes, and osteoblasts to orthodontic forces. Specifically, evidence points to the conversion of orthodontic forces into temporally sequenced catabolism followed by anabolism in alveolar bone. Taken together, the data on tooth movement led us to develop the Biphasic Theory of Tooth Movement to not only explain the biological consequences of orthodontic treatment, but to also guide researchers to develop accelerated, efficacious, and safe orthodontic treatments.

The Biphasic Theory states that orthodontic tooth movement results from two sequential phases of alveolar bone remodeling induced by orthodontic force. The Catabolic Phase precedes the Anabolic Phase, with distinct cellular and molecular events establishing the limits for each phase.

4. The Catabolic Phase of tooth movement

4.1. Classical theories of initiation of tooth movement

Orthodontic forces and couples generate stresses that are transmitted through the PDL to the alveolar bone to produce tooth movement. According to the classical theories, the biology of tooth movement rests on three pillars:

1. Cells involved: Compression activates osteoclastogenesis and osteoclast activation, whereas tension activates osteoblasts; therefore, osteoclasts should populate compression sites and osteoblasts should populate tension sites.
2. Location: The catabolic and anabolic responses occur independently of each other in the PDL, on opposite sides of the tooth.
3. Timing: Although independent, the catabolic and anabolic phases occur simultaneously, because both compression and tension occur simultaneously.

Numerous proposals explaining the initial events leading to catabolism at compression sites fall into two main camps: 1) The Direct Theory proposes that bone cells (especially osteocytes) are the direct target of orthodontic forces, and 2) the Indirect Theory proposes that the PDL is the direct target of orthodontic forces (Fig. 1). Importantly, there is agreement in both theories that osteoclasts are the target cells that resorb bone, and therefore, are the cells that control the rate of tooth movement.

Based on stress responses in weight-bearing bones, Direct Theory proponents suggest that there are two possible mechanisms by which direct loading activates osteocytes. First, osteocytes detect different components of normal, physiological stress (such as matrix deformation) and direct the bone-remodeling machinery to strengthen bone in line with the direction of the stress. This is accomplished by triggering osteoclasts to remove weakened bone and osteoblasts to rebuild new load-tolerant bone at the site of greatest weakness. Second, osteocytes detect higher, pathologic stress by sensing microfractures in the matrix, resulting in increased bone remodeling at the damaged site.

Although the osteocyte-driven bone-remodeling response to physiologic or pathologic stress is accepted for weight-bearing bones, applying the Direct Theory to alveolar bone remodeling triggered by orthodontic forces is questionable. Experiments in long bones and alveolar bone demonstrate that osteocytes cannot detect static forces at physiologic levels [13,14]. Because orthodontic forces are static and within physiologic limits, this argues against orthodontic tooth movement being a physiological adaptation to mechanical stimulation. Moreover, dental implants used as orthodontic anchorage do not move when a static force is applied, suggesting that the Direct Theory is not correct.

Perhaps orthodontic forces stimulate tooth movement by inducing microfractures in bone [15]. The possibility that this is the main mechanism triggering tooth movement is low because, as with implants, orthodontic force cannot move an ankylosed tooth. Thus, the presence of microfractures is not sufficient for orthodontic force to move teeth. Moreover, the relationship between force magnitude and tooth movement is not linear, and soon after applying orthodontic force, the bone-remodeling rate reaches a saturation point. If microfractures are the trigger for tooth movement, higher forces should continually increase the rate of movement, without ever reaching a saturation point [16]. It should be

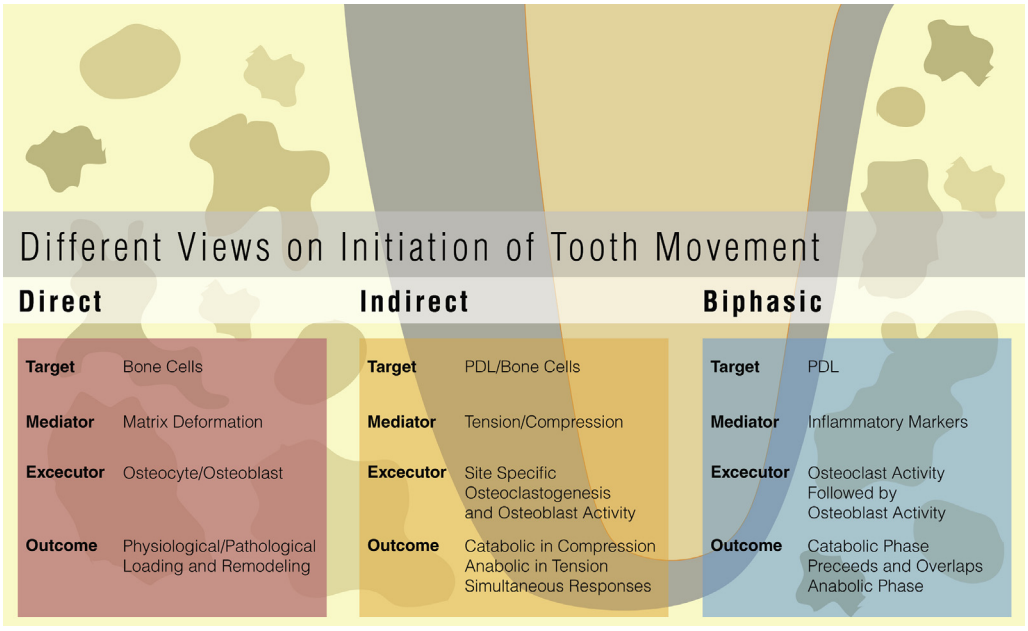

Fig. 1. Theories on Initiation of Tooth Movement. Histological studies have supported classic theories on the biological mechanism of tooth movement. This figure summarizes the differences among currently accepted theories that involve targets, mediators, activators, and outcomes. The Direct and Indirect views have different targets for the initial orthodontic force; however, they assume that catabolic and anabolic responses in bone are independent, simultaneous, and geographically limited to areas exposed to compression and tension stresses, respectively. The Biphasic Theory incorporates the latest evidence on the biology of tooth movement, and proposes an initial Catabolic Phase in response to trauma and inflammation, followed by an Anabolic Phase. Geographically, these catabolic and anabolic responses can overlap due to extensive coupling of osteoclast and osteoblast activation. Used with permission from Teixeira et al. [12].

emphasized that although application of pathological, high-magnitude forces may damage the bone around an implant to the point of failure, high-magnitude forces do not move an implant. Taken together with the fact that physiological, low-magnitude forces applied during orthodontics move teeth, these data strongly suggest that microfractures are not the trigger for orthodontic tooth movement.

Supporters of the Indirect Theory of tooth movement propose that the primary target of orthodontic forces is the PDL. This is evidenced by the fact that we cannot move ankylosed teeth. Based on the Indirect Theory, different orthodontic forces produce characteristic, duration-dependent compression and tension patterns within the PDL. For example, if a compressive force is applied for only a few seconds (i.e., intermittently), incompressible

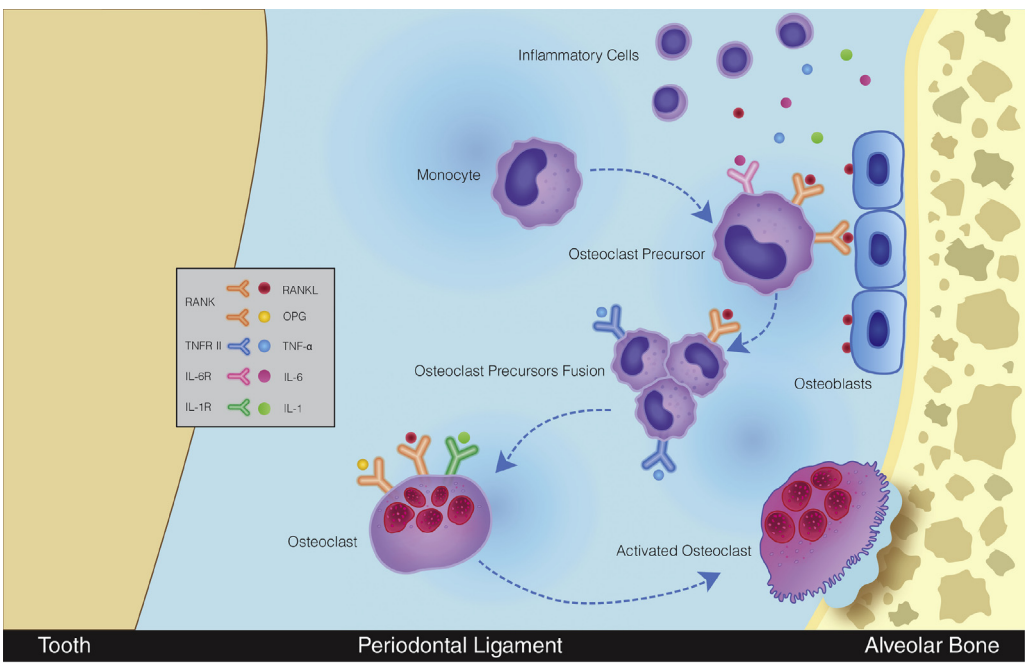

Fig. 2. Cytokines regulate osteoclastogenesis. Cytokines are important mediators of osteoclastogenesis that perform varied roles throughout the differentiation of monocyte-macrophage precursors into mature osteoclasts. Inflammatory cells (which migrate from the bloodstream into the PDL in response to orthodontic forces) and local cells (such as osteoblasts) express RANKL, which then binds to its receptor (RANK) on the surface of osteoclast precursors. RANK-RANKL binding initiates adhesion of the precursor cells to form multinucleated osteoclasts. Although some of these cytokines induce osteoclast precursors to differentiate into osteoclasts (RANKL, TNF-α), others directly stimulate osteoclast activation (RANKL, IL-1). Additionally, local cells can also downregulate osteoclastogenesis by producing a RANKL decoy receptor, OPG. Used with permission from Teixeira et al. [12].

fluids fill the PDL spaces and prevent quick displacement of the tooth. However, if a compressive force is sustained (i.e., static, as in orthodontics), incompressible fluids are squeezed out of the PDL space, allowing teeth to move and further compress the PDL. The immediate result of this compression is blood vessel constriction and decreased blood flow and nutrient and oxygen levels (hypoxia) at the compression site. Depending on the pressure level and blood flow impairment, some cells undergo apoptosis, whereas others die nonspecifically, resulting in necrosis that is identified histologically as the cell-free zone. It should be emphasized that apoptotic or necrotic changes are not limited to PDL cells, as osteoblasts and osteocytes in adjacent alveolar bone may also die in response to orthodontic forces.

4.2. Chemokines and cytokines in the Catabolic Phase

Although physiological and pathological responses to orthodontic force may have different outcomes, both responses produce an initial aseptic, acute inflammatory response marked by the early release of chemokines from local cells (Fig. 2), critical for triggering

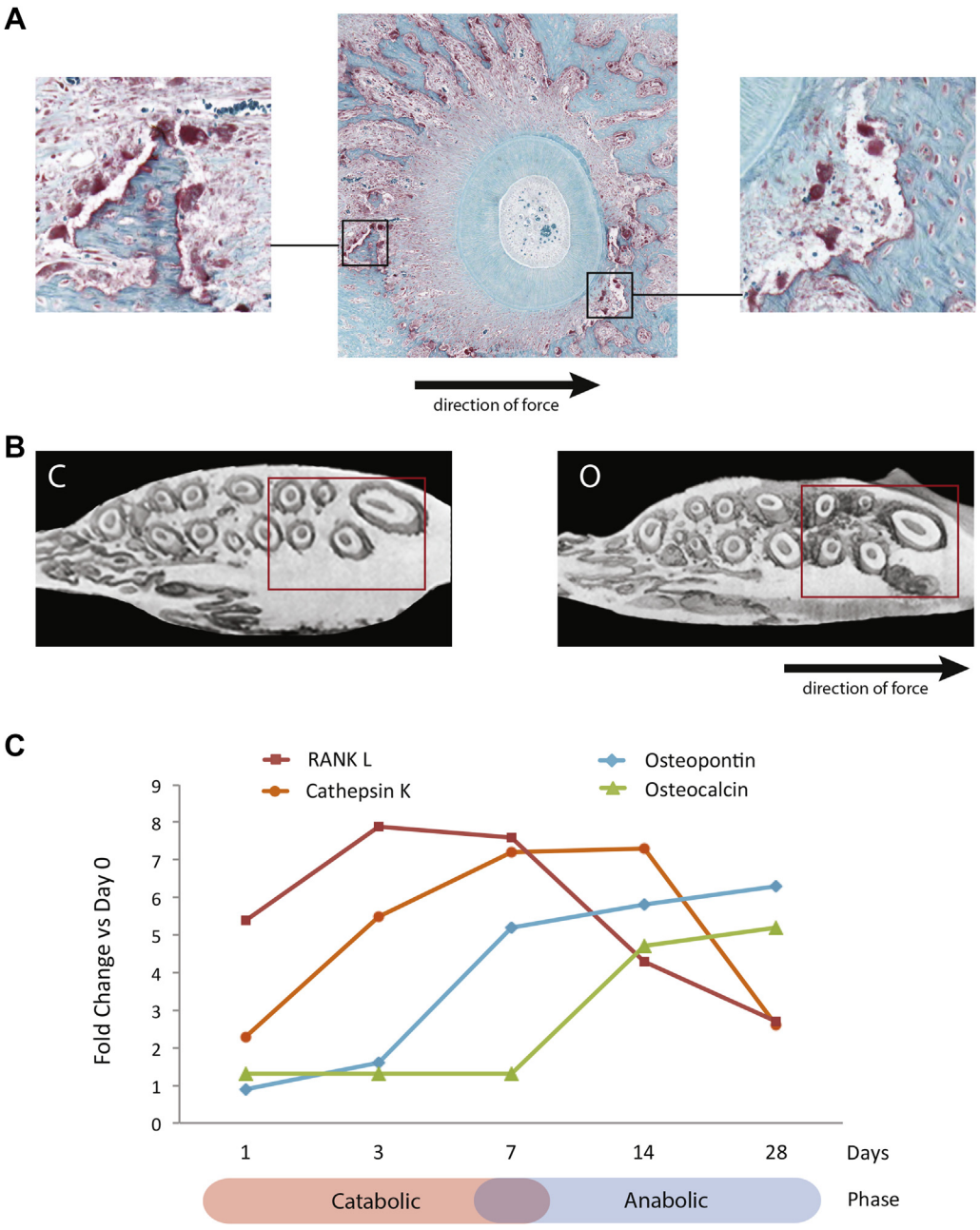

Fig. 3. Evidence supporting the Biphasic Theory of Tooth Movement. Rat hemimaxilla were collected at different time points after application of force (25 cN) to mesialize the first molar. Control animals did not receive any force. (A) Immunohistochemical staining for tartrate-resistant acid phosphatase 3 days after force application. Axial section shows osteoclasts (red cells) in both the tension and compression sides of the moving root. (B) Micro computed tomography images of maxillary right molars of control (C) and orthodontic force (O) animals, 14 days after application of force show significant osteopenia surrounding the moving first molar (red rectangular area). (C) Reverse transcription polymerase chain reaction analysis of osteoclast (RANKL and cathepsin-K) and osteoblast (osteocalcin and osteopontin) markers in the hemimaxilla of rats at different time points after force activation. Data are presented as fold increase in expression in response to orthodontic force compared with day 0, and as mean ± SEM of three experiments. The onset of significantly differences in RANKL and Cathepsin-K were observed at day 3, and for osteopontin and osteocalcin at days 7 and 14, respectively, supporting the Catabolic Phase preceding the Anabolic Phase during tooth movement. Used with permission from Teixeira et al. [12].

inflammation-dependent bone resorption. Specifically, they induce monocytes from the bloodstream to enter the surrounding tissue where they become tissue macrophages or, importantly to us, osteoclasts [17]. Cytokine levels increase in the gingival crevicular fluid after initial orthodontic tooth movement [18] and further promote the initial aseptic inflammatory catabolism. In addition to their potent proinflammatory functions, cytokines secreted from local cells (osteoblasts, fibroblasts, endothelial cells) also prevent runaway inflammation by secreting anti-inflammatory mediators.

Without the inflammatory chemokines and cytokines to trigger osteoclast formation and activation, we could not move teeth. Thus, we must discuss the mechanisms used by inflammatory mediators to regulate this important step in orthodontic treatment.

4.3. Inflammation-dependent osteoclastogenesis

As we have seen, localized inflammation recruits monocyte-macrophage precursors to the PDL where they differentiate into osteoclasts under the control of local inflammatory cells and osteoblasts either indirectly by secreting osteoclast differentiation factors or directly by expressing RANKL. Cells responding to orthodontic forces secrete cytokines into the extracellular environment, which then bind to their receptors on the precursor cells to trigger osteoclastogenesis and activation. For example, tumor necrosis factor (TNF)-α and interleukin (IL)-1 bind to their receptors, TNFRII [19] and IL-1R [20], respectively, and directly stimulate osteoclast formation activation. Additionally, IL-1 and IL-6 [21] indirectly stimulate local cells or inflammatory cells to express M-CSF (macrophage colony-stimulating factor) and RANKL, which then induce cell-to-cell interactions through their respective receptors, c-Fms and RANK, on the osteoclast precursors (Fig. 2).

Of the osteoclast differentiation factors, RANKL is especially important, as evidenced by the numerous inflammatory mediators that induce RANKL expression. PGE_2 has been studied extensively for its role in mediating orthodontic tooth movement through RANKL induction [22]. As with all inflammatory pathways, the RANK-RANKL pathway is tightly controlled to prevent pathology. Local cells downregulate RANK-RANKL–induced osteoclastogenesis by producing a RANKL decoy receptor, osteoprotegerin (OPG) [23]. Therefore, OPG levels must decrease to enable tooth movement.

Cytokine control of tooth movement is further supported by studies that block their effects. IL-1 receptor antagonist or TNF-α receptor antagonist (sTNF-α-RI) reduces tooth movement by 50% [24–27]. Similarly, tooth movement is reduced in mice lacking the TNF type II receptor [28], chemokine receptor 2 (which binds chemokine ligand 2), or chemokine ligand 3 [29]. Nonsteroidal anti-inflammatory drugs also reduce tooth movement by inhibiting PG synthesis [30,31]. Inhibiting other arachidonic acid derivatives, such as leukotrienes, also significantly decreases tooth movement [32].

4.4. Saturation of the biological response

We know that inflammatory markers play a critical role in orthodontic tooth movement by controlling the rate of osteoclastic bone resorption. It logically follows that increasing the magnitude of orthodontic forces would increase inflammatory marker expression and osteoclastogenesis, resulting in faster tooth movement. Surprisingly, there is a major controversy regarding the relation between force magnitude and the rate of tooth movement. Some studies show that higher force does not increase the rate of tooth movement [33,34], whereas others argue the opposite [35]. This controversy exists because researchers inappropriately equate the distance teeth move with the rate that teeth move for a given magnitude of force. This difference is not trivial. Although we want to know the distance teeth move in response to a given force magnitude, what we actually want to focus on is the relation between force magnitude and the biological response that regulates the rate of tooth movement.

Although we are focusing on the biological mediators of orthodontic tooth movement, many other factors affect orthodontic tooth movement. These factors can be intrinsic, such as root shape and alveolar bone density, or extrinsic, such as occlusal forces or limitation of the orthodontic appliance's mechanical design. These variables are difficult to accurately assess in humans because of the need for a large number of subjects with similar anatomic features, age, gender, and type of malocclusion. Although these limitations are easier to control in animal models, using tooth movement as the sole measure of the force effect can still produce conflicting results because the biological response to force varies throughout tooth movement.

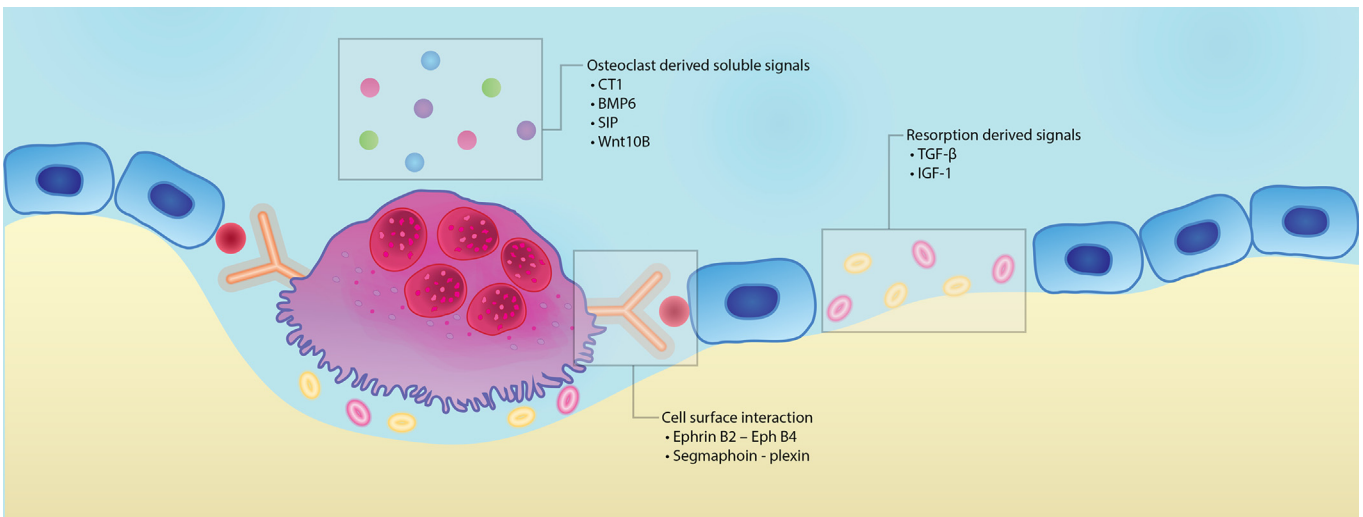

Fig. 4. Coupling of osteoclast and osteoblast activities. The coupling of the Catabolic Phase (osteoclast activity) with the Anabolic Phase (osteoblast activity) during orthodontic tooth movement can occur through different pathways: 1) osteoclast-derived signals working in a paracrine fashion (such as BMP6 or Wnt10B); 2) direct cell-cell interaction (such as Ephrin B2-Eph B4); 3) growth factors released from the matrix during bone resorption (such as transforming growth factor [TGF]-β and insulin like growth factor [IGF]-1). Used with permission from Teixeira et al. [12].

Because of biological and experimental design limitations mentioned previously, researchers use rats that share a similar genetic background, and measure molecular and cellular changes, rather than the magnitude of tooth movement, to assess force effects on the rate of tooth movement. Using this approach, we know that increasing the magnitude of orthodontic force increases inflammatory marker levels, osteoclast recruitment and formation, alveolar bone resorption, and the rate of tooth movement. Unexpectedly, we also know that there is a force magnitude above which no further biological responses are induced [36]. Thus, the cytokine release produced by orthodontic forces has an upper limit and consequently the osteoclast activity initiated by orthodontic forces has a saturation point [36]. Although the saturation point varies with the type of tooth movement, patient anatomy, bone density, and duration of treatment, the range of this variation is limited and, therefore, the rate of tooth movement is usually predictable. Although increasing the force magnitude does not overcome this limitation, any method that increases osteoclast numbers in the area where tooth movement is desired could be the answer to enhancing this biological response.

5. Anabolic phase of tooth movement

In the Biphasic Theory of Tooth Movement, the Catabolic Phase is followed by the Anabolic Phase, which maintains the new morphological relation of teeth and alveolar bone with adjacent structures. Importantly, the Anabolic Phase must involve both the trabecular and cortical bone. However, the molecular events that initiate the Anabolic Phase are not clear.

Alveolar bone on the side opposite to the compression side experiences tensile stresses. Osteoblasts are active under tension, and according to the classical theories of tooth movement, tensile forces directly stimulate osteoblasts [37]. However, experiments in long bones and alveolar bone demonstrate that, at physiologic levels, osteoblast activation requires intermittent loads of specific frequency and acceleration [16,36,38,39]. Therefore, application of static tensile forces, such as orthodontic forces, does not explain bone formation during orthodontic tooth movement. Furthermore, it has been shown that static tensile forces on long bones cause bone resorption [40]. Interestingly, tensile forces similar to compression forces that are applied with high frequency and acceleration are osteogenic [13,41]. Thus, other factors must explain the anabolic phase of orthodontic tooth movement.

Histological sections at early time points of force application demonstrate osteoclast activation at both compression and tension sites (Fig. 3A). This also demonstrates unequivocally that osteoclastogenesis is not limited to the compression side. This can clearly be seen in micro computed tomography scans of alveolar bone around moving teeth, which show increased radiolucency all around the entire tooth, not only on the compression side (Fig. 3B).

The basis for the Biphasic Theory is the timing of the Catabolic and Anabolic Phases. According to the theory, there is a measurable delay between the initiating Catabolic Phase and the subsequent Anabolic Phase. The Catabolic Phase is marked by the high expression of osteoclast markers during early tooth movement, whereas the Anabolic Phase is marked by the high expression of osteogenic markers later in tooth movement (Fig. 3C). If the Anabolic Phase resulted directly from tensile stress, then one would expect the Catabolic and Anabolic Phases to occur simultaneously. Furthermore, when anti-inflammatory medication is given (with a subsequent decrease in osteoclastogenesis), osteogenic activity decreases significantly as measured by decreased osteogenic marker expression [42].

In the Biphasic Theory of Tooth Movement, osteoclasts play an important role in the activation of osteoblasts. This agrees with numerous studies that suggest osteoclasts are the principal osteoblast regulators [43]. In healthy individuals, osteoclast activation is tightly coupled to osteoblast activation. This effect can occur through different pathways: 1) osteoclasts release paracrine factors that directly recruit and activate osteoblasts; 2) osteoclasts activate osteoblasts through direct cell-cell interaction; and 3) bone resorption by osteoclasts exposes bone matrix proteins that then indirectly attract and activate osteoblasts (Fig. 4). Although these pathways differ fundamentally, they do share an important feature. In each case, osteoclast activity precedes osteoblast activity. This

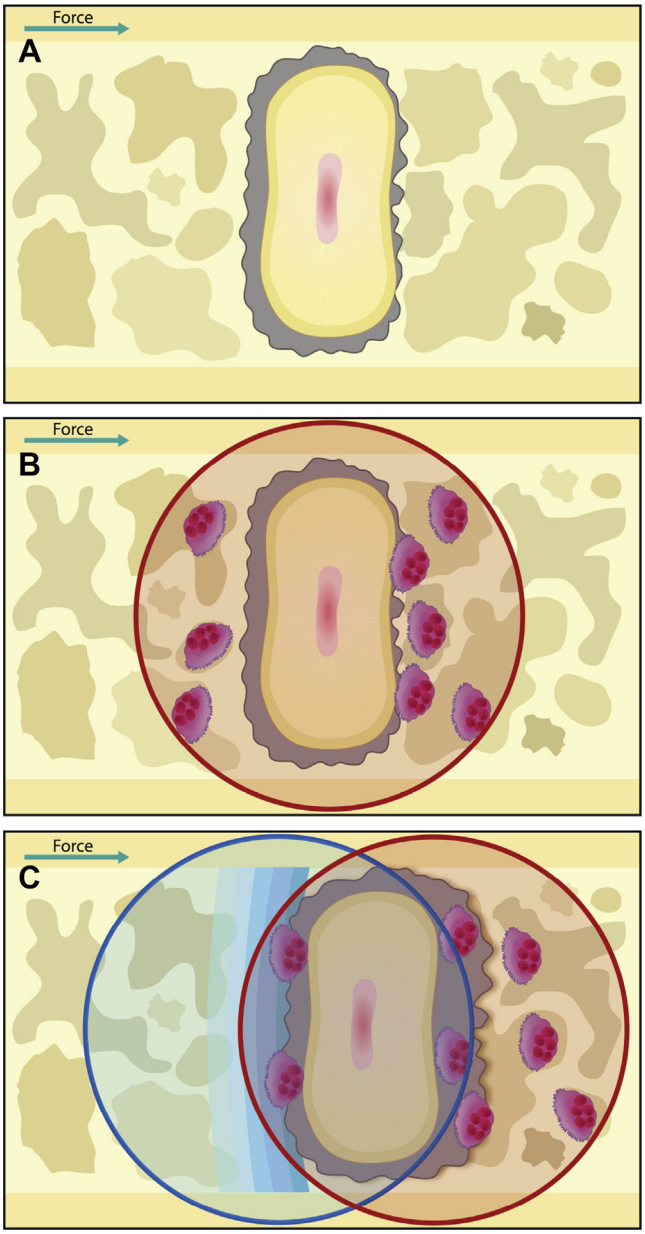

Fig. 5. Schematic of Biphasic Theory of Tooth Movement. The biologic response during tooth movement comprises two clearly separated phases. After application of an orthodontic force (A), both the compression and tensile stresses generated by displacement of the tooth cause damage to the PDL, stimulating a perimeter of osteoclastogenesis (B). Once the tooth moves in the direction of the orthodontic force into the space created by osteoclast activity, a perimeter of osteogenesis is created in roughly in the same area of the alveolar bone where the catabolic response took place (C). As a result, the tooth moves in the direction of the force. Used with permission from Teixeira et al. [12].

temporality occurs any time osteoclasts are activated, not just during orthodontic tooth movement, and is best visualized by the remodeling cone where the head of the cone is occupied by osteoclasts and the tail of the cone is filled with osteoblasts. By harnessing this repeatable and predictable sequential process, we can increase the anabolic effect of orthodontics in both trabecular and cortical bone.

6. Conclusion

Based on these observations, it is clear that the biologic response during tooth movement comprises two separated phases that are not site-specific. Indeed, both compression and tension damage the PDL, stimulating an aseptic inflammatory response that generates a perimeter of osteoclastogenesis (Fig. 5B). The tooth then moves into the space created by osteoclasts, while the perimeter of osteoclastogenesis simultaneously drifts in the direction of the force. As the Catabolic Phase dissipates, the Anabolic Phase ensues with osteoblasts creating a perimeter of osteogenesis (Fig. 5C). The osteoclastogenesis perimeter is a prerequisite for activation of the osteogenic perimeter. It is important to note that in considering the histological evidence for the Biphasic Theory, it may appear that the two phases are independent events. Remember, histological sections are deceiving because they are static representations of a dynamic process. Instead, the evidence on osteoresorptive and osteogenic marker expression clearly supports the temporal relationship that we propose in this new theory: the Biphasic Theory of Orthodontic Tooth Movement.

References

[1] Shen Z, Crotti TN, Flannery MR, Matsuzaki K, Goldring SR, McHugh KP. A novel promoter regulates calcitonin receptor gene expression in human osteoclasts. Biochim Biophys Acta 2007;1769:659–67.

[2] Park JK, Rosen A, Saffitz JE, et al. Expression of cathepsin K and tartrate-resistant acid phosphatase is not confined to osteoclasts but is a general feature of multinucleated giant cells: systematic analysis. Rheumatology (Oxford) 2013;52:1529–33.

[3] Guha M, Srinivasan S, Koenigstein A, Zaidi M, Avadhani NG. Enhanced osteoclastogenesis by mitochondrial retrograde signaling through transcriptional activation of the cathepsin K gene. Ann N Y Acad Sci 2016;1364:52–61.

[4] Dolci GS, Ballarini A, Gameiro GH, Onofre de Souza D, de Melo F, Fossati ACM. Atorvastatin inhibits osteoclastogenesis and arrests tooth movement. Am J Orthod Dentofacial Orthop 2018;153:872–82.

[5] Teixeira CC, Khoo E, Tran J, et al. Cytokine expression and accelerated tooth movement. J Dent Res 2010;89:1135–41.

[6] Tompkins KA. The osteoimmunology of alveolar bone loss. Connect Tissue Res 2016;57:69–90.

[7] Liu J, Chen B, Yan F, Yang W. The influence of inflammatory cytokines on the proliferation and osteoblastic differentiation of MSCs. Curr Stem Cell Res Ther 2017;12:401–8.

[8] Uda Y, Azab E, Sun N, Shi C, Pajevic PD. Osteocyte mechanobiology. Curr Osteoporos Rep 2017;15:318–25.

[9] 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;92:340–5.

[10] Joeng KS, Lee YC, Lim J, et al. Osteocyte-specific WNT1 regulates osteoblast function during bone homeostasis. J Clin Invest 2017;127:2678–88.

[11] Odagaki N, Ishihara Y, Wang Z, et al. Role of osteocyte-PDL crosstalk in tooth movement via SOST/sclerostin [published online ahead of print June 1, 2018]. J Dent Res doi: 10.1177/0022034518771331.

[12] Teixeira CC, Alansari S, Sangsuwon C, Nervina J, Alikhani M. Biphasic theory and the biology of tooth movement. In: Alikhani M, editor. Clinical guide to accelerated orthodontics. Springer, Heidelberg, Germany; 2017. p. 1–18.

[13] Rubin CT, Lanyon LE. Regulation of bone formation by applied dynamic loads. J Bone Joint Surg Am 1984;66:397–402.

[14] Alikhani M, Khoo E, Alyami B, et al. Osteogenic effect of high-frequency acceleration on alveolar bone. J Dent Res 2012;91:413–9.

[15] Verna C, Dalstra M, Lee TC, Melsen B. Microdamage in porcine alveolar bone due to functional and orthodontic loading. Eur J Morphol 2005;42:3–11.

[16] Alikhani M, Alyami B, Lee IS, et al. Saturation of the biological response to orthodontic forces and its effect on the rate of tooth movement. Orthod Craniofac Res 2015;18:8–17.

[17] Taddei SR, Andrade Jr I, Queiroz-Junior CM, et al. Role of CCR2 in orthodontic tooth movement. Am J Orthod Dentofacial Orthop 2012;141:153–60.

[18] Grant M, Wilson J, Rock P, Chapple I. Induction of cytokines, MMP9, TIMPs, RANKL and OPG during orthodontic tooth movement. Eur J Orthod 2013;35:644–51.

[19] Fuller K, Kirstein B, Chambers TJ. Murine osteoclast formation and function: differential regulation by humoral agents. Endocrinology 2006;147:1979–85.

[20] Jimi E, Ikebe T, Takahashi N, Hirata M, Suda T, Koga T. Interleukin-1 alpha activates an NF-kappaB-like factor in osteoclast-like cells. J Biol Chem 1996;271:4605–8.

[21] O'Brien CA, Gubrij I, Lin SC, Saylors RL, Manolagas SC. STAT3 activation in stromal/osteoblastic cells is required for induction of the receptor activator of NF-kappaB ligand and stimulation of osteoclastogenesis by gp130-utilizing cytokines or interleukin-1 but not 1,25-dihydroxyvitamin D3 or parathyroid hormone. J Biol Chem 1999;274:19301–8.

[22] Suzawa T, Miyaura C, Inada M, et al. The role of prostaglandin E receptor subtypes (EP1, EP2, EP3, and EP4) in bone resorption: an analysis using specific agonists for the respective EPs. Endocrinology 2000;141:1554–9.

[23] Yasuda H, Shima N, Nakagawa N, et al. Osteoclast differentiation factor is a ligand for osteoprotegerin/osteoclastogenesis-inhibitory factor and is identical to TRANCE/RANKL. Proc Natl Acad Sci U S A 1998;95:3597–602.

[24] Andrade Jr I, Silva TA, Silva GA, Teixeira AL, Teixeira MM. The role of tumor necrosis factor receptor type 1 in orthodontic tooth movement. J Dent Res 2007;86:1089–94.

[25] Iwasaki LR, Haack JE, Nickel JC, Reinhardt RA, Petro TM. Human interleukin-1 beta and interleukin-1 receptor antagonist secretion and velocity of tooth movement. Arch Oral Biol 2001;46:185–9.

[26] Jager A, Zhang D, Kawarizadeh A, et al. Soluble cytokine receptor treatment in experimental orthodontic tooth movement in the rat. Eur J Orthod 2005;27:1–11.

[27] Kesavalu L, Chandrasekar B, Ebersole JL. In vivo induction of proinflammatory cytokines in mouse tissue by *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans*. Oral Microbiol Immunol 2002;17:177–80.

[28] Yoshimatsu M, Shibata Y, Kitaura H, et al. Experimental model of tooth movement by orthodontic force in mice and its application to tumor necrosis factor receptor-deficient mice. J Bone Miner Metab 2006;24:20–7.

[29] DeLaurier A, Allen S, deFlandre C, Horton MA, Price JS. Cytokine expression in feline osteoclastic resorptive lesions. J Comp Pathol 2002;127:169–77.

[30] Knop LA, Shintcovsk RL, Retamoso LB, Ribeiro JS, Tanaka OM. Non-steroidal and steroidal anti-inflammatory use in the context of orthodontic movement. Eur J Orthod 2012;34:531–5.

[31] Chumbley AB, Tuncay OC. The effect of indomethacin (an aspirin-like drug) on the rate of orthodontic tooth movement. Am J Orthod 1986;89:312–4.

[32] Mohammed AH, Tatakis DN, Dziak R. Leukotrienes in orthodontic tooth movement. Am J Orthod Dentofacial Orthop 1989;95:231–7.

[33] Quinn RS, Yoshikawa DK. A reassessment of force magnitude in orthodontics. Am J Orthod 1985;88:252–60.

[34] Ren Y, Maltha JC, Kuijpers-Jagtman AM. The rat as a model for orthodontic tooth movement—a critical review and a proposed solution. Eur J Orthod 2004;26:483–90.

[35] Yee JA, Turk T, Elekdag-Turk S, Cheng LL, Darendeliler MA. Rate of tooth movement under heavy and light continuous orthodontic forces. Am J Orthod Dentofacial Orthop 2009;136:150.e1–9. discussion 150-1.

[36] Alikhani M, Alyami B, Lee IS, et al. Biological saturation point during orthodontic tooth movement. Orthod Craniofac Res 2015;18:8–17.

[37] Ikegame M, Ishibashi O, Yoshizawa T, et al. Tensile stress induces bone morphogenetic protein 4 in preosteoblastic and fibroblastic cells, which later differentiate into osteoblasts leading to osteogenesis in the mouse calvariae in organ culture. J Bone Miner Res 2001;16:24–32.

[38] Rubin CT, Sommerfeldt DW, Judex S, Qin Y. Inhibition of osteopenia by low magnitude, high-frequency mechanical stimuli. Drug Discov Today 2001;6:848–58.

[39] Garman R, Rubin C, Judex S. Small oscillatory accelerations, independent of matrix deformations, increase osteoblast activity and enhance bone morphology. PLoS One 2007;2:e653.

[40] Bassett CA. Biologic significance of piezoelectricity. Calcif Tissue Res 1968;1:252–72.

[41] Hert J, Liskova M, Landrgot B. Influence of the long-term, continuous bending on the bone. An experimental study on the tibia of the rabbit. Folia Morphol (Praha) 1969;17:389–99.

[42] Alikhani M, Alanari S, Sangsuwon C, Teo MC, Hiranpradit P, Teixeira CC. Anabolic effects of MOPs: cortical drifting. In: Alikhani M, editor. Clinical guide to accelerated orthodontics. Springer, Heidelberg, Germany; 2017. p. 79–98.

[43] Matsuo K, Irie N. Osteoclast-osteoblast communication. Arch Biochem Biophys 2008;473:201–9.