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Mechanobiology of orthodontic tooth movement: An update

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ABSTRACT

The purpose of this review is to provide an update on the changes at the cellular and tissue level occurring during orthodontic force application. For the understanding of this process, knowledge of the mechanobiology of the periodontal ligament and the alveolar bone are essential. The periodontal ligament and alveolar bone make up a functional unit that undergoes robust changes during orthodontic tooth movement. Complex molecular signaling is responsible for converting mechanical stresses into biochemical events with a net result of bone apposition and/or bone resorption. Despite an improved understanding of mechanical and biochemical signaling mechanisms, it is largely unknown how mechanical stresses regulate the differentiation of stem/progenitor cells into osteoblast and osteoclast lineages. To advance orthodontics, it is crucial to gain a better understanding of osteoblast differentiation from mesenchymal stem/progenitor cells and osteoclastogenesis from the hematopoietic/monocyte lineage.

1. Introduction

Orthodontic tooth movement (OTM) occurs when an external force is applied to a tooth. The direct effect of such a force is a, sometimes minute, deformation or strain in the tooth and its surrounding tissues, the periodontal ligament (PDL), and the alveolar bone. Cells within these tissues detect the strain and respond to the deformation of the extracellular matrix (ECM) or to their own deformation by the synthesis and secretion of various mediators, such as cytokines and growth factors. Ultimately, this leads to bone resorption at the front side of the moving tooth and to bone deposition at the back, as well as to remodeling of the PDL.

The purpose of the present overview is to provide information on the changes at the cellular and tissue level occurring during orthodontic force application. For the understanding of this process, knowledge of the mechanobiology of the PDL and the alveolar bone are essential. This review provides an update on the mechanical and biological processes and their interactions, aiming at a better understanding of the underlying mechanisms of OTM.

To describe the consecutive processes that occur during OTM, we take a more or less chronological approach to describe the effects of force application on the different components of the PDL and the alveolar bone. Important structures and phenomena involved in OTM are schematically visualized in Fig. 1A and B.

2. Matrix strain

The initial effect of the application of an external force to a tooth is its displacement within its socket, causing deformation or strain of the PDL. At the back side of the moving tooth, a tensional force on the PDL fibers leads to an increase in the PDL volume, and thus a positive strain (Fig. 1A), and stretching of the PDL fibers, while compression at the front side results in a decrease in the volume, relaxation of the PDL fibers, and thus a negative strain (Fig. 1B). The amount of strain at both sides of the tooth depends on the applied force and the material properties of the PDL.

Numerous studies have been performed on the PDL material properties, and there is growing evidence for a nonlinear and time-dependent relationship between force and displacement, indicating that the PDL is viscoelastic. This data have been used in finite element models in an attempt to calculate the strain distribution

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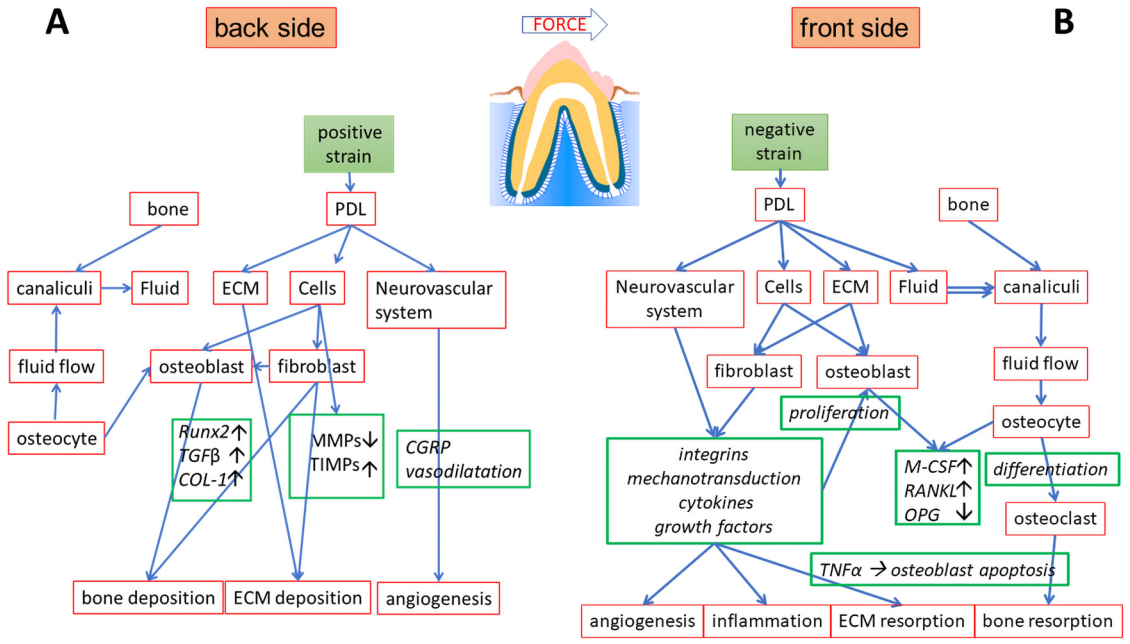

Fig. 1. Schematic representation of the most important structures and phenomena involved in orthodontic tooth movement. The tooth is moving to the right. (A) Back side of the tooth; (B) front side of the tooth.

within the PDL under specific loading conditions [1–3], and the most recent studies indicate that the PDL can be described as a biphasic poroviscoelastic material [4–6].

The porosity of the PDL allows for the redistribution of the free fluid phase within the periodontal space, resulting within a few seconds in uniform pressure throughout the PDL [3,7]. In the subsequent period of about 5 hours, a more gradual creep displacement is seen because of the viscoelastic stretching of the PDL fibers at the back side and relaxation at the front side [3,7,8].

Furthermore, minor fluid flow occurs out of the bone canaliculi at the tension sides, whereas fluid influx occurs at the compression side into the bone canaliculi, resulting in fluid shear stress within the canaliculi and the lacunar fluid surrounding the osteocytes [9]. This indicates that the biphasic poroviscoelastic material formulation can account for the microscopic, as well as the time-dependent, large deformation behavior of the PDL and the alveolar bone [5,10].

3. Strain and blood flow

Strain in the periodontal ECM also leads to a change in the blood flow. In the clinical situation, it is almost impossible to avoid blood vessel occlusion completely, and consequently, in almost all cases, an anoxic situation and local necrosis, known as hyalinization, will occur [11]. This leads to a period of arrest of OTM that lasts until the hyalinized tissue is completely removed [12]. Although hyalinization is considered to be an undesirable side effect of OTM, little attention has been paid to the phenomenon itself and its possible relationship with stress/strain levels in the PDL and alveolar bone [13].

Macrophages are responsible for the resorption of the hyalinized tissue, but the mechanisms involved in the removal of necrotic cells have remained relatively unexplored in the past. However, recently, new in vitro and in vivo models have been developed that have identified different classes of “find-me” and “eat-me” signals presented by necrotic cells and their receptors on macrophages that regulate the phagocytosis of necrotic debris [14]. It is suggested that tooth movement only starts once this process is completed at the compression side [11].

4. Strain in periodontal fibroblasts

The binding of periodontal fibroblasts to the ECM matrix through focal adhesion complexes (FACs) triggers strain in these cells. FACs comprise specific transmembrane proteins, the so-called integrins, which are bound extracellularly through arginylglycylaspartic acid-peptide sequences to matrix components, such as collagen, fibronectin, and vitronectin, and intracellularly to cytoplasmic focal adhesion proteins, including vinculin, paxillin, and talin. The FACs transmit mechanical stimuli from the ECM through the cytoskeleton to the nucleus by a process called mechanotransduction. In the nucleus, transcription factors activate gene expression [15].

Within a few hours after force application, periodontal fibroblasts are the first cells to respond to mechanical strain in the ECM and they show activation of various intracellular signaling pathways, such as the mitogen-activated protein kinases (MAPKs), the Rho-signaling pathways, and the c-fos pathways [16–21]. The MAPK pathway activation lasts for about 2 weeks, and subsequent gene expression is involved in the onset of bone remodeling, inflammation, ECM reorganization, and angiogenesis in the PDL [21,22].

Activated fibroblasts are stimulated to secrete plasminogen activator and its inhibitor, as well as matrix metalloproteases (MMPs) and the tissue inhibitor of MMP (TIMP), depending on the mechanical conditions (positive or negative strain). These factors act in concert to regulate the ECM remodeling and show localized expression patterns, suggesting careful coordination of turnover. Furthermore, the activated fibroblasts synthetize cytokines, such as prostaglandin E2 (PGE2) and interleukins (IL-1b, IL-6, IL-10), the

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growth factors transforming growth factor β (TGF-β), and tumor necrosis factor α (TNF-α), as well as nitric oxide (NO), all of which are involved in inflammatory processes [10,16,19,23–25].

5. Strain in neural tissues and blood vessels

Mechanical forces change vascularity and blood flow, as well as the neural components of the PDL. The nerve endings within the PDL contain mechanoreceptors and nociceptors. When orthodontically induced strain in the ECM distorts these nerve endings, they release vasoactive neuropeptides, such as calcitonin gene-related peptide (CGRP) and substance P, which then interact with vascular endothelial cells [26]. The reduction in oxygen tension results in the expression of hypoxia-inducible factor-1, a transcription factor that activates vascular endothelial growth factor and receptor activator of nuclear factor κB (RANKL), as well as prostaglandins and cytokines, e.g., IL-1b, IL-6, and IL-17, and TNF-α in PDL fibroblasts and in the osteoblasts at the front side of the moving tooth [10,27,28]). The expression of these factors leads to vasodilation, increased permeability, and subsequent plasma leakage [29–31]. Activated endothelial cells recruit circulating leukocytes, monocytes, and macrophages, indicating the onset of acute inflammation in the PDL [15,32,33].

At the back side of the moving tooth, under positive strain, the periodontal nerve fibers react by increasing the expression of CGRP, which acts as a vasodilator and stimulates plasma extravasation and leukocyte migration [34]. Moreover, CGRP has a stimulatory effect on osteoblast activity, and it inhibits osteoclast activity [35]

6. Strain and Osteoblasts

6.1. Negative strain

At the front side of the moving tooth, there is a negative strain present in both the PDL and the bone canaliculi (Fig. 1B). This has a fourfold effect.

First, the force application temporarily stimulates osteoblast apoptosis through the activity of apoptosis mediators, such as caspase-3, BCL-2-associated X protein, and B-cell lymphoma 2 [24,36,37]. After the first 3 days of force application, the synthesis of apoptosis mediators decreases again [38]. Second, the expression of vascular endothelial growth factor and RANKL in PDL fibroblasts and osteoblasts is upregulated because of the hypoxic situation and the subsequent stabilization of hypoxia-inducible factor-1 [10,27,28]. Third, the hypoxic situation leads to the activation of the P38 MAPK pathway, resulting in an elevated level of cycloxygenase-2 that co-catalyzes the synthesis of prostaglandins, including PGE2, from arachidonic acid [25,28]. PGE2, in turn, stimulates osteoblast differentiation and the expression of macrophage colony-stimulating factor (M-CSF) and RANKL and inhibits the expression of osteoprotegerin (OPG) [28,29,39]. OPG acts as a decoy receptor for RANKL and subsequently inhibits osteoclast differentiation and thus bone resorption. Finally, PDL cells at the front side express increased amounts of TNF-α, which stimulates the production of MMPs and elevates the levels of RANKL, to be directly involved in bone resorption [40].

6.2. Positive strain

At the back side of the moving tooth, there is a positive strain present in the PDL, as well as in the bone canaliculi (Fig. 1A). This strain causes a fluid flow from the bone into the PDL, which activates the osteocytes. These cells, in turn, stimulate PDL stem cells to express the extracellular signal-regulated kinase 1/2-Runx2 pathway, which is an early and essential pathway for the synthesis of Runx2. Runx2 stimulates the synthesis of a variety of structural bone proteins, such as collagen type 1, bone sialoprotein, osteocalcin, and osteopontin [41–43]. In addition, the canonical Wnt-signaling pathway is activated and this is important for bone formation because osterix and osteocalcin are downstream targets that are expressed during the first week of OTM [44,45].

Furthermore, bone deposition is stimulated under positive strain through the increased action of IL-10 that stimulates OPG synthesis and inhibits the synthesis of RANKL, thus preventing the differentiation of osteoclasts in that area [46]. Activated osteocytes stimulate the differentiation of precursors into osteoblasts through different cytokines, growth factors, and NO [12,28,47–49].

Also, TGF-β synthesis is upregulated under positive strain. It induces proliferation and chemotaxis of PDL cells and upregulates the collagen gene-1, leading to collagen type 1 production. Furthermore, TGF-β recruits osteoblast precursors and induces their differentiation into osteoblasts, and it down-regulates MMPs and upregulates TIMPs, thus avoiding ECM breakdown [32,50]. Their localized expression patterns suggest a careful coordination [30,50]. Overall, the upregulation of TGF-β under positive strain results in increased osteoblast and reduced osteoclast activity, leading to production of bone and remodeling of PDL fibers.

7. Biomechanical effects on Osteocytes

7.1. Negative strain

In response to negative strain at the front side, not only are osteoblasts in the PDL activated, but osteocytes within the alveolar bone are also activated (Fig. 1B). Osteocytes are important mechanosensors and transducers that are very sensitive to modulation of the fluid flow and the subsequent fluid shear stress within the canaliculi. In vitro studies in the 1990s have already suggested that fluid shear stress of very low magnitude is more effective in inducing biochemical reactions in osteocytes than hydrostatic compression [51,52].

The canalicular fluid flow hypothesis states that when bone is loaded, interstitial fluid is squeezed through the thin layer of nonmineralized matrix surrounding cell bodies and cell processes, thereby producing fluid shear stress at the osteocyte cell membrane [51]. Under negative strain, the fluid flow is from the PDL into the canaliculi [51]. The effect of shear stress in the osteocyte/canalicular system is comparable with the effects of negative strain on osteoblasts, namely, the differentiation of osteoclasts and the resorption of the alveolar bone [12,53].

The specific pathways for these processes are different for the front area of the moving tooth with negative strain and fluid flow into the bone and the back area with positive strain and a fluid flow from the canaliculi into the PDL [29,53,54].

7.2. Positive strain

At the back side of the moving tooth, a positive strain is present in both the PDL and the bone canaliculi, ultimately leading to bone deposition in that area (Fig. 1A). The osteocytes are activated by the fluid flow from the bone into the PDL and undergo more or less similar phenomena that occur in the osteoblasts. Also, in the osteocytes, IL-10 stimulates the synthesis of OPG and the reduction of RANKL synthesis, thus inhibiting osteoclast differentiation and favoring bone deposition [28,53].

TGF-β is also highly expressed under tension. It induces proliferation and chemotaxis of PDL cells, upregulates collagen gene-1 [55], recruits osteoblast precursors and induces their differenti-

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ation, and down-regulates MMPs and upregulates TIMPs [32,50]. This suggests a careful coordination of turnover [30,50]. The cumulative result is increased osteoblast and reduced osteoclast activity, resulting in bone production and remodeling of PDL fibers at the back side of a moving tooth.

We can conclude that cell activation, differentiation, and recruitment of osteoclasts are mediated by osteocytes, osteoblasts, and PDL cells. However, osteogenic differentiation is only observed in the osteoblast precursor cells present in the PDL. In addition, the recently discovered ephrin/Ephs seem to play a role parallel with the thoroughly investigated RANKL/OPG system in mediating bone resorption during OTM [56]. It has been suggested that osteocyte apoptosis occurs in areas of reduced canalicular fluid flow, subsequently attracting osteoclasts to the site [57,58]. This is likely the case at the front side of the moving tooth, where bone unloading might result in a reduction of fluid flow. Indeed, it has been shown that unloading of the bone leads to increased osteocyte apoptosis, followed by bone resorption [25,28,59]. In its turn, PGE2 stimulates osteoblast differentiation and the expression of M-CSF and RANKL, and inhibits the expression of OPG [28,29,39]. OPG acts as a decoy receptor for RANKL and subsequently inhibits osteoclast differentiation and thus bone resorption. Therefore, in compression areas, the ratio of RANKL/OPG favors osteoclast differentiation and bone resorption [60].

8. Strain and Osteoclasts

At the front side of the moving tooth, osteocytes within the alveolar bone are activated and stimulate the MAPK signaling pathway and subsequent PDL cell activation. The RANKL/OPG ratio is increased, allowing monocytes/macrophages to differentiate into osteoclast precursors. The differentiation from osteoclast precursor to osteoclast is dependent on cytokines and growth factors, such as M-CSF, TNF-α, the RANKL/OPG ratio, and NO [60–62]. In the meantime, TNF-α induces apoptosis of the osteoblasts, enabling the young osteoclasts to attach to the bare bone surface. However, the mechanism underlying this migration is not yet clear. Probably, the fluid shear stress from the canaliculi and/or the Ca++ gradient at the bone surface where the osteoid is removed through the action of MMPs might be leading this event [63]. Once landed at the bone surface, the osteoclasts adhere to bone surfaces by integrins and start to form resorptive lacunae [64]. Between an osteoclast and the alveolar bone, an isolated lacuna arises, called Howship's lacuna. In this lacuna, the pH decreases by the secretion of H+ ions and proteolytic enzymes, such as cathepsins and MMPs, including collagenases, degrade the ECM of the PDL and the organic matrix of the alveolar bone [26].

In addition, another pathway that stimulates osteoclastogenesis under negative strain is through an increase in ephrin-A2 and EphA2 expression. This pathway may play a role as important as the RANKL/OPG, but further investigation is needed [65].

9. Conclusions

The PDL and alveolar bone make up a functional unit that undergoes robust remodeling in OTM. Complex molecular signaling is responsible for converting mechanical stresses into biochemical events, with a net result of bone apposition and/or bone resorption. Despite our improved understanding of mechanical and biochemical signaling mechanisms, it is still largely unknown how mechanical stresses regulate the differentiation of stem/progenitor cells into osteoblast and osteoclast lineages. To advance orthodontics, it is crucial to gain a better understanding of osteoblast differentiation from mesenchymal stem/progenitor cells and osteoclastogenesis from the hematopoietic/monocyte lineage.

The field of orthodontics has come a long way since the Angle era, where the design of orthodontic force systems was largely empirical based. The orthodontic community now has tools for exploring the cellular and molecular events involved in OTM, including how stem cells differentiate into osteoblasts and osteoclasts. This newfound understanding will take orthodontics to new heights, beyond the technological achievements of the last decades.

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