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Biomodulator Cascade during Orthodontic Tooth Movement

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Abstract

Bone is highly dynamic tissue. It's the plastic nature of bone which is responsible for orthodontic tooth movement upon application of force. It is the inherent property of any cell to react to a mechanical stimulus of extracellular or intracellular nature. The generation and propagation of signaling cascades molecules and associated tissue remodeling in adjacent tissues response to applied mechanical loads form the central theme of orthodontic tooth movement. Orthodontic forces deform the extracellular matrix and activate cells of the paradental tissues, facilitating tooth movement. Findings in mechanobiology have illuminated sequential cellular and molecular events, such as signal generation and transduction, cytoskeletal re-organization, gene expression, differentiation, proliferation, synthesis and secretion of specific products, and apoptosis. Orthodontists work in a biological environment, wherein applied forces engender remodeling of both mineralized and non-mineralized periodontal tissues, including the associated blood vessels and neural elements.

Keywords: Tooth movement; Cellular mechanotransduction; Orthodontic tooth movement; Biomodulators

Review

Bone is highly dynamic tissue. It's the plastic nature of bone which is responsible for orthodontic tooth movement upon application of force. It is the inherent property of any cell to react to a mechanical stimulus of extracellular or intracellular nature. The generation and propagation of signaling cascades molecules and associated tissue remodeling in adjacent tissues response to applied mechanical loads form the central theme of orthodontic tooth movement. Capability of adaptive response to applied orthodontic force rests in the DNA of periodontal ligament (PDL) and alveolar bone cells. Cell vitality and numbers determine the molecular genetic responses making tooth movement possible. In the dramatic words of Kiberstis et al., [1] "the robust and unceasing activities of osteoblasts and osteoclasts imbue humans with the mechanical prowess to climb mountains or run marathons".

This article reviews and concludes the current biomedical literature on processes in orthodontic tooth movement. It seeks to link clinical orthodontics with the basic research involved in molecular-genetics.

Discoveries in the molecular biology and genetics of bone and connective tissue physiology permit appreciation of the complexity and regulatory sophistication of orthodontic tooth movement [2,3].

Cellular and Molecular Events Associated with Orthodontic Tooth Movement

In order to achieve tooth movement, remodeling of the alveolar bone surrounding the dental roots is required. Bone remodeling involves a complex network of cells (osteoblasts and osteoclasts), cell interactions and cell matrix interactions, all of which are regulated by hormones, growth factors and cytokines (some of which are a result of the strained PDL).

Mechanotransduction induced by orthodontic force occurs when external strain induces mechanosensing, transduction, and cellular response in several paradental tissues. This process leads to vasculature and extracellular matrix remodeling in the periodontal ligament (PDL), gingiva, and alveolar bone. This remodeling is facilitated by proliferation, differentiation, and apoptosis of local periodontal cells, bone cell precursors, and leukocyte migration from the microvascular compartment [4,5]. In this context, an aseptic acute inflammatory response is occurring in the early phase of orthodontic tooth movement (OTM), followed by an aseptic and transitory chronic inflammation. As orthodontic forces (continuous, interrupted, or intermittent) are not uniform throughout the applied region, areas of tension or compression are developed leading to varied inflammatory processes resulting in different tissue remodeling responses.

Cytokines and Tooth Movement

Cytokines are extracellular signaling proteins directly involved in the bone remodeling and inflammatory process during OTM, which act directly or indirectly, to facilitate bone and PDL cells differentiation, activation, and apoptosis [4,5]. Investigations of their

mechanisms of action have identified their effector (proinflammatory) and suppressive (anti-inflammatory) functions during OTM.

The receptor activator of nuclear factor-kappa B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) expressed by osteoblast and apoptotic osteocyte are the most important pro-inflammatory cytokines responsible for recruitment, differentiation, activation, and survival of osteoclasts [6]. These cytokines bind to their respective receptors, RANK and c-Fms, expressed in osteoclast precursors and mature osteoclasts, to produce these events through osteoclast–osteoblast communication [7,8]. By contrast, osteoblasts also express osteoprotegerin (OPG), a decoy receptor of RANKL, which inhibits the RANK/RANKL interaction, preventing osteoclastogenesis and accelerating mature osteoclast apoptosis [4,8].

When subjected to continuous (0.5-3.0 g/cm^2) or intermittent (2.0 or 5.0 g/cm^2) mechanical compressive force, PDL cells induce osteoclastogenesis in vitro through down regulation of OPG expression and upregulation of RANKL expression, via prostaglandin E 2 (PGE 2) and interleukin (IL)-1 β synthesis [9,10]. In accordance, mice research also demonstrated that osteoclastogenesis appears to be primarily regulated through M-CSF and RANKL signaling by PDL cells in the compression side in the first week of orthodontic force application. In the compression sites during human OTM (250 g), the same standard of RANKL and OPG expression is observed in gingival crevicular fluid (GCF) after 24 hours [11].

Tumor necrosis factor (TNF) - α is another proinflammatory cytokine that has been investigated in OTM and is involved in bone resorption and acute as well as chronic inflammation. TNF- α is produced primarily by activated monocytes and macrophages, but also by osteoblasts, epithelial cells, and endothelial cells [12]. *In vitro* studies have demonstrated that in bone, TNF- α can directly and indirectly induce osteoclastogenesis by binding to its p55 receptor on osteoclast precursors and by upregulating expression of RANKL, M-CSF, and other chemokines on osteoblasts [4,13]. TNF- α is also an apoptotic factor for osteocytes, which could be the signal for osteoclast recruitment to resorb bone in the PDL pressure side, at the same time inhibiting osteoblasts [14]. The real role of TNF-α in bone resorption, upregulating and increasing the amount of OTM, was shown in rodent models with TNF- α receptor impairment [15,16]. A recent in vitro study suggested that PDL fibroblasts secrete higher levels of TNF- α at the PDL compression side than at the tension side [17]. This imbalance leads to RANKL expression by activating CD4+ T cells, thereby facilitating bone resorption during OTM.

Like TNF- α, IL-1 (alpha and beta) is a proinflammatory cytokine that is highly expressed on the PDL pressure side of humans and animals and the adjacent alveolar bone in the early stages of OTM [18-20]. Its role in OTM has been the focus of previous human studies [20] that demonstrated an increase in osteoclast activity and survival, while at the same time inducing bone marrow cells and osteoblasts to produce RANKL in the early phase of OTM [21].

Under 24 hours of continuous compressive forces in vitro (3.0 g/cm^2), osteoblastic cells respond by expressing IL-1 α , IL-6, IL-11, TNF- α and receptors for IL-1, IL-6 and IL-8, suggesting an osteoblastic autocrine mechanism induced by mechanical stress. Indeed, animal studies with absence of IL-1 α and/or TNF-α signaling demonstrated impaired tooth movement, [15,16] but the mechanisms behind this finding remain unknown.

Other cytokines, such as IL-6, IL-8 and IL-11, also stimulate alveolar bone resorption during OTM by acting early in the inflammatory response [22]. These cytokines can be enhanced by, or can act synergistically with, TNF- α andIL-1 [23]. By contrast, IL-11 can have anabolic effects, alone or in association with bone morphogenetic protein-2 (BMP-2), inducing osteoblastic differentiation in mouse mesenchymal cells [24]. Different anti-inflammatory cytokines play inhibitory effects, controlling inflammation and bone resorption. IL-18 and IL-10 are also expressed in the PDL during OTM, and both inhibit osteoclastogenesis and bone resorption [25,26]. Furthermore, IL-10 inhibits the production of IL-1, IL-6, and TNF- α and its expression is higher in PDL tension than in compression sites [27].

From a clinical standpoint, analysis of cytokine levels in gingival crevicular fluid (GCF) during OTM may, in the future, reveal the rate of OTM and determine the optimum force level that should be applied by orthodontic devices. Analysis of cytokine levels in GCF may also be helpful in monitoring the biological activities in the periodontium during the retention period, which could provide information about possible relapse.

Chemokines and Tooth Movement

Chemokines belong to the superfamily of small heparin-binding cytokines [28]. The ability to induce cell migration is the common feature that distinguishes this group of cytokines [29]. Structurally, the chemokines are classified in 4 subfamilies based on the position of 2 highly conserved cysteine residues at the N-terminus: C, CC, CXC, and CX3C. To mediate their cellular effects, these molecules bind to selective 7-transmembrane domain receptors, which are coupled to heterotrimeric G proteins, differentiating also from other cytokines. The chemokine receptors are named according to their ligand family, such as CCR for receptors of CC ligands and CXCR for CXC ligands [28]. The chemokine system is promiscuous or redundant, as different chemokines can bind to a given chemokine receptor, and a given chemokine may bind to different chemokine receptors [28,29]. However, binding of chemokines to their respective receptors does not necessarily achieve the same functions in vivo [29]. Chemokines present different biological outcomes in different tissues, which are controlled by geography and timing [28,29]. They play a central role in trafficking and homing of leukocytes, immune cells, and stromal cells, during physiological (homeostatic chemokines) and inflammatory conditions (inflammatory chemokines) [29]. In addition, chemokines induce other biological processes, such as angiogenesis, cell proliferation and apoptosis [28].

Previous studies in vitro have demonstrated that CC-chemokine ligand 3 (CCL3), CCL2,CCL5, and CXC-chemokine ligand (CXCL9) chemokines promote chemotaxis of osteoclasts when binding to their respective CC receptors(CCR1, CCR2, CCR3, CCR5, and CXCR3), which are expressed by osteoclast precursors [30-32]. Others have shown that CCL5, CCL7, CCL2, CCL3, CXCL12, and IL-8 (CXCL8) promote RANKL-induced differentiation of osteoclast precursors [33,34]. Chemokines also stimulate activity of osteoclasts, such as CCL2, CCL3 and IL-8, [35,36] and prolong osteoclast survival, such as CCL3 and CCL9 (ligands CCR1) [35]. Moreover, RANKL induces osteoclast production of CCL2, CCL3 and CCL5, which suggests an autocrine and paracrine signalization during osteo-clastogenesis and an increase of bone resorption.

Chemokines can also induce recruitment, proliferation, and survival of osteoblasts. Osteoblasts express chemokine receptors, such as CXCR1, CXCR3, CXCR4, CXCR5, CCR1, CCR3, CCR4, and CCR5 [38]. CCL5, a ligand of CCR1, CCR3, CCR5, and CCR4, can induce

osteoblast recruitment and avoid apoptosis of this cell [38]. The chemokine CXCL10 induces osteoblast proliferation and release of alkaline phosphatase and β-acetyl hexosaminidase, while CXCL12 andCXCL13 induce both proliferation and collagen type I mRNA expression in osteoblasts [16].

Growth Factors and Tooth Movement

Growth Factors (GF) are substances that bind to specific receptors on the surface of their target cells, stimulating cell proliferation, migration, and differentiation. Moreover, they display important roles in hematopoiesis, the inflammatory process, angiogenesis, and tissue healing [38]. GF may also act locally to modulate bone remodeling, and consequently, OTM [38].

Vascular endothelial growth factor (VEGF) is an essential mediator of angiogenesis and increased vascular permeability [38]. As osteoblast and osteoclast express VEGF receptor-1, some studies have investigated the effect of VEGF on bone remodeling under mechanical loading [39,40]. In vitro studies have shown that PDL cells and apoptotic osteocytes increase VEGF production after compressive force application. VEGF can modulate the recruitment, differentiation, and activation of osteoclast precursors, increasing bone resorption [38]. The transforming growth factor (TGF) - β superfamily (TGF- β 1 to - β3) is another important GF related to bone and PDL tissue remodeling during OTM. Under mechanical loading, the cyclic tensile force upregulates TGF- β expression in osteoblasts and also in PDL cells invitro [17]. Furthermore, TGF- β stimulates OPG production and down regulates IL-6 expression, which inhibits the osteoclastogenesis –supporting activity of these cells [9].

Bone Morphogenetic Proteins (BMPs)

Bone morphogenetic proteins are multifunctional GFs that belong to the TGF- β super-family and play an important role in upregulating various transcription factors involved in osteoblastic differentiation and consequently, in bone formation [41]. To date, more than 20 BMPs have been discovered, but BMP-2, BMP-6, BMP-7 and BMP-9seem to have the most potent osteogenic activity [41-42]. Studies have shown that under tensile strain, human PDL cells in culture increaseBMP-2 and BMP-6 expression, suggesting that these BMPs might play an important role in PDL tensile sites during OTM [42-43]. However, there is a lack of information on the actual role of BMPs in OTM.

Insulin-like growth factors (IGFs) are involved in bone formation by inducing proliferation, differentiation, and apoptosis of osteoblasts [44]. The IGFs effect is regulated by growth hormone, parathyroid hormone, vitamin D3, corticosteroids, TGF- α, IL-1 and platelet-derived growth factor. Studies have shown that under continuous tensile mechanical loading, rat tibiae osteocytes and calvaria osteoblasts increase IGF-I synthesis, which stimulates bone formation [45,46]. In PDL tissues, IGF also acts as anti-apoptotic and proliferative factor for fibroblasts and osteoblasts in vitro [46]. Accordingly, an in vivo study using Wistar rats demonstrated that 4hours of a continuous tensile force (0.1-0.5 N) applied to a tooth induces increased expression of IGF-I and IGF-I receptor in PDL cells in tension sites, but a decreased expression in compression sites [47]. Therefore, a local increase of IGF-I appears to provide a link between the mechanical loading and tissue remodeling in the tensile site during OTM.

Fibroblast growth factors (FGFs) belong to a family of 23 members that bind to 4 structurally related high-affinity receptors [48]. Among FGFs, FGF-2 can regulate bone remodeling by stimulating osteoblast-like cell proliferation and differentiation in vitro, and by increasing osteoclast formation and activity [49]. An in vitro study demonstrated that compressive forces induce production of FGF-2 by human PDL cells, which stimulates RANKL expression.

It can be concluded that orthodontic tooth movement is produced by mechanical means that evoke biological responses. These two entities, mechanics and biology, act in concert to produce desirable and predictable alterations in the form and function of the dento-alveolar complex. The actual performers of this force-induced remodeling are the native cells of the treated teeth and their surrounding tissues.

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