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CRANIOFACIAL SKELETON (G ROBERTS, SECTION EDITOR)

Bone Response of Loaded Periodontal Ligament

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Abstract The tooth-periodontal ligament-alveolar bone complex acts symbiotically to dissipate the mechanical loads incurred during mastication and/or orthodontic tooth movement. The periodontal ligament functions both in the tension and compression. At the molecular and celleular levels, the loads in the periodontal ligament trigger mechanobiological events in the alveolar bone, which leads to bone modeling and remodeling. The current review focuses on the bone response to mechanical loading of the periodontal ligament on the tension and pressure sides. Understanding the bone response has major implications for dentistry, including a better understanding of the different types of orthodontic tooth movement.

Keywords Periodontal ligament · Alveolar bone · Mechanotransduction · Orthodontic tooth movement

Introduction

Periodontal ligament (PDL) is a fibrous articulation that modulates bone adaptation (modeling and remodeling) in response to mechanical strains. When the PDL is loaded, such as during orthodontic tooth movement, distinct synchronized scenarios take place at the pressure and tension side. There is an adaptive response to the application of force with reorganization of the intracellular and the extracellular matrix, in addition to a change of local vascularization. The classical model of tooth movement suggests that on the pressure side, there is a disturbance of blood flow and cell death, followed by removal of hyalinized tissue. Meanwhile, stretching of PDL fibers on the tension side leads to an increase in blood flow, cell division, and fiber production [1–4]. These changes in the PDL homeostasis are transferred to the surrounding alveolar bone. A network of consecutive events occurs leading to bone resorption on the pressure side and osteogenesis on the tension side, as teeth are moved within the alveolar bone [5]. Animal studies and the analysis of gingival crevicular fluid of orthodontic patients are the available tools for understanding the bone responses and cellular changes resulting from a loaded PDL.

The Pressure Side: Compressed PDL Attracts Inflammatory Factors and Osteoclasts

Disturbance in blood flow due to compressed PDL fibers causes local sterile necrosis and release of prostaglandin [6–9], cytokines [10–12], and colony-stimulating factors to form leucocytes, macrophages, and monocytes [13]. Most of the chemical and cellular changes occurring at the pressure side aim to recruit and differentiate cells into osteoclasts to resorb the adjacent bone and destroy the necrotic hyalinized tissue caused by hypoxia. The RANK/RANKL/OPG signaling pathway is classically described as crucial for osteoclastogenesis [14, 15]. RANKL and its receptor RANK are expressed in osteoclast precursors. They are the critical factors for osteoclast formation and function. RANKL is secreted by osteoblasts/stromal cells, which can also secrete OPG, a decoy receptor for RANKL. OPG can reduce the production of

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osteoclasts by inhibiting the differentiation of osteoclast precursors. So osteoblasts have a role in attracting and promoting osteoclast differentiation by secreting RANKL, but can also block this signaling pathway by secreting OPG. The ratio RANKL/OPG is the determinant factor for osteoclastogenesis and for orthodontic tooth movement [16]. Macrophage colony-stimulating factor (MCS-F) is another essential player for osteoclast differentiation produced by osteoblasts. Injection of exogenous MCS-F directly at the PDL of mice induced osteoclast differentiation and faster tooth movement [17]. MCS-F has also been identified in crevicular fluid of orthodontic patients [11].

An invasion of inflammatory factors takes place at the pressure side. Cytokines are small secreted proteins, with a pro- or anti-inflammatory effect, released by cells in response to local injury or stress [18]. Inflammatory cytokines such as IL-1, IL-6, IL-8, and TNF-α stimulate bone resorption by upregulating RANKL and have been shown to be elevated in gingival crevicular fluid collected from patients under orthodontic treatment [10–12, 19, 20]. In addition, CC chemokine ligands produced by osteoblast and its receptors expressed in osteoclast precursors (CCL2, CCL5, CCL9, CCL12, CCL20, CCR1, CCR2, CCR3, and CX3CR1) [21–24]. were found to be increased during orthodontic movement [25, 26]. Meanwhile, CCR5 seems to downregulate bone resorption in orthodontic tooth movement; it has been shown that CCR5-deficient mice have a much higher rate of tooth movement and increased numbers of osteoclasts in comparison to WT mice. In addition, markers for osteoblast differentiation (Runx2 and osteocalcin) and negative regulators of osteoclast differentiation (IL-10 and OPG) were significantly decreased in the CCR5-deficient mice [27].

Fluid flow theory is consistent with PDL behaving as a dynamic hydrostatic system, and changes in the fluid homeostasis have the potential to stimulate sensing mechanisms that mediate a cellular response. The alveolar bone wall of the dental socket contains fenestrations that allow compressed fluid in the PDL to be sensed not only by PDL cells but also by osteocytes located in the adjacent bone, and by cells in the marrow spaces [28, 29]. In fact, it is widely accepted that osteocytes are sensitive to loading changes and act as mechanoreceptors in bone [30, 31•]. Osteocytes appear to play a fundamental role in osteoclastogenesis and bone resorption during orthodontic movement. It was shown in an experimental model that ablation of osteocytes results in a significantly curtailled tooth movement response in the transgenic mice compared to controls. In addition, reduced numbers of osteoclasts and an eroded area were found on the pressure side of the ablated osteocyte group [32••]. Osteocyte apoptosis is thought to trigger bone remodeling and osteoclast function [33, 34]. It has also been suggested as an important osteoclast recruiting mechanism during orthodontic tooth movement, because increased osteocyte apoptosis has been observed on the pressure side as early as 12 h after induced tooth movement in mice [35]. Moreover, osteocyte protein expression appears to change in response to pressure during orthodontic loading, as will be discussed in the next section.

Primary cilia appear to be mechanosensors in osteocytes [36], and the transmembrane protein polycystin-1 (PC1) is one the proteins located at the calcium channel complex that mediates the sensing of cilia bending. Recent discoveries have suggested that PC1 acts as a mechanical sensor to recruit osteoclasts in orthodontic tooth movement; tooth movement is inhibited in a mouse model in the absence of PC1 expression in the craniofacial region [37].

Renewal of the vascular supply in compressed PDL contributes to osteoclast recruitment and differentiation; it is also an important process for healing and remodeling of the periodontium. It has been shown that PDL cells adjacent to hyalinized tissue and alveolar bone on the pressure side, during experimental tooth movement in rats/mice, presented substantial expression of vascular endothelial growth factor (VEGF), an important factor for angiogenesis [13, 38].

The Tension Side: Stretched PDL Fibers Lead to Osteogenesis

Stretched PDL fibers may generate tension where the fibers are inserted into alveolar bone. Mechanical tension of the PDL also alters local vascularization and triggers a cascade of signal transduction pathways such as arachidonic acid metabolites [39], neuropeptides [40], cytokines [41], and growth factors [42]. Changes occurring in the microenvironment at the tension side triggers PDL turnover, as well as bone deposition as specific cell-signaling pathways are activated. Expression of osteoblast-associated genes fluctuates in response to PDL deformation. It has been shown that expression of alkaline phosphate (ALP), bone sialoprotein (BSP), osteocalcin (OC), and collagen type I significantly increases during the first days of induced orthodontic movement in mice [43]. Furthermore, the increased expression of these genes was considerably greater than the increase in the number of osteoblasts, suggesting an induction of cell differentiation and increased function, rather than an increase in cell number after tensile loading [44]. However, the expression of dentine matrix protein-1 (DMP1) in osteoblasts appears transient, showing a decreased expression until day 6 of tooth movement on both sides of the PDL. The expression increased after day 7, suggesting dynamic changes in adaptation to cellular changes or protein interactions after loading [45]. The expression of DMP1 in the osteocytes was consistently higher after loading. There was significantly increased expression as early as 6 h after initiation of tooth movement, not only at the tension but also at the pressure side [45]. Gluhak-Heinrich et al. [46] have shown that the expression of matrix extracellular phosphoglycoprotein (MEPE) and DMP1, proteins that

modulate mineralization within the osteocyte canaliculi and lacunar walls, oscillate during the initial stage of induced tooth movement in mice, on both the pressure and tension sides. These reports and the studies discussed in the previous section suggest that osteocytes are important mechanoreceptors for mineralization and also for osteoclast recruitment during PDL loading.

However, bone formation during orthodontic tooth movement does not seem to be restricted to bone formation on the tension side. The regional acceleratory phenomenon results in bone formation also on the pressure side of the PDL, as well as distant to the immediate sites of tooth movement, as indicated by bone labeling of experimental tooth movement in animals [47, 48]. In addition, the bone remodeling response to orthodontic stimulation differs in the maxilla and mandible, which helps explain more rapid tooth movement in the maxilla compared to mandible [48].

Compliance with Ethical Standards

Conflict of Interest Sumit Yadav, Ravindra Nanda, and Eliane Dutra declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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