HHS Public Access

Author manuscript

Front Oral Biol. Author manuscript; available in PMC 2017 January 01.

Published in final edited form as:

Front Oral Biol. 2016 ; 18: 1–8. doi:10.1159/000351894.

Periodontal Ligament and Alveolar Bone in Health and Adaptation: Tooth Movement

Nan Jiang, **Weihua Guo**, **Mo Chen**, **Ying Zheng**, **Jian Zhou**, **Sahng Gyoon Kim**, **Mildred C. Embree**, **Karen Songhee Song**, **Heloisa F. Marao**, and **Jeremy J. Mao***

Center for Craniofacial Regeneration, Columbia University Medical Center, 630 W. 168 St. – PH7E, New York, NY 10032

Abstract

The periodontal ligament (PDL) and alveolar bone are two critical tissues for understanding orthodontic tooth movement. The current literature is replete with descriptive studies of multiple cell types and their matrices in the PDL and alveolar bone, but is deficient with how stem/progenitor cells differentiate into PDL and alveolar bone cells. Can one type of orthodontic force with a specific magnitude and frequency preferably activate osteoblasts, whereas another force type activates osteoclasts? This chapter will discuss the biology of not only mature cells and their matrices in the periodontal ligament and alveolar bone, but also stem/progenitor cells that differentiate into fibroblasts, osteoblasts and osteoclasts. Key advances in tooth movement rely on further understanding of osteoblast and fibroblast differentiation from mesenchymal stem/progenitor cells, and osteoclastogenesis from the hematopoietic/monocyte lineage.

Keywords

Periodontal ligament; Alveolar bone; Orthodontic tooth movement; Extracellular matrix; Stem cells; Bone remodeling; Matrix; Protein

1. Introduction

The alveolar bone, periodontal ligament (PDL) and cementum are intimately related structures in development and functions. Collectively, they form the periodontium that is of critical relevance not only to orthodontic tooth movement, but also periodontal disease. There are myriads of descriptive studies of multiple cell types and their gene expression profiles of the PDL and alveolar bone, often separately in orthodontics and periodontal research literatures. Matrix synthesis is another area of focus of numerous investigations of the PDL and alveolar bone. Far deficient is our understanding of how stem/progenitor cells differentiate into mature cells in the PDL and alveolar bone, including fibroblasts, osteoblasts and osteoclasts [1]. This deficiency applies to not only our understanding in homeostasis, but also as adaptive responses during tooth movement and periodontal disease.

*Jeremy J. Mao, DDS, PhD, Professor and Edwin S. Robinson Endowed Chair, Director, Center for Craniofacial Regeneration, Columbia University Medical Center, 630 W. 168 St. - PH7E - CDM, New York, NY 10032, Phone: 212-305-4475, Fax: 212-342-0199, jmao@columbia.edu.

This chapter focuses on three related topics: 1) fundamental cell and matrix structures of the PDL and alveolar bone, 2) PDL and alveolar bone remodeling during orthodontics tooth movement, and 3) how our understanding of PDL and alveolar bone stem/progenitor cells may help advance orthodontics. Orthodontic tooth movement is typically divided into three phases by clinical observation: the initial phase, the lag phase, and the post-lag phase [2]. The initial phase occurs 24 to 48 hours after force application. The lag phase lasts multiple days with little tooth movement. The post-lag phase is when clinically noticeable tooth movement is observed. Up to date, our understanding of how stem/progenitor cells are involved in orthodontic tooth movement remains at an infancy stage.

2. The Periodontal Ligament

The periodontal ligament (PDL) connects the cementum to the alveolar bone by bundles of type I collagen named Sharpey's fibers. The width of a periodontal ligament in homeostasis is ~0.15-0.38 mm, depending on the tooth type. The PDL has two primary functions: 1) to transmit and absorb mechanical stresses, and 2) to provide vascular supply and nutrients to the cementum, alveolar bone and the PDL itself [3]. The PDL is a connective tissue and shares certain similarities with tendons and other ligaments in the appendicular skeleton [4].

2.1 Cells

Fibroblasts constitute ~50-60% of the total PDL cellularity [5]. PDL fibroblasts consist of multiple subpopulations and thus are heterogeneous. PDL cells experience and respond to mechanical stresses [6], such as those in orthodontic tooth movement. Other PDL cells include macrophages, lymphocytes and endothelial cells that form the lining of blood vessels [7]. When forces are applied to the tooth, PDL fibroblasts react by activating stretch-sensitive Ca^{2+}-permeable channels and increase actin polymerization and yield a rapid and transient increase in c-fos expression that in turn stimulates their proliferation and differentiation [8]. Activated fibroblasts secrete plasminogen activator as well as its inhibitor, matrix metalloproteases and their inhibitors, cytokines (PGE-2) and Interleukin-6 [9].

The PDL further consists of defense cells such as macrophages and mast cells. Epithelial remnants of Malassez are descents of dental epithelium cells in the PDL, following amelogenesis. In addition, osteoblasts, osteoclasts and cementoblasts are present in the PDL and participate in the homeostasis of the periodontium. The osteoblasts and osteoclasts reside in the PDL on the surface of lamina dura and in endosteal surfaces of the alveolar bone, and are also responsive to mechanical stresses.

PDL and alveolar bone readily remodel in homeostasis and orthodontic tooth movement. Osteoblasts in the PDL and alveolar bone are replaced every few months [10]. Most biological tissues adapt and self-renew, serving as an indication that there must be stem cells, which replenish and replace terminally differentiated cells that periodically undergo apoptosis. Stem cells are immature and unspecialized cells that can 1) self-renew and 2) undergo asymmetrical differentiation: producing precise copies of stem cells and at the same time differentiate into specialized cell types such as fibroblasts and osteoblasts. In a developing embryo, embryonic stem cells can differentiate into every single 200 types of

specialized cells in the body, and therefore, are called pluripotent stem cells [11]. In the adult, stem cells are likely more restricted and can differentiate into a limited number of cell types, but nonetheless, can replenish mature cells that are lost to apoptosis ([12]. Postnatal stem/progenitor cells are more restricted in the number of lineages that they can differentiate into. Typically, progenitor cells differentiate into only one type of mature cells during homeostasis.

There are two types of dental stem cells: epithelial stem cells and mesenchymal stem cells (MSCs) [13, 14]. Epithelial and mesenchymal stem cells intimately interact during tooth development: epithelial stem cells giving rise to ameloblasts, whereas mesenchymal stem cells differentiating into fibroblasts, odontoblasts, cementoblasts, osteoblasts, and perhaps other cells in the periodontal ligament [15].

Periodontal ligament cells have been studied for decades, due to their significance in periodontal disease and also orthodontic tooth movement. Dental follicle cells, which originate from neural crest derived mesenchyme, differentiate into cells that form the periodontium and are present in the developing tooth germ prior to root formation [16]. Among fibroblast-like cells in the periodontal ligament, stem/progenitor cells have been identified [17]. Typically, soft tissue is scraped from the root of an extracted tooth and enzyme-digested to release a small number of cells. Morphologically, it is impossible to separate PDL fibroblasts from PDL stem/progenitor cells. Nonetheless, certain PDL cells yield progenies upon single cell colony assay and can differentiate into multiple cell lineages in vitro. In chemically defined culture conditions, specific PDL cells differentiate into cementoblast-like cells, adipocytes, and collagen-forming cells. When transplanted into immune-compromised rodents, PDL fibroblast-like cells generated a cementum/PDL-like structure [17]. To date, little is known how PDL stem/progenitor cells respond to mechanical forces such as those in orthodontic tooth movement.

2.2 Fibrous matrix

Collagen fibers, reticulin fibers and oxytalan fibers form the PDL fibrous matrix. Collagen accounts for over 90% PDL fibers. Type I collagen fibers in the PDL are 45-55 nm in diameter and have somewhat uniform morphology [18]. PDL fiber bundles are arranged in directions that reflect their functional properties. PDL collagen fibers grow separately from bone and cementum surfaces, and gradually elongate and approximate each other [19].

Upon application of orthodontic forces, PDL nerve fibers release calcitonin gene related peptide (CGRP) and substance P [20]. CGRP and substance P serve as vasodilators and stimulate plasma extravasation and leukocyte migration. CGRP has been shown to induce bone formation through stimulation of osteoblasts and inhibition of osteoclast activity [21].

3. The Alveolar Bone

A better name for the alveolar bone is dental bone or tooth bone, for tooth loss leads to disappearance of the alveolar bone. Although the bulk of the alveolar bone is trabecular bone, it does contain a plate of compact bone adjacent to the periodontal ligament called the lamina dura. The PDL pierces through the lamina dura and anchors to the alveolar bone,

with the other end connected to the cementum [22]. The inner (lingual) and outer (labial) cortical plates are also composed of compact bone.

Alveolar bone is a mineralized connective tissue and consists of mineral tissue, organic matrix and water. In the alveolar bone, 23% is mineralized tissue; 37% is the organic matrix which mostly is collagen, and the other 40% is water [23].

3.1 Cells

Multiple cell types are responsible for the homeostasis and functions of the alveolar bone. The most obvious cell types are osteoblasts, osteocytes and osteoclasts. However, other cell types are also important, including adipocytes, endothelial cells that form the lining of blood vessels and immune competent cells such as macrophages.

Osteoblasts are mononucleated and specialized cells that are responsible for bone apposition. Osteoblasts and fibroblasts share a key functional similarity in that they both synthesize type I collagen matrix. Osteoblasts, however, distinguish from fibroblasts by expressing Cbfa1 or Run×2 that is a master switch for the differentiation of stem/progenitor cells into osteoblasts [24]. Although myriad genes control the complex process of osteogenesis, Cbfa1 or Run×2 is the earliest transcriptional factor and signals the initiation of bone formation [25]. Other osteogenesis genes include bone morphogenetic proteins (BMPs), transforming growth factor-beta (TGF-β), Indian hedgehog and ostrix [26-29]. Bone is a dynamic tissue and constantly remodels by osteoblasts and osteoclasts, the two of which function by cross talk and signaling [25]. The number of osteoblasts decreases with age, affecting the balance of bone deposition and resorption and potentially leading to osteoporosis [30].

Mesenchymal stem/progenitor cells have been isolated from jaw bones of both humans and rodents [31-33]. Stem/progenitor cells from the jaw bone were clonogenic and had potent osteogenic potential in vitro and in vivo [33]. Compared with iliac crest cells, mandibular mesenchymal stem/progenitor cells appear to proliferate rapidly with delayed senescence, express robust alkaline phosphatase and accumulate more calcium in vitro [31]. Specifically, mesenchymal stem/progenitor cells from long bones yield greater bone marrow area than mandibular mesenchymal stem/progenitor cells when transplanted heterotopically *in vivo [32].*

Osteocyte is the most numerous cells in mature bone, and can live as long as the organism itself [34]. Osteocytes are derived from functional osteoblasts that are embedded in mineralized bone in the process of bone apposition. The space that an osteocyte occupies is called a lacuna. Hydroxyapatite, calcium carbonate and calcium phosphate is deposited around osteocytes [35, 36].

Whereas osteoblasts (and osteocytes) derive from the mesenchymal/mesodermal lineage, osteoclasts originate from an entirely different source: the hematopoietic/monocyte lineage [37, 38]. Osteoclasts are formed by the fusion of multiple monocytes, and therefore, are multi-nucleated [39, 40]. Their unique properties include adherence to endosteal bone surfaces, and secret acid and lytic enzymes that destroy mineral and protein structures. An

array of transcription factors controls osteoclast differentiation [40]. Osteoclasts are characterized by robust expression of tartrate resistant acid phosphatase (TRAP), specified osteoprotegerin (OPG), cathepsin K, and chloride channel 7 (ClCN7) [41]. OPG blocks nuclear factor kappa B (RANK) and RANK ligand (RANKL) docking; cathepsin K destroys bone matrix proteins, whereas chloride channel 7 maintains osteoclast neutrality by shuffling chloride ions through the cell membrane. RANKL, a key regulator of osteoclast function [39, 40], is synthesized by osteoblasts and promotes osteoclast differentiation, suggesting that osteoblasts control osteoclast differentiation, but not function [42].

3.2 Matrix proteins

In the alveolar bone, the most abundant extracellular matrix (ECM) component is collagen type I [43]. In addition, alveolar bone contains non-collagenous proteins such as osteocalcin, osteopontin, osteonectin, bone sialoprotein and fibronectin as well as proteoglycans including lumican, fibromodulin, decorin, biglycan and versican. Osteocalcin acts as a hormone and causes pancreatic beta cells to release more insulin, and at the same time directs adipocytes to release adiponectin, which increases sensitivity to insulin [44]. Osteopontin is a phosphorylated, sialic acid containing glycoprotein that can be extracted from the mineralized bone matrix. Matrix metalloproteinase-1, 2 [43, 45] and cathepsin [46, 47] are considered to be particularly important in bone resorption. They cleave type I collagen most efficiently within the triple-helical body of the native conformation and is active at neutral pH, whereas cathepsin K degrades type I collagen in a similar manner but is active at low pH in the acidic microenvironment beneath the ruffled border of osteoclasts [48].

4. PDL and alveolar bone resorption and remodeling

Can one type of force with a specific magnitude and frequency preferably activate osteoblasts, whereas another force type preferably activates osteoclasts [49]. One can only begin to address a question such as this by understanding how stem/progenitor cells in the PDL and alveolar differentiate into mature cells, including fibroblasts, osteoblasts, osteoclasts and endothelial cells. Two interrelated processes in orthodontic tooth movement are deflection (bending) of the alveolar bone and remodeling of the periodontium: the periodontal ligament, alveolar bone and cementum [50]. In the “pressure-tension theory”, the PDL senses a change in mechanical forces or stresses. The theory proposes that PDL progenitor cells differentiate into compression-associated osteoclasts and tension-associated osteoblasts, causing bone resorption and apposition, respectively [51]. The following biological processes are proposed on the compression side: disturbance of blood flow in the compressed PDL, cell death in the compressed area of the PDL (hyalinization), resorption of the hyalinized tissue by macrophages, and undermining bone resorption by osteoclasts beside the hyalinized tissue. It is proposed that tooth movement follows the completion of these processes on the compression side, but not before.

On the tension side, it is proposed that the periodontium, including the PDL, alveolar bone and cementum remodels and undergoes bone apposition. Osteoblasts differentiate from mesenchymal stem/progenitor cells. Mature osteoblasts form the osteoid or type I collagen

matrix, which is followed by mineralization [52]. Endothelial nitric oxide synthase (eNOS) mediates bone formation on the tension side of orthodontic forces [53].

Force magnitude has been associated with biological events, although most of these associations are conjectures. “Direct resorption” is associated with light force application, tissue and cell preservation, and vascular potency. “Indirect resorption” and hyalinization are associated with heavy forces that cause crushing injury to PDL tissues, cell death, hemostasis, and cell-free PDL and adjacent alveolar bone zones [54]. Mechanical forces often cause hyalinization leading to necrosis in the PDL and lead to delayed bone resorption. Hyalinization occurs in the PDL and is proposed to indicate hyaline-like tissue formation that no longer has normal tissue architecture. Macrophages are responsible for removing the hyalinized tissues prior to which little tooth movement occurs [55]. Extracellular matrix and cell distortion causes structural and functional changes in cell membrane, and cytoskeletal proteins. At the same time, numerous submembrane proteins associate in cellular focal adhesions. These complex structural or functional adaptations will transmit signals to the cytoplasm and mediate cell adhesion by integrin activation [56].

Alveolar bone resorption occurs on the compression side during tooth movement. Bone resorption occurs through osteoclastic activity, thus creating irregular cavities in bone that later will be filled by newly formed bone owing to osteoblast activity. Two processes involved in bone resorption are the dissolution of minerals and the degradation of the organ matrix, which consists of type I collagen. These processes are driven by enzymes, including matrix metalloproteinase and lysosome cysteine proteinases [48]. Orthodontic forces result in the deformation of blood vessels and disarrangement of surrounding tissues. Subsequently, blood flow and periodontal tissue adapt to the compression force, or when they fail, are responsible for cell death and tissue necrosis [57].

The rate of orthodontic tooth movement is affected by multiple factors such as the magnitude, frequency, and duration of mechanical forces that are applied to the teeth or bone. Mechanical forces change vascularity and blood flow, resulting in the synthesis and release of molecules such as neurotransmitters, cytokines, growth factors, colony-stimulating factors that regulate leucocyte, macrophage, and monocyte lines [58, 59].

Protein phosphorylation mediated by protein kinase enzymes is critical to the understanding of orthodontic tooth movement [56, 60, 61]. Cytoplasmic signaling proteins Hh, sonic hedge-hog, the TGF-β superfamily, and many transcriptional factors and ions (Ca++, PO3−) enhance or suppress gene expression. Matrix metalloproteinases (MMP) is an indispensable enzyme in bone remodeling. MMP-2 protein is induced by compression and increases significantly in a time-dependent fashion, reaching a peak after eight hours of force application. On the tension side, MMP-2 significantly increases after one hour of force application but gradually returns to baseline within eight hours [62]. The cleavages of procollagen yields procollagen type I C-terminal propeptide (PICP) and procollagen type I N-terminal propeptide (PINP) that may serve as bone formation markers [63]. Normal chloride channels play a key role in osteoclastic alveolar bone resorption in orthodontic tooth movement [40]. Cystic fibrosis, a pathological bone condition is characterized by

mutated cellular chloride channels encoded by polymorphic nucleotide sequences in the ClCN7 gene [50].

5. Summary

The periodontal ligament and alveolar bone are a functional unit and undergo robust remodeling in orthodontic tooth movement. Complex molecular signaling is responsible for transducing mechanical stresses to biochemical events with a net result of bone apposition and/or bone resorption. Despite our improved understanding of mechanical and biochemical signaling mechanisms, how mechanical stresses regulate the differentiation of stem/progenitor cells into osteoblast lineage and osteoclast lineage is largely unknown. An improved understanding of osteoblast differentiation from mesenchymal stem/progenitor cells and osteoclastogenesis from the hematopoietic/monocyte lineage is essential to advance orthodontics. Design of orthodontic force systems has been largely empirical since the Angle era. The orthodontics community is now equipped with tools to begin advancing the understanding of orthodontic tooth movement via cellular and molecular events, including how stem cells differentiate into osteoblasts and osteoclasts.

Acknowledgements

The authors wish to thank F. Guo, H. Keyes and J. Melendez for technical and administrative assistance. The effort for composition of this article is supported by NIH grants R01DE018248, R01EB009663, and RC2DE020767 to J.J. Mao.

References

1. Mao JJ, Robey PG, Prockop DJ. Stem cells in the face: tooth regeneration and beyond. Cell Stem Cell. 2012; 11(3):291–301. [PubMed: 22958928]
2. Krishnan V, Davidovitch Z. Cellular, molecular, and tissue-level reactions to orthodontic force. Am J Orthod Dentofacial Orthop. 2006; 129(4):469 e461–432. [PubMed: 16627171]
3. Storey E. The nature of tooth movement. Am J Orthod. 1973; 63(3):292–314. [PubMed: 4631333]
4. Nanci A, Bosshardt DD. Structure of periodontal tissues in health and disease. Periodontol 2000. 2006; 40:11–28. [PubMed: 16398683]
5. McCulloch CA, Bordin S. Role of fibroblast subpopulations in periodontal physiology and pathology. J Periodontal Res. 1991; 26(3 Pt 1):144–154. [PubMed: 1830616]
6. Phipps RP, Borrello MA, Blieden TM. Fibroblast heterogeneity in the periodontium and other tissues. J Periodontal Res. 1997; 32(1 Pt 2):159–165. [PubMed: 9085227]
7. Naveh GR, Lev-Tov Chattah N, Zaslansky P, Shahar R, Weiner S. Tooth-PDL-bone complex: Response to compressive loads encountered during mastication - A review. Arch Oral Biol. 2012
8. Yamaguchi N, Chiba M, Mitani H. The induction of c-fos mRNA expression by mechanical stress in human periodontal ligament cells. Arch Oral Biol. 2002; 47(6):465–471. [PubMed: 12102763]
9. Lekic PC, Rajshankar D, Chen H, Tenenbaum H, McCulloch CA. Transplantation of labeled periodontal ligament cells promotes regeneration of alveolar bone. Anat Rec. 2001; 262(2):193–202. [PubMed: 11169914]
10. Davidovitch Z. Tooth movement. Crit Rev Oral Biol Med. 1991; 2(4):411–450. [PubMed: 1742417]
11. Boyer LA, Lee TI, Cole MF, Johnstone SE, Levine SS, Zucker JP, Guenther MG, Kumar RM, Murray HL, Jenner RG, et al. Core transcriptional regulatory circuitry in human embryonic stem cells. Cell. 2005; 122(6):947–956. [PubMed: 16153702]
12. Scholer HR. [The potential of stem cells. A status update]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2004; 47(6):565–577. [PubMed: 15221108]

13. Harada H, Kettunen P, Jung HS, Mustonen T, Wang YA, Thesleff I. Localization of putative stem cells in dental epithelium and their association with Notch and FGF signaling. J Cell Biol. 1999; 147(1):105–120. [PubMed: 10508859]
14. Sonoyama W, Liu Y, Fang DAJ, Yamaza T, Seo BM, Zhang CM, Liu H, Gronthos S, Wang CY, Shi ST, et al. Mesenchymal Stem Cell-Mediated Functional Tooth Regeneration in Swine. Plos One. 2006; 1(1)
15. Bluteau G, Luder HU, De Bari C, Mitsiadis TA. Stem Cells for Tooth Engineering. Eur Cells Mater. 2008; 16:1–9.
16. Yao S, Pan F, Prpic V, Wise GE. Differentiation of stem cells in the dental follicle. J Dent Res. 2008; 87(8):767–771. [PubMed: 18650550]
17. Seo BM, Miura M, Gronthos S, Bartold PM, Batouli S, Brahim J, Young M, Robey PG, Wang CY, Shi S. Investigation of multipotent postnatal stem cells from human periodontal ligament. Lancet. 2004; 364(9429):149–155. [PubMed: 15246727]
18. MacNeill S, Walters DM, Dey A, Glaros AG, Cobb CM. Sonic and mechanical toothbrushes. An in vitro study showing altered microbial surface structures but lack of effect on viability. J Clin Periodontol. 1998; 25(12):988–993. [PubMed: 9869348]
19. Sawhney RK, Howard J. Molecular dissection of the fibroblast-traction machinery. Cell Motil Cytoskel. 2004; 58(3):175–185.
20. Hall M, Masella R, Meister M. PDL neuron-associated neurotransmitters in orthodontic tooth movement: identification and proposed mechanism of action. Todays FDA. 2001; 13(2):24–25. [PubMed: 15025038]
21. Anderson LE, Seybold VS. Calcitonin gene-related peptide regulates gene transcription in primary afferent neurons. J Neurochem. 2004; 91(6):1417–1429. [PubMed: 15584918]
22. Blum IR. Contemporary views on dry socket (alveolar osteitis): a clinical appraisal of standardization, aetiopathogenesis and management: a critical review. Int J Oral Maxillofac Surg. 2002; 31(3):309–317. [PubMed: 12190139]
23. Moss-Salentijn L. Melvin L. Moss and the functional matrix. J Dent Res. 1997; 76(12):1814–1817. [PubMed: 9390473]
24. Ehrlich PJ, Lanyon LE. Mechanical strain and bone cell function: a review. Osteoporos Int. 2002; 13(9):688–700. [PubMed: 12195532]
25. Ducy P, Schinke T, Karsenty G. The osteoblast: A sophisticated fibroblast under central surveillance. Science. 2000; 289(5484):1501–1504. [PubMed: 10968779]
26. Winkler DG, Sutherland MK, Geoghegan JC, Yu CP, Hayes T, Skonier JE, Shpektor D, Jonas M, Kovacevich BR, Staehling-Hampton K, et al. Osteocyte control of bone formation via sclerostin, a novel BMP antagonist. Embo J. 2003; 22(23):6267–6276. [PubMed: 14633986]
27. Mackie EJ. Osteoblasts: novel roles in orchestration of skeletal architecture. Int J Biochem Cell B. 2003; 35(9):1301–1305.
28. Bu RF, Borysenko CW, Li YN, Cao LH, Sabokbar A, Blair HC. Expression and function of TNF-family proteins and receptors in human osteoblasts. Bone. 2003; 33(5):760–770. [PubMed: 14623051]
29. Ducy P, Schinke T, Karsenty G. The osteoblast: a sophisticated fibroblast under central surveillance. Science. 2000; 289(5484):1501–1504. [PubMed: 10968779]
30. D'Ippolito G, Schiller PC, Ricordi C, Roos BA, Howard GA. Age-related osteogenic potential of mesenchymal stromal stem cells from human vertebral bone marrow. Journal of Bone and Mineral Research. 1999; 14(7):1115–1122. [PubMed: 10404011]
31. Akintoye SO, Lam T, Shi S, Brahim J, Collins MT, Robey PG. Skeletal site-specific characterization of orofacial and iliac crest human bone marrow stromal cells in same individuals. Bone. 2006; 38(6):758–768. [PubMed: 16403496]
32. Yamaza T, Ren G, Akiyama K, Chen C, Shi Y, Shi S. Mouse mandible contains distinctive mesenchymal stem cells. J Dent Res. 2011; 90(3):317–324. [PubMed: 21076121]
33. Matsubara T, Suardita K, Ishii M, Sugiyama M, Igarashi A, Oda R, Nishimura M, Saito M, Nakagawa K, Yamanaka K, et al. Alveolar bone marrow as a cell source for regenerative medicine: differences between alveolar and iliac bone marrow stromal cells. J Bone Miner Res. 2005; 20(3): 399–409. [PubMed: 15746984]

34. Mullender MG, van der Meer DD, Huiskes R, Lips P. Osteocyte density changes in aging and osteoporosis. Bone. 1996; 18(2):109–113. [PubMed: 8833204]
35. Noble BS. The osteocyte lineage. Arch Biochem Biophys. 2008; 473(2):106–111. [PubMed: 18424256]
36. Marotti G, Ferretti M, Muglia MA, Palumbo C, Palazzini S. A Quantitative-Evaluation of Osteoblast-Osteocyte Relationships on Growing Endosteal Surface of Rabbit Tibiae. Bone. 1992; 13(5):363–368. [PubMed: 1419377]
37. Nijweide PJ, Burger EH, Feyen JH. Cells of bone: proliferation, differentiation, and hormonal regulation. Physiol Rev. 1986; 66(4):855–886. [PubMed: 3532144]
38. Holtrop ME, King GJ. The ultrastructure of the osteoclast and its functional implications. Clin Orthop Relat Res. 1977; (123):177–196. [PubMed: 856515]
39. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. Nature. 2003; 423(6937):337–342. [PubMed: 12748652]
40. Teitelbaum SL. Bone resorption by osteoclasts. Science. 2000; 289(5484):1504–1508. [PubMed: 10968780]
41. Harada S, Rodan GA. Control of osteoblast function and regulation of bone mass. Nature. 2003; 423(6937):349–355. [PubMed: 12748654]
42. Karsenty G. The complexities of skeletal biology. Nature. 2003; 423(6937):316–318. [PubMed: 12748648]
43. Delaisse JM, Eeckhout Y, Neff L, Francois-Gillet C, Henriet P, Su Y, Vaes G, Baron R. (Pro)collagenase (matrix metalloproteinase-1) is present in rodent osteoclasts and in the underlying bone-resorbing compartment. J Cell Sci. 1993; 106(Pt 4):1071–1082. [PubMed: 8126092]
44. Lee NK, Sowa H, Hinoi E, Ferron M, Ahn JD, Confavreux C, Dacquin R, Mee PJ, McKee MD, Jung DY, et al. Endocrine regulation of energy metabolism by the skeleton. Cell. 2007; 130(3): 456–469. [PubMed: 17693256]
45. Chambers TJ, Revell PA, Fuller K, Athanasou NA. Resorption of bone by isolated rabbit osteoclasts. J Cell Sci. 1984; 66:383–399. [PubMed: 6746762]
46. Drake FH, Dodds RA, James IE, Connor JR, Debouck C, Richardson S, Lee-Rykaczewski E, Coleman L, Rieman D, Barthlow R, et al. Cathepsin K, but not cathepsins B, L, or S, is abundantly expressed in human osteoclasts. J Biol Chem. 1996; 271(21):12511–12516. [PubMed: 8647859]
47. Bossard MJ, Tomaszek TA, Thompson SK, Amegadzie BY, Hanning CR, Jones C, Kurdyla JT, McNulty DE, Drake FH, Gowen M, et al. Proteolytic activity of human osteoclast cathepsin K. Expression, purification, activation, and substrate identification. J Biol Chem. 1996; 271(21): 12517–12524. [PubMed: 8647860]
48. Domon S, Shimokawa H, Matsumoto Y, Yamaguchi S, Soma K. In situ hybridization for matrix metalloproteinase-1 and cathepsin K in rat root-resorbing tissue induced by tooth movement. Arch Oral Biol. 1999; 44(11):907–915. [PubMed: 10580538]
49. Mao JJ. Orthodontics at a pivotal point of transformation. Seminars in Orthodontics. 2010; 16:143–146. [PubMed: 25018618]
50. Masella RS, Meister M. Current concepts in the biology of orthodontic tooth movement. Am J Orthod Dentofacial Orthop. 2006; 129(4):458–468. [PubMed: 16627170]
51. Henneman S, Von den Hoff JW, Maltha JC. Mechanobiology of tooth movement. Eur J Orthod. 2008; 30(3):299–306. [PubMed: 18540017]
52. Sprogar S, Vaupotic T, Cor A, Drevensek M, Drevensek G. The endothelin system mediates bone modeling in the late stage of orthodontic tooth movement in rats. Bone. 2008; 43(4):740–747. [PubMed: 18656564]
53. Tan SD, Xie R, Klein-Nulend J, van Rheden RE, Bronckers AL, Kuijpers-Jagtman AM, Von den Hoff JW, Maltha JC. Orthodontic force stimulates eNOS and iNOS in rat osteocytes. J Dent Res. 2009; 88(3):255–260. [PubMed: 19329460]
54. Brudvik P, Rygh P. The repair of orthodontic root resorption: an ultrastructural study. Eur J Orthod. 1995; 17(3):189–198. [PubMed: 7621920]

55. von Bohl M, Maltha JC, Von Den Hoff JW, Kuijpers-Jagtman AM. Focal hyalinization during experimental tooth movement in beagle dogs. Am J Orthod Dentofacial Orthop. 2004; 125(5):615–623. [PubMed: 15127031]

56. McLean GW, Komiyama NH, Serrels B, Asano H, Reynolds L, Conti F, Hodivala-Dilke K, Metzger D, Chambon P, Grant SG, et al. Specific deletion of focal adhesion kinase suppresses tumor formation and blocks malignant progression. Genes Dev. 2004; 18(24):2998–3003. [PubMed: 15601818]

57. Kitase Y, Yokozeki M, Fujihara S, Izawa T, Kuroda S, Tanimoto K, Moriyama K, Tanaka E. Analysis of gene expression profiles in human periodontal ligament cells under hypoxia: the protective effect of CC chemokine ligand 2 to oxygen shortage. Arch Oral Biol. 2009; 54(7):618–624. [PubMed: 19406381]

58. Zainal Ariffin SH, Yamamoto Z, Zainol Abidin IZ, Megat Abdul Wahab R, Zainal Ariffin Z. Cellular and molecular changes in orthodontic tooth movement. ScientificWorldJournal. 2011; 11:1788–1803. [PubMed: 22125437]

59. Bartzela T, Turp JC, Motschall E, Maltha JC. Medication effects on the rate of orthodontic tooth movement: a systematic literature review. Am J Orthod Dentofacial Orthop. 2009; 135(1):16–26. [PubMed: 19121496]

60. York JD, Hunter T. Signal transduction. Unexpected mediators of protein phosphorylation. Science. 2004; 306(5704):2053–2055. [PubMed: 15604398]

61. Bettencourt-Dias M, Giet R, Sinka R, Mazumdar A, Lock WG, Balloux F, Zafiropoulos PJ, Yamaguchi S, Winter S, Carthew RW, et al. Genome-wide survey of protein kinases required for cell cycle progression. Nature. 2004; 432(7020):980–987. [PubMed: 15616552]

62. Cantarella G, Cantarella R, Caltabiano M, Risuglia N, Bernardini R, Leonardi R. Levels of matrix metalloproteinases 1 and 2 in human gingival crevicular fluid during initial tooth movement. Am J Orthod Dentofacial Orthop. 2006; 130(5):568 e511–566. [PubMed: 17110252]

63. Hannon RA, Eastell R. Bone markers and current laboratory assays. Cancer Treat Rev. 2006; 32(Suppl 1):7–14. [PubMed: 16680832]