Accelerated orthodontic tooth movement: Molecular mechanisms

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Accelerating orthodontic tooth movement can significantly reduce treatment duration and risks of side effects. The rate of orthodontic tooth movement is chiefly determined by the remodeling of tissues surrounding the roots; this in turn is under the control of molecular mechanisms regulating cellular behaviors in the alveolar bone and periodontal ligament. This review summarizes the current knowledge on the molecular mechanisms underlying accelerated orthodontic tooth movement, and the clinical and experimental methods that accelerate orthodontic tooth movement with possible molecular mechanisms. The review also shows directions for future studies to develop more clinically applicable methods to accelerate orthodontic tooth movement. (Am J Orthod Dentofacial Orthop 2014;146:620-32)

Orthodontic movement of teeth under mechanical force depends on the remodeling of tissues surrounding the roots. Accelerating orthodontic tooth movement has long been desired for its multiple potential benefits, including shorter treatment duration, reduced side effects (such as oral-hygiene related problems, root resorption, and open gingival embrasure spaces[1-5]), enhanced envelope of tooth movement, differential tooth movement, and improved posttreatment stability.[6] Attempts to accelerate tooth movement can be dated back to the 1890s, almost contemporary with Angle's groundbreaking work in modern orthodontics.[7] For the next half century, the intervention to accelerate tooth movement involved osteotomy, the surgical procedure that completely cuts both the cortex and the medulla of the alveolar bone. The rationale for performing osteotomy was to reduce mechanical resistance during tooth movement. In the 1950s, Köle[8] introduced corticotomy, the perforation of the cortex of the bone alone without intrusion into the medulla, to replace osteotomy except in the subapical region, to reduce invasiveness. Since it was less destructive, corticotomy completely replaced osteotomy as the preferred surgical method to accelerate tooth movement.[9] Despite the evolution of clinical methods, the scientific explanation of accelerated tooth movement was still believed to be reduced mechanical resistance after osteotomy or corticotomy, enabling the teeth to be moved en bloc with the tissues surrounding them.[10-12] This view was challenged by Wilcko et al[13] (including a periodontist and an orthodontist) circa 2000. They described the demineralization and remineralization process of the alveolar bone after corticotomy that resembled the regional acceleratory phenomenon (RAP), indicating increased bone remodeling activity. Consistent with this observation, other studies also showed that nonsurgical interventions stimulating bone remodeling can accelerate orthodontic tooth movement.[14-19]

BONE MODELING, REMODELING, AND ORTHODONTIC TOOTH MOVEMENT

Bone modeling is the uncoupled process of activation-resorption (catabolic) or activation-formation (anabolic) on bone surfaces, resulting in changes of the shape, size, or position of the bone.[20] Bone remodeling or turnover, on the other hand, is a tightly coupled local process, which starts with bone resorption, followed by reversal and bone formation phases, resulting in the replacement of old bone with new bone.[21,22] Both bone modeling and remodeling are determinants for the rate of orthodontic tooth movement. Bone modeling during orthodontic tooth movement is an inflammatory process, and the rate-limiting factor for tooth movement is bone resorption at the bone and

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periodontal ligament (PDL) interface.[23] Even though bone remodeling renews the internal content of the bone without changing the size or shape of the bone under physiologic conditions, it also affects the rate of orthodontic tooth movement.[24]

Both bone modeling and remodeling are controlled by the cellular activities of osteoclasts, osteoblasts, and osteocytes. Apparently, osteoclasts carry out resorption, whereas osteoblasts carry out bone formation during bone modeling. The resorption-formation sequence of the bone remodeling process is performed by basic multicellular units, which are organized osteoclasts and osteoblasts.[25] Both biochemical and mechanical factors regulate the rates of bone modeling and remodeling.[22,26,27] Previous studies have shown that orthodontic treatment stimulates alveolar bone modeling,[23] as well as bone remodeling that resembles RAP[28] with increased number and function of osteoclasts and osteoblasts, and more active bone resorption-formation cycles.[29-31] Activation of osteoblasts by mechanical forces, inflammatory stimuli, or hypoxia appears to be the first and necessary step in orthodontic tooth movement. Activated osteoblasts are responsible for the expression of specific mediators of osteoclast formation and initiation of bone resorption.

OSTEOCLAST FORMATION AND BONE RESORPTION

The rate-limiting step in orthodontic tooth movement is considered to be bone resorption at the leading (compression) side. Histologic studies show that the formation of osteoclasts is induced at the compression side during orthodontic tooth movement.[32-35] Alveolar corticotomy and nonsurgical interventions that accelerate tooth movement significantly increase the numbers and functions of osteoclasts.[14-17,32-45] The formation of osteoclasts depends on the effects of stromal and osteoblastic cell-derived factors on osteoclast precursors. One of these factors is receptor activator of nuclear factor kappa B ligand (RANKL), which binds to its receptor, RANK, on the surface of developing osteoclastic cells. The RANKL/RANK binding is crucial for the differentiation, function, and survival of osteoclasts. On the other hand, osteoprotegerin (OPG), another osteoblastic cell-derived factor, interrupts the RANKL/RANK binding as a decoy receptor of RANKL, inhibiting osteoclastogenesis. Therefore, the RANKL/OPG ratio expressed by osteoblastic cells and the RANK expression by osteoclast precursor cells largely determine the formation of functional osteoclasts and the activation of the initial step of bone remodeling.[46] RANKL level in the gingival crevicular fluid becomes significantly higher than in the contralateral control side after 24 hours of continuous compressive force in adolescent patients.[47] RANKL expression is increased in the osteoblasts, osteocytes, and fibroblasts in the PDL and the alveolar bone, especially by the compressive force, as early as 3 hours after orthodontic force application and remains elevated after at least 5 days.[48-55] Tensile strain, however, significantly reduces the mRNA level of RANKL in osteoblastic cell cultures.[56] Local delivery of RANKL with gene therapy significantly stimulates osteoclast formation and speeds up orthodontic tooth movement.[57,58] Contrary to RANKL, OPG concentration in the gingival crevicular fluid at the compression side is decreased compared with the basal level as early as 1 hour after orthodontic force application in adolescent patients[59] and becomes significantly lower than at the contralateral side after 24 hours in these patients.[47] Other studies have shown that OPG expression is decreased by the compressive force but increased by the tensile force during orthodontic tooth movement, opposite to the effects on RANKL.[52-54,56,60] As expected, local delivery of OPG significantly inhibits bone remodeling and orthodontic tooth movement.[61,62] The reciprocal regulation of RANKL and OPG expression by the compressive and tensile strains coordinates predominant bone resorption at the leading side and predominant bone formation at the trailing side, enabling normal tooth movement.

Macrophage colony-stimulating factor (M-CSF) is another stromal and osteoblastic cell-derived factor that is crucial for recruitment and differentiation of early precursors of osteoclasts.[63] M-CSF expression is detected in osteoblasts and fibroblasts in the PDL and in the alveolar bone at early time points during orthodontic tooth movement.[55,64] Compressive force increases the expression of M-CSF in osteoblastic MC3T3-E1 cell cultures.[54] Local administration of an optimum dose of M-CSF significantly increases the number of osteoclasts and accelerates orthodontic tooth movement in rats.[65] Daily local injections of an antibody to c-Fms, the receptor of M-CSF, significantly inhibit tooth movement with compromised osteoclast formation.[66] Early upregulation of M-CSF is evident and important for orthodontic tooth movement.

Therefore, the expression patterns of M-CSF, RANKL, and OPG by osteoblasts play key roles in tooth movement. Mechanical force induction of M-CSF and RANKL in osteoblastic cells is mediated by other factors. Compressive force significantly stimulates the expression of cyclooxygenase (COX)-2, the chief enzyme responsible for the majority of prostaglandin (PG) production, in the PDL and osteoblastic cells,[54,67] and thus increases the production of prostaglandin