Thinking Beyond the Wire: Emerging Biologic Relationships in Orthodontics and Periodontology

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Orthodontic tooth movement (OTM) is a biologic event. It involves a series of sophisticated signal transduction processes that result in alveolar bone remodeling. Interplay of the gene expression activities between osteoblasts and osteoclasts regulate the alveolar bone adaptation to orthodontic forces. The mechanisms that sense and translate the mechanical stimulus into molecular events have remained a puzzle to current scientists for a long period of time. The mechanosome is a recently discovered cytoplasmic communication mechanism that can possibly explain the signaling between treatment and the bone cell response. That is, it may detect mechanical loads and in turn activate the downstream nuclear gene expression. Advancement in molecular biology is likely to make the manipulation of bone remodeling and control of tooth movement easier and more predictable in the future. Pharmaceutical intervention and genetic enhancement are examples of clinical applications promised by current researchers in basic science. This article reviews the biomedical literature and plots the trend in understanding the biochemical basis of OTM to date. Future dentofacial orthopedists will likely integrate both conventional orthodontic mechanotherapy and applications of molecular biology in orthodontic treatment suggested by concepts in this article. (Semin Orthod 2008;14: 290-304.) © 2008 Published by Elsevier Inc.

Engineered alveolar ridge topography and bone regeneration are commonly used by periodontal specialists to repair alveolar bone defects damaged by disease. Some of the indications include periodontal attachment (bone) maintenance, postextraction socket regeneration, and implant site preparation. However, loss of vertical bone height (attachment loss) as a result of periodontal disease is often difficult to overcome with hard tissue grafting alone. Even where successful the outcome is often unpredictable.

However, orthodontic tooth movement (OTM), as demonstrated by clinical findings, is an alternative method to induce bone regeneration and morphotype modification through force-mediated remodeling. More importantly, orthodontics has recently become an important adjunct to implant dentistry because orthodontists can open edentulous spaces for implant placement. Preimplant orthodontics has also been performed to generate alveolar bone height at periodontally compromised areas. Gunduz and coworkers have shown that bodily tooth movement into an edentulous area with a transversely thinned alveolar ridge resulted in therapeutic bone remodeling. A dental implant could then be placed into the orthodontically developed
edentulous site. A case report by Biggs and Beagle showed that orthodontic intrusive and extrusive forces were exerted on “hopeless” teeth to gain alveolar bone height in the future implant site. Orthodontic alveolar site development is also employed in the replacement of congenitally missing maxillary lateral incisors with single-tooth implants. The permanent canines are moved distally after being allowed to erupt merially when lateral incisors are congenitally absent. Adequate alveolar ridge width will then be established for future implants.

These newly emphasized clinical phenomena suggest that facial and alveolar bone may not be as immutable as previous generations of dentists were taught. The aim of this article is to present molecular and tissue level biochemical concepts that might explain exactly how this newly described bone malleability can occur and provoke the reader to innovative solutions to physical and intellectual limits that have challenged our specialty for a century.

Histochemical Perspectives

Contrary to some popular perceptions, therapeutic tooth movement is not essentially a function of Newtonian mechanics. Tooth movement is a biologic event, in fact encompassing a cascade of histological and biochemical reactions. Once the mechanical stimulus is applied, a phenomenon referred to as “signal transduction” converts mechanical strain to biochemical events. For the 21st century clinician, only a biologic orientation can capture the full scope of orthopedic tissue engineering concepts that often escape our consciousness when we preoccupy ourselves with mechanical manipulation or the cosmetic enhancement of individual teeth for popular and even fatuous affectations. In fact, an overemphasis on superficial cosmetic mechanics, ignoring a century of scientific theory, in the long run can produce severe biologically harmful treatment outcomes for the patient. Thus, the periodontal biologic message to all orthodontists, especially in the treatment of a mother’s child, is one of profound and prudential caution. This begins with respect for health of the gingiva and periodontal ligament (PDL).

The PDL is generally considered a specialized connective tissue responsible for the dramatic alveolar bone remodeling process. Yet, application of orthodontic force triggers remodeling responses far beyond the ligament. Bone remodeling consists of interplay between osteoclastic resorption and osteoblastic deposition (new bone formation). In general, bone remodeling and modeling can occur by a kind of spatial “drift” that adds new bone tissue on one side of the cortex and takes it away from the contralateral cortex. (These are not fundamentally new concepts, but merely embellished. See a classical, nuanced review by Roberts WE, in Graber T, Vanarsdall R, Vig K, eds: Orthodontics: Current Principles and Techniques. 4th ed. St. Louis, Mosby, 2005.) According to Enlow, the periosseal surface receiving new bone in the direction of the OTM vector undergoes deposition and the periodontal ligament origin of the vector undergoes resorption. Yet, the PDL and cribriform plate activity have been traditionally characterized quite the opposite, with resorption and deposition occurring on the “pressure” and “tension” side of the ligament, respectively. The reconciliation of this conceptual dissonance lies in viewing the alveolus as a “whole bone” and the PDL-cribriform plate complex as analogous to endosteal surfaces.

Two proposed classical mechanisms attempt to explain the bone physiology reaction to stress: the popular but simplistic “pressure-tension” construct and the “bioelectric” theories. The pressure-tension model proposes the tooth as lying in a connective fiber “sling” attached to the socket, with fiber stretch (tension) eliciting osteogenesis and fiber compression eliciting osteoclastic resorption on the PDL side (frontal resorption) or endosteal side (undermining or “rear” resorption) of the cribriform plate depending on pressure gradients. While easy to understand in a grossly mechanical way for patients, it fails to respect myriad biochemical responses by the cells and extracellular matrix (ECM) of the PDL and alveolar bone. The “bioelectric” theory relates tooth movement to the movement of charged particles produced when alveolar bone is flexed. Specifically this refers to hydroxyapatite crystals (immediate and rapidly dissipating piezoelectric potential) and the slower ionic flux at fluid-solid interfaces within the living osteocyte-cannaliculi syncytium. Potential differences created by forcing these charged particles or electrolytes through narrow
channels within the bone are “streaming potentials.”

At this juncture, it is probably appropriate to avoid falling into a common misconception. Neither theory completely explains the OTM phenomenon; both theories are involved in the biologic control of tooth movement. Thus, integration offers insights into techniques that may allow the dentofacial orthopedist to engineer an “optimal response” of bone with as much alacrity as the holy-grail search for an elusive “optimal force.” Contemporary clinical and basic science research suggests this may be achieved through such seemingly disparate methods as electromagnetic manipulation, surgical provocation to accelerate OTM, genetic testing and enhancement, or even pharmacologic supplementation in situ.

**Pressure-Tension Model**

A more detailed pressure-tension theory states that chemical signals stimulate cellular differentiation and ultimately tooth movement. When orthodontic forces are applied to the tooth, and after capillary damping of initially applied force, extracellular fluids of the PDL, a viscoelastic gel, shift distorted cells and ECM. This force alters blood flow within the PDL, namely blood flow is maintained or increased where the PDL is under tension and restricted in areas of pressure. Migration of leukocytes into the extravascular space (a mild, aseptic inflammation) occurs in areas of both tension and pressure through different mechanisms. Blood flow is decreased where the PDL is compressed. The alterations in blood flow induce chemical changes, directly and indirectly through chemical messengers. This process of “signal transduction,” a biological event, is what proximately stimulates cellular differentiation and bone remodeling, thus facilitating tooth movement.

The reader should bear in mind that the pressure/tension model may be inaccurate to the extent it is oversimplified and generalized. In common use it emerges as a rarefied theory that may have little predictive power since the PDL is roughly 0.25 to 0.33 mm wide, a dimension smaller than a wire activation seeking to gain the usual rate of activation to elicit the expected 1 mm of tooth movement per month. This observation suggests a need to widen the conceptual horizons of orthodontic therapy, taking it from a strict “Newtonian mechanical model’s” (bias) to incorporate biochemical concepts and the burgeoning science of tissue engineering.

**Bioelectric Model**

The PDL histological model that cannot fully explain tooth movement must be supplemented with physical, chemical and molecular biologic concepts of biomechanics if OTM is to be fully and accurately conceptualized in a modern scientific context. The “bioelectric” theory claims that movement of charged particles may also play a role in tooth movement. Two types of charge movement proposed by researchers include piezoelectric and streaming potential signals.

In terms of physical mechanics, the piezoelectric effect is a phenomenon where an electric polarity is created in crystals when deformed. (When a bone crystal is compressed, tissue ions in the surrounding fluid also migrate along the easiest axis pathways.) The net movement of negative charge in the crystal in one direction is enhanced by the movement of positive charge in the opposite direction, creating a net dipole moment. The displacement of electron density leads to a voltage across opposite sides of the crystal, and to an electric current if a conductive material connects the opposite sides. Thus, an electric current can be generated between the two oppositely charged surfaces of each crystal and can flow from one part of the crystal lattice to another, creating piezoelectric signals.

Piezoelectric effects were initially thought to be materially effective signals responsible for tooth movement because bone consists of an inorganic phase of hydroxyapatite crystals and organic phase of mainly type I collagen. When a force is applied against bone, these hydroxyapatite crystals bend due to the elasticity of the organic collagen phase, creating a piezoelectric effect within the bone. However, piezoelectric phenomena are brief and effete and should not be conflated with the longer lasting and apparently more influential ion flux that occurs simultaneously in tissue fluid.

Many studies have shown that dry bone does indeed undergo a piezoelectric effect; however, in vivo, bone is very complex tissue and is sur-
rounded by a wet environment. When charged ions or electrolytes within solution are forced through a narrow channel, the term “streaming potentials” more accurately portrays the bioelectro signals or potential differences created along that channel. While certain ions of the same sign are attracted to the channel walls, other charged ions of opposite charge become concentrated in the remaining fluid that is passing through. Osteocyte cell processes in canaliculi apparently “communicate” at a gap junction. These types of signals are somewhat analogous to action potentials through nerves at synapses. Thus, the mechanotransduction system, the osteocyte-cannaliculi syncytium, facilitates cell-to-cell “communication” as the ion flux occurs from fluid movement within the Haversian systems (osteons) in bone under variable strain.7

The bioelectric theory incorporates both the piezoelectric and the streaming potential types of potential differences and ionic movement, implying that structural alterations throughout the bone are conducted and/or triggered by ionic charge differences. Thus, when an orthodontic force is applied to the tooth, the tooth pushes against the bone, bending the crystalline structure of alveolar bone and collagen and tissue fluid far beyond the PDL.11,12 Electric stimulation can enhance cellular enzymatic phosphorylation activities in periodontal tissues and may be a potent method in accelerating alveolar bone turnover.8 Therefore, in theory, electric and electromagnetic influences can modify the bone remodeling involved in OTM, even when externally applied as therapeutic adjuncts to healing as demonstrated in the “electric braces” research of Davidovitch and co-workers.8

Contemporary Concepts

The Baumrind Model

The research conducted by Baumrind and co-workers gave orthodontists an interesting perspective on OTM as early as 1965.13,14 In contrast to the “pressure-tension” theory of Schwarz,15 Baumrind proposed that the PDL is a continuous hydrostatic system; any force delivered to it will be transmitted equally to all regions of the PDL. Such a model refers to a kind of “viscoelastic system,” recalling Pascal’s law, which states that when there is an increase in pressure at any point in a confined fluid, there is an equal increase at every other point in the container. Differential stresses and strains in the periodontium can therefore only be developed at the interface of more solid parts: bone, tooth, the collagen fibers of the PDL, and the surrounding alveolus and facial bones. This perspective calls for a wider conceptualization to explain OTM more accurately with emerging histometric, biochemical, cellular genetic, and molecular biological concepts.16

Also, Baumrind found that bone deflection can be produced routinely by forces lower than those required to produce consequential changes in PDL width. This further strengthens his point that seeing the PDL as a viscous gel system may be more productive in everyday clinical practice. If fluid in the periodontium were to be “squeezed out” in one region by orthodontic force, it would have to be squeezed out in all regions, thus producing an immediate “damping” phenomenon. He also questioned the observation of “undermining resorption” in pressure-tension theory, since similar marrow space activity is also observed in the “tension” side of the periodontal ligament during OTM. Baumrind therefore proposed an alternative hypothesis: When orthodontic appliances are placed, forces delivered to the tooth are transmitted to all the tissues in the region of force application.14 All three structures, tooth, PDL, and alveolar bone, are deformed. The amount of deformation (measured as microstrain) is determined by the elastic properties (elastic modulus) of each tissue component. In contrast to the narrow “pressure-tension” model, remote areas of bone may be involved in tooth movement as Melsen suggested in 200111; the results of orthodontic intrusion could be perceived as bending of alveolar bone produced by the pull from Sharpey’s fibers.

Further Reductionist Analysis

Piezoelectric effects and the pressure-tension models suggest that when the mechanical force on bone is removed, the once-loaded system reverts back to its original homeostatic or steady state of dynamic equilibrium. However, it should be remembered that studies from Johnson state that the effects of forces on the bone are trans-
duced into another form in which “a biochemical cascade remains activated long after the mechanical stimulation has been removed.”

These studies report that strain-induced fluid flow stimulates the production and/or release of various bioactive substances, including potent morphogens, directly from osteoblasts and osteocytes. Coincidentally, these substances include second messengers and inflammatory mediators mentioned previously, namely prostaglandin E2 (PGE₂), inorganic phosphate 3 (IP₃), calcium, cyclic adenosine monophosphate (cAMP), and nitrous oxide (NO), a particularly important morphogen in osteoblasts and osteocytes. Specifically, NO is shown to regulate bone remodeling by inhibiting resorption and by possibly stimulating osteoblastic proliferation. This is important because a recent animal study suggested a more optimal response (enhanced osteoclasia) can be engineered by injecting L-arginine, an NO precursor, in situ during OTM. NO also exerts effects within endothelial cells, causing vasodilation of blood vessel walls, resulting in multiple and variable cell migration and differentiation. Thus, osteoblasts and endothelial cells both respond to fluid flow similarly, and therefore, both play a role at the most fundamental molecular level in mediating bone remodeling through altering the dynamic balance between osteoblast and osteoclast activity.

Functional Matrix Hypothesis of Moss

A fundamental epistemological schism has plagued orthodontics for nearly a century. This is not idle internecine or ideological bickering because the polar philosophical “truths” can have profound clinical ramifications such as extracting teeth, flattening facial profiles, or risking gingival dehiscence on teeth in growing children. The vexing question is whether the alveolar form in any one patient is fundamentally immutable in health and disease or whether alveolar bone, like liquids or gels in a container, assumes the shape of its containing matrix following the movement of the teeth. Moss nicely synthesizes these aforementioned concepts and orchestrates them into the functional matrix hypothesis (FMH), arguing that shape and dimensions of alveolar bone, through single-generation phenotypic plasticity, can indeed be defined by a functional matrix (“container”), the dental roots. If he is correct then teeth may be moved beyond a restricted limit of malocclusion with relative impunity. While clinical data demonstrate that this may be possible, especially in the transitional dentition, others contend that moving teeth “off the alveolar housing” risks bony and ultimately gingival dehiscence. Fortunately, researchers have observed that in monkeys reposition of labial bone can occur in a coronal direction after teeth in extreme labial position with bone dehiscence and consequent gingival recession were moved to a more normal position.

Several variables play a role in his hypothesis: (1) the skeletal or bone units and the functional matrices (the nonskeletal remainder including the related cells, tissue, organs, fluid, and even spaces); (2) the hierarchy of bone organization ranging from the level of the whole skeleton (higher attributes) to the level of a single bone cell (lower attributes); and (3) the intrinsic (genomic) and extrinsic (epigenetic) factors. All three variables contribute to the entire skeletal system’s development and adaptation to functional loads.

Moss stated that the lower attributes of single bone cells cannot predict the higher attributes of the whole skeleton or bone tissue in the hierarchy of bone organization. G.D. Singh, relying on the accuracy of finite element analysis methodologies, elaborates on the FMH by asking us to view spatio-temporo matrices as affecting morphogenesis in an attempt to achieve a structural balance and physiologic tissue homeostasis. His term for this natural adaptive phenomenon is the spatial matrix hypothesis (SMH). We propose that the modern orthodontic clinician should consider a coherent, comprehensive, and fully integrated theoretical systems approach that appreciates the biology from the intracellular biochemical dynamics of single bone cells, through tissue level interactions, to the clinical changes we induce in skeletal form grossly.

This concept has been shared by medical physiologists and orthopedists for many years under the rubric Utah Paradigm of Bone Physiology. This model suggests that a “nephron-equivalent” entity called the basic multicellular unit (BMU) is largely responsible for regional bone remodeling. Wilcko and Ferguson have presented compelling evidence and clinical studies of dentoalveolar surgical techniques that demonstrate this phenomenon at work in a very
meaningful and clinically practical way. They cite the regional acceleratory phenomenon (RAP) of medical orthopedist, H.M. Frost, as the essential operative physiologic mechanism responsible for their astonishing clinical revelations and stable treatment outcomes.

The surgical techniques included buccal and lingual full-thickness flaps, a kind of scarification of the cortical plates (selective decortication), concomitant bone grafting/augmentation, and primary flap closure. Their treatment of Class I cases of severe crowding and constricted maxillary alveoli were completed in approximately 6 months. They suggested that the incorporation of the bone augmentation into a decortication surgical protocol makes it possible to complete the orthodontic treatment with a more intact periodontium. As a workable, pragmatic clinical guideline, the Utah Paradigm developed through the collaboration of Drs. Harold M. Frost and Webster S.S. Jee, conceptually compatible with Baumrind’s model, explains and predicts OTM behavior in the larger periodontal context in a manner superior to the classic pressure-tension construct. Thus, the best course for the clinician is a full integration of all theories because even the novel approach of the Wilcko-Ferguson studies may depend on intrinsic biochemical mediators to enhance the effects of natural ligands or pharmaceutical agents such as recombinant bone morphogenetic protein (rhBMP-2).

Williams, Singh, and Damon have also alluded to principles that mimic both the RAP and FMH in their nonsurgical approaches to alveolar and dentofacial orthopedic therapy, “osteoblastic recruitment,” “spatial matrix,” and “physiologically adaptive force,” respectively.

While enterprising clinical innovators and keen scientific observers, they are not initiators of this concept, because according to Melsen, the woven bone formation seen “ahead of” alveolus in the direction of the movement could be interpreted as an expression of RAP. According to Frost, any regional noxious stimulus, chemical, surgical, or mechanical, of sufficient magnitude can evoke RAP. The extension of the affected region and the intensity of the response vary directly with the magnitude and the nature of the stimulus as long as it occurs above a minimal effective strain (MES), the borderline strain below which appropriate bone modeling does not occur. The daunting clinical challenge for each practitioner is to become sensitive to the fact that strain for each patient in a widely biodiverse biological and psychosocial milieu. This is where an understanding of biochemistry sharpens the “mind’s eye” to see and think beyond bends in a wire.

Observing this at the biochemical and molecular level, a single bone cell undergoes its own mechanotransduction through a series of biochemical cascades whereas a whole multicellular system such as the osteocyte-cannaliculi syncytium can function as a connected cellular network utilizing the summation of the biochemical attributes of many cells. The bioelectric theory concedes just this, in that each small contribution from the simple flow of fluid after deformation can actually lead to an enormous change through biochemical amplification. This is the tissue level mechanism thought to be responsible for gross anatomical alteration in alveolar bone shape and dimension. The self-regulatory (second order) cybernetic mechanism is called a “mechanostat,” a concept developed by the Frost and Jee collaboration. This is a biological “machine” that determines whole-bone strength and forms a tissue-level negative feedback system. Two thresholds define a range of bone strains that determine the organ’s form and function by switching on and off the necessary biologic mechanisms that increase or decrease its local physiologic activity.

Moss’ FMH, Singh’s SMH, and the Utah Paradigm in synthesis allow us a fully integrated intellectual infrastructure within which molecular or ionic triggering of intrinsic or genomic factors, which ultimately lead the system to express the necessary biological tools for bone remodeling, can be organized. With orthodontic forces as the extrinsic or epigenetic factor, as seen in Baumrind’s model, the skeletal components are manipulated to allow the movement of teeth through this functional matrix of bone, tissue, and fluid, and redefining it structurally and functionally.

**Specific Molecular Mechanisms**

Transcription factor (TF) biology is a key component of the molecular response to orthodontic force. TFs are specialized proteins formed in the cytoplasm that migrate into the nucleus and
attach to very short nucleotide segments of DNA. This binding of TFs either promotes gene expression or suppression. The overall process by which molecules transmit mechanical force into bone cell genomes is the forementioned "signal transduction" (Figs 1, 2).

We may ask how bone cells sense the presence of mechanical load. This is done through physical distortion of the force-affected cells. This cell deformation triggers a whole complex of molecular events or biochemical cascade (pathways) exemplified in Fig 2. It is important to bear in mind that orthodontic force directed into the PDL and adjacent alveolar bone causes structural alterations in tensegrity (tensional integrity) of the cytoskeleton and nucleus; (see: http://www.childrenshospital.org/research/ingber) and functional changes in the extracellular matrix, the cell membrane and the nuclear matrix proteins. This is immediately followed by nucleotide activation by single or multiple TFs and subsequent gene suppression or expression ultimately affecting ribosomal activity (translation; Fig 3).

Investigations into the relationship between bone stress and cellular responses have been performed for some time, but the exact pathways remain unclearly defined. Pavalko and co-workers discuss an interesting concept termed the “mechanosome,” which is conjectured to function as an intermediate biochemical pathway. A proposed genomic communication signal, the mechanosome may mediate external mechanical stimuli from the extracellular matrix to influence architectural transcription factors in the nucleus. While very little experimental data have explicated the exact nature of a mechanosome, it serves as an interesting working hypothesis (Figs 4, 5). In the words of Pavalko and coworkers:

We propose that mechanical information is relayed from the bone to the gene in part by a succession of deformations, changes in conformations, and translocations. The load-

Figure 1. Intracytoplasmic schematic of bone cell showing nuclear envelop on the left. Various cytoplasmic proteins are evident, with a helical protein touching the nuclear envelope as part of signaling. Signal transduction from cell membrane via second messengers to nuclear pores. The mechanosome is conjectured to work with second messengers activated by external mechanical stimuli from the extracellular matrix taking in data to architectural transcription factors. Many molecular biologists emphasize the importance of studying morphogenesis as a transcriptional event so tissue engineering may be based on pharmaceutical aids. (Source: http://www.temple.edu/stl/. The Signal Transduction Lab, as envisioned by Audre Geras. Reprinted with permission. ©2008 Audra Geras, Geras Healthcare Productions. www.audrageras.com) (Color version of figure is available online.)
induced deformation of bone is converted into the deformation of the sensor cell membrane. This, in turn, drives conformational changes in membrane proteins of which some are linked to a solid-state signaling scaffold that releases protein complexes capable of carrying mechanical information, “mechanosomes,” into the nucleus. These mechanosomes translate this information into changes in the geometry of target gene DNA, altering gene activity; bending bone ultimately bends genes.

While there is dispute about the exact nature of these mechanisms it would seem that Ingber’s work intimates what Pavalko has stated, indeed “bending bone ultimately bends genes.”

Recent studies have investigated the molecular mechanisms of PDL cells regulating the bone remodeling process. When compressive force is not present, PDL cells secrete osteoprotegerin...
(OPG) to inhibit the differentiation of the osteoclasts.\textsuperscript{25} Secretion of OPG by PDL cells prevents resorption of alveolar bone and subsequent disruption of the PDL. This osteoclastic inhibitory mechanism maintains the teeth in the alveolar socket in the physiologic but dynamic steady state. Tooth eruption is the only period of time when the secretion of OPG by dental follicle (precursor of PDL cells) is not present because osteoclast formation and activation are necessary to form an eruption pathway.\textsuperscript{26}

Orthodontic treatment, however, changes this secretion process. Compressive force triggers the secretion of another factor, called the ligand receptor activator of NF-κB (RANKL) from PDL cells (Fig 2). RANKL is an important regulator of osteoclast differentiation and activity. Upregulation of RANKL induces osteoclastogenesis resulting in alveolar bone resorption and subsequent OTM. Increased RANKL expression in compressed PDL cells was also observed in patients with severe external apical root resorption induced by orthodontic treatment.\textsuperscript{27} This resorption was mainly caused by upregulated osteoclastogenesis. The RANKL:OPG ratio can be used as a potential diagnostic assay and as the determinant factor for root resorption.

PDL cells, therefore, influence osteoclast differentiation through RANKL stimulation and OPG inhibition. Orthodontic compressive force significantly increased the release of RANKL and decreased that of OPG in human PDL cells in a time- and force magnitude-dependent manner in gingival crevicular fluid (GCF).\textsuperscript{28} Such increase of RANKL levels was approximately 16.7-fold, and the decrease of

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**Figure 3.** Stimulus at the cell membrane, for example, cell deformation, triggers a whole complex of molecular events or biochemical cascade exemplified in Fig 2, immediately followed by nucleotide activation by single or multiple transcription factors and subsequent gene suppression or expression ultimately affecting ribosomal activity (translation). (Source: http://stemcells.nih.gov/info/scireport/appendixA.asp. Reprinted with permission.©2001 Terese Winslow www.teresewinslow.com) (Color version of figure is available online.)
OPG was 2.9-fold, as compared to the control. Local transfer of OPG gene to periodontium neutralized the RANKL-mediated osteoclastogenesis induced by compressive force and inhibited OTM.\(^{29}\)

**Clinical Significance**

**Bone Response**

The understanding of biochemical mechanisms of OTM allows the orthodontist to control the nature of tooth movement so physiologic variation does not become pathologic. Reciprocal oscillating force on a tooth constitutes the “jiggling” movement associated with the occlusal trauma and accelerated irreversible bone loss in periodontitis.\(^{30}\) Indeed, reciprocating trauma, moving a tooth in and out of a prematurity under parafunction, may even alter the qualitative nature of the subjacent bacterial flora creating a pathological bacterial biofilm (dental plaque) dynamic clinically undetectable by the busy orthodontist.\(^{31}\)

However, OTM, dangerously characterized as a kind of “controlled version of occlusal trauma,” differs from irreversible trauma in that OTM produces a net displacement of the tooth in space. The difference that distinguishes disease from therapy, where similar physiologic processes are at work, is the ability to control the clinical outcome. This is why the biologic approach to orthodontic care and an intellectual
appreciation of periodontal pathophysiology, alveolar bone dynamics, and biologic engineering of the surrounding bone tissue is so critical to successful therapy. When physiologic force can be modulated to benefit and protect the patient from therapeutic excess, the orthodontist or more specifically the dentofacial orthopedist, is acting as kind of “applied biological scientist” and not merely a technically proficient artisan who can move clinical crowns.

This is true not merely for adult patients. Capelli and coworkers published compelling epidemiological and microbiological data suggesting that frank attachment loss may be demonstrated in significant adolescent cohorts. Without some biological awareness, the clinical artisan, focusing on mechanistic art, may jeopardize the patients’ long-term periodontal health since an increase in postdebonding tissue tonus mimics but hides subjacent periodontal attachment loss and self-perpetuating disease beyond the reach of oral hygiene aids even when used assiduously.

The Pharmacological Dimension

In the future, pharmacologic products may be used in regulating the rate of orthodontic tooth movement. They may work by regulating the cytokines, growth factors, or systemic factors involved in bone remodeling. Drugs that can influence the rate of tooth movement can be characterized into five main categories: hormones, bisphosphonates, vitamin D metabolites, fluoride, and nonsteroidal anti-inflammatory drugs (NSAIDs). Systemic hormones such as estrogen, androgen, and calcitonin cause an increase in bone mineral content, bone mass, and a decrease in the rate of bone resorption. As a result, they could delay OTM. On the other hand, thyroid hormones and

Corticosteroids increase osteoclast bone resorption and inhibit osteoblastic function, respectively, which might increase the rate of OTM contributing to a less stable orthodontic result.

Drugs such as bisphosphonates, vitamin D metabolites, and fluorides can delay OTM. Bisphosphonates, contemporarily popular in our society, are potent blockers of bone resorption. They inhibit osteoclastic metabolism and decrease numbers of osteoclasts. Vitamin D₃ regulates the physiologic amount of calcium and phosphorus. Research shows that vitamin D₃ also increases bone mass and reduces fractures in osteoporotic patients. Fluoride stimulates the growth and synthetic activity of osteoblasts and bone formation. In the form of sodium fluoride, it inhibits the osteoclastic activity and reduces the number of active osteoclasts.

Nonsteroidal anti-inflammatory drugs (NSAIDs), commonly employed analgesics in daily dental treatment, also have been shown to reduce bone resorption and delay the bone response to respective tooth-borne pressure. They inhibit cyclooxygenase enzyme involved in prostaglandin synthesis. Aspirin and other acetylsalicyclic acids (ASAs), such as ibuprofen, are able to slow down orthodontic tooth movement as may indomethacin-related agents.

Locally applied statins may also have some future relevance to alveolus engineering because they are capable of inducing both angiogenesis and regional osteogenesis necessary for regeneration. Statin, a coenzyme A reductase inhibitor, increases BMP-2 gene expression for bone formation by blocking the mevalonate pathway in cholesterol production. In an in vivo study, the amount of new bone formed by statin mixed with a collagen carrier was quantitatively assessed and results showed that 308% more new bone was formed in defects grafted with statin than those grafted with the carrier alone. Immunolocalization studies on the early healing of the defects grafted with statin showed vascular endothelial growth factor (VEGF), BMP-2, Cbfa-1 expression, and new bone formation occurred 1 day earlier than those grafted with the carrier alone.

Prostaglandins and leukotrienes have the potential to enhance tooth movement and are foci for clinical investigations. They stimulate bone resorption by increasing the number of osteoclasts and activating existing osteoclasts. The injection of prostaglandin has been shown to accelerate OTM in both animals and humans. Oral administration of misoprostol, a prostaglandin E₁ analog, has been shown to enhance OTM with minimal root resorption. Administration of prostacyclin (PGI₂) and thromboxane A₂ (TxA₂) analogs in rats have been shown to increase the number of osteoclasts, osteoclastic bone resorption, and rate of OTM. Therefore, while some pharmaceutical agents hold promise of enhanced bone remodeling, long-term administration of NSAIDs or ASAs should be avoided during orthodontic therapy.

Cytokines OPG and RANKL could become the next targets of pharmaceutical approach in controlling tooth movement. As previously described, OPG released by PDL cells inhibits the differentiation of osteoclasts and prevents bone resorption. RANKL, however, induces osteoclastogenesis resulting in alveolar bone resorption. In fact, Keles and coworkers recently designed a constant orthodontic force model and demonstrated that tooth movement is reduced when OPG is systemically administrated in mice. Biological modulators could be administrated locally to control undesired tooth movement at anchor units or systemically to enhance post treatment stability.

Twenty-first Century Research and Clinical Protocols

Genetic Tests

Proinflammatory cytokines play an important role in periodontal diseases. Interleukin-1β (IL-1β), in particular, has been well demonstrated in bone destruction commonly seen in adult periodontitis. IL-1β is increased in inflamed gingival tissue and GCF in patients with periodontitis. Treatment with scaling and root planing decreases IL-1β levels in the GCF.

The IL-1 gene cluster on human chromosome 2q15 contains 3 genes. Two genes (IL-1α and IL-1β) encode proinflammatory cytokine proteins IL-1α and IL-1β, respectively. The third gene (IL-1RN) encodes a related protein (IL-1ra) that acts as a receptor antagonist. Recent research has improved public knowledge on the role of the proinflammatory cytokine in OTM. Both IL-1β and tumor necrosis factor-α (TNF-α) have been implicated in osteoclastic bone resorption accompanying OTM. Studies from Al-
hashimi and coworkers\textsuperscript{43} have shown the increased levels of IL-1\textbeta in vivo mRNA expression during orthodontic treatment. And such increased levels of IL-1\textbeta are measurable in GCF and gingival tissues of patients.\textsuperscript{40}

Research has shown that such increased IL-1\textbeta expression is associated with the polymorphisms of IL-1\textbeta gene clusters. IL-1\textbeta gene has 2 alleles at the +3954 position. Allele 1 of the IL-1\textbeta gene results in low production of IL-1\textbeta. On the other hand, allele 2 is associated with adult periodontitis. A change in IL-1\textbeta allele to allele 2 at +3954 position can result in a 4-fold increase in IL-1\textbeta production leading to bone destruction in adult periodontitis.\textsuperscript{44} Kornman and coworkers\textsuperscript{10} reported that patients who were nonsmokers and positive for allele 2 at IL1\textalpha -899 and IL1\textalpha +9954 loci had a 6.8 times greater chance of having severe periodontitis than those who did not possess these alleles. IL-1 genotype can thus be a strong predictor of susceptibility to severe periodontitis in adults.

Research has demonstrated that IL-1\textbeta gene polymorphism at the +3954 position can also predispose patients to external apical root resorption (EARR), in which dental hard tissues are attacked by osteoclasts. Individuals homozygous for the IL-1\textbeta allele 1 have a 5.6-fold increased risk of EARR greater than 2 mm, as compared with heterozygocity for the IL-1\textbeta allele 1. The diallelic variation of IL-1\textbeta gene between individuals results in different expression levels of IL-1\textbeta, leading to various physiological responses of apical roots to orthodontic forces. Decreased IL-1\textbeta expression in individuals homozygous for the IL-1\textbeta allele 1 may result in relatively less catabolic bone resorption at the cortical bone interface with the PDL, which in turn may traumatize the root of the tooth, triggering a cascade of fatigue-related events leading to root resorption.\textsuperscript{45} Recent studies by Jager and coworkers in rats have shown that inhibition of cytokine activity by soluble receptors to IL-1 and TNF-\textalpha reduces the number of osteoclasts on the bone surface and inhibits OTM.\textsuperscript{46} Although such application of soluble receptors does not seem to be a specific treatment regimen for preventing root resorption in the course of OTM, there is progress toward prediction of unwanted side effects in creation of adjunctive pharmaceutical therapy.

The findings of genetic components such as IL-1\textbeta involved in periodontitis and OTM will allow orthodontists to employ genetic susceptibility testing for possible complications before orthodontic treatment when the clinical process is rendered more practical and conceptually more refined. Presently a reliable and practical market to patient sampling is in the development stage. GCF or buccal mucosal epithelial cells can be collected and assessed for IL-1\textbeta genetic polymorphism. In this way, orthodontists can screen patients for DNA markers suggesting susceptibility to periodontitis or EARR. Orthodontists can then better inform patients of periodontal and orthodontic risks. Currently, a genetic susceptibility test is available for severe chronic periodontitis based on the study by Greenstein and colleagues.\textsuperscript{47} In the future, similar genetic tests could be developed to assess the risk of EARR or even manipulate sufficient limited inflammatory events to facilitate movement or enhance stability. Such tests offer an intriguing tool for biologic orthodontists and dento-facial orthopedists to develop a thorough biologically based diagnosis and treatment plan.

**Conclusion**

Recently, developments in clinical practice have incorporated OTM as a sophisticated therapeutic adjunct in dental arch development, bone regeneration, and preprosthetic periodontal therapy. The relationships between orthodontics and periodontology are closer than ever and complicated also by the popular incorporation of dental implants and temporary anchorage devices (TADs). These evolutionary developments in the orthodontic specialty suggest the presence of equally sophisticated biological events within the PDL and alveolar bone during OTM.

In the past, scholars have proposed several theories regarding bone remodeling during OTM, which in light of modern cell biology can be viewed as overly simplistic and unproductive by contemporary societal needs and 21st century patient expectations of applied biological science. Contemporary models include Baumrind’s viscoelastic\textsuperscript{13} and Johnson’s fluid flow theories,\textsuperscript{12} which may help link clinical practice with pharmacologic and tissue engineering, a
nascient science already being developed in other fields of clinical care. Recent discoveries of the interplay between RANKL and OPG molecules in regulating bone remodeling demonstrate the potential of molecular biology in widening the clinical horizon of dentofacial orthopedics. It is possible that a combination of all the theories can be synthesized under the theories proposed by Moss, Singh, Frost, and Jee and the intrepid research of Drs. Wilcko and Ferguson.

The biochemical mechanisms of OTM mimic on a smaller scale some inflammatory events that occur during occlusal trauma and the accelerated bone loss in periodontitis. Consequently, clinicians who ensure that concomitant periodontal care accompany their mechno-therapeutic protocol can minimize the likelihood of permanent damage to the periodontal tissues apparently initiated by deceptively “benign” gingival hyperplasia. Thus, caution, informed consent, and prudent concern are always wise practices. With understanding of histobiological mechanisms underlying OTM, future dentofacial orthopedics involving pharmacological treatment may be as common as interarch elastics are now. Certainly, “growing bone,” a common practice in distraction osteogenesis and regeneration, is quite possible in the alveolus, and may promise some relief from the timid reliance clinicians place on patient cooperation and extraction protocols. We hope that other colleagues will share our trust and eager interest in these applications of modern life science in our specialty, so that investigation of various drugs and hormones to enhance orthodontic movement may someday lead to their use as pharmacological modifiers of OTM.

Our view is that future orthodontic specialists’ training should and will, by the natural evolution of scientific pedagogical imperatives, eventually supplement but not replace conventional orthodontic mechanotherapy and integrate it with the sciences of clinical pharmacology, periodontics, cellular genetics, and molecular biology. The question remains whether we shall do it as a reflex to regulation, as homage to earlier scholars, or simply to provide optimal patient care. The integration of contemporary science and clinical orthodontics is a professional imperative, lest our future be defined by others less qualified, be they bureaucratic usurpers or crass retail marketers.

Acknowledgments
We greatly appreciate the invaluable insights and suggestions from Dr. Neal C. Murphy, Lecturer at the Department of Orthodontics at UCLA School of Dentistry, Associate Professor in Orthodontics at Case Western University. Dr. Murphy is a great teacher. Carpe Diem! We wish to acknowledge Shelby Padua, UCLA School of Dentistry, for proofreading and contributing to this study. Thanks also to Dr. Chin-Yu Lin, Director of Orthodontics at Harvard School of Dental Medicine, for giving insights and providing references on the molecular basis of OTM. Thanks also to the advice tendered by Dr. A. Lala, Lecturer at Harvard School of Dental Medicine. Special appreciation is extended to Joseph P. Bidwell, PhD, whose development of the “mechanosome model,” in collaboration with colleagues at Indiana University-Purdue University at Indianapolis consortium of clinicians and scientists, helped stimulate interest in the fascinating molecular genetic biology that underlies the science and art of the orthodontic specialty.

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