

MOLECULAR MECHANISMS OF ORTHODONTIC TOOTH MOVEMENT

A Narrative Review

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ORCID: <https://orcid.org/0000-0002-2623-4273>**ABSTRACT**

Orthodontic tooth movement (OTM) is a mechanobiological process in which controlled mechanical loading is converted into coordinated cellular and molecular responses within the periodontal ligament (PDL), alveolar bone, vasculature, immune system, and neural microenvironment. Mechanical deformation, fluid shear stress, extracellular-matrix strain, and local vascular changes activate mechanosensitive pathways in periodontal ligament fibroblasts, osteocytes, osteoblast-lineage cells, and progenitor cells. These signals initiate sterile inflammation and the release of cytokines, chemokines, prostaglandins, growth factors, and matrix-remodeling enzymes. The receptor activator of nuclear factor- κ B ligand (RANKL)/RANK/osteoprotegerin (OPG) axis, together with macrophage colony-stimulating factor, is central to osteoclast differentiation and bone resorption. Recent evidence also indicates that orthodontic remodelling is temporally and spatially asynchronous and cannot be fully explained by a simple pressure-tension model. The biphasic concept, consisting of an early catabolic response followed by an anabolic/adaptive response, provides a useful contemporary framework. Mechanotransduction pathways involving integrins, mitogen-activated protein kinases, mechanosensitive ion channels, and YAP/TAZ connect physical loading to gene regulation. Neuropeptides and neuronal guidance molecules further demonstrate that sensory and autonomic neural components interact with immune, vascular, periodontal, and bone cells during OTM. Biomarkers detected in gingival crevicular fluid and saliva, including RANKL, OPG, inflammatory cytokines, prostaglandin E₂, matrix metalloproteinases, alkaline phosphatase, osteocalcin, and root-resorption-associated proteins, may provide information about tissue remodeling, although clinical application remains limited by methodological heterogeneity. Emerging studies on biological modulation, including nutritional, pharmacological, and biomaterial-based approaches, illustrate the translational potential of understanding these pathways. This narrative review integrates current evidence from mechanical force application to mechanotransduction, inflammation, osteoclastogenesis, bone resorption, osteogenesis, remodeling, root resorption, and relapse, highlighting the interconnected molecular mechanisms that determine orthodontic tooth movement.

Keywords: orthodontic tooth movement; periodontal ligament; mechanotransduction; RANKL; OPG; osteoclastogenesis; cytokines; hypoxia; neuropeptides; biomarkers; bone remodeling

INTRODUCTION

Orthodontic tooth movement is the displacement of a tooth through the alveolar socket in response to a controlled mechanical stimulus. Although orthodontic force is the initiating event, tooth movement is not a simple mechanical displacement. The periodontal ligament and alveolar bone form a functional mechanobiological unit in which physical deformation is translated into biochemical signals, cellular recruitment, extracellular-matrix turnover, and coordinated bone resorption and formation. Current evidence emphasizes that the biological response depends not only on force magnitude but also on strain distribution, force duration, loading history, tissue condition, and the local cellular microenvironment [1,2].

Mechanical loading alters the extracellular matrix, cytoskeleton, vascularity, interstitial fluid flow, and cell-matrix interactions. These changes activate mechanosensitive signaling systems and promote the release of inflammatory mediators, prostaglandins, growth factors, chemokines, and osteoclastogenic signals [1-3]. The response involves periodontal ligament fibroblasts, periodontal ligament stem/progenitor cells, osteocytes, osteoblasts, osteoclast precursors, macrophages, lymphocytes, endothelial cells, and neural elements. Thus,

OTM should be considered a coordinated multicellular response rather than an isolated reaction of the compression and tension sides.

The purpose of this narrative review is to synthesize recent evidence on the molecular mechanisms underlying OTM, with emphasis on mechanotransduction, the biphasic concept, RANKL/RANK/OPG signaling, inflammatory modulation, hypoxia, matrix remodeling, neurovascular regulation, biomarkers, biological acceleration, root resorption, and relapse.

PHASES AND CONTEMPORARY CONCEPT OF OTM

Classical descriptions divide OTM into initial, lag, and post-lag phases. This temporal framework remains clinically useful, but contemporary evidence suggests that the underlying tissue response is more dynamic than a prolonged period of complete biological inactivity. Mechanical deformation and inflammatory signaling begin rapidly after force application, followed by recruitment and activation of osteoclast-lineage cells and subsequent osteogenic adaptation [1,2].

Biphasic theory

The biphasic theory provides a more contemporary conceptual model of OTM. It proposes an early catabolic phase characterized by tissue injury, sterile inflammation, and osteoclast-mediated bone resorption, followed by an anabolic phase characterized by bone formation and adaptation around the new tooth position [4]. This concept is supported by newer evidence showing that bone remodeling after orthodontic loading is temporally and spatially asynchronous. In an experimental study, osteoclast recruitment was observed at both compression and tension sites during the early response, whereas osteoblast accumulation was more prominent later, indicating that the traditional strict separation of resorption to compression and formation to tension is an oversimplification [5].

Therefore, compression and tension should be regarded as different mechanical microenvironments rather than isolated biological compartments. The balance and timing of osteoclastogenesis, matrix degradation, progenitor-cell activation, osteoblast differentiation, and inflammatory resolution ultimately determine the direction and rate of tooth movement [2,5].

MECHANICAL FORCE AND MECHANOTRANSDUCTION

The first biological event after orthodontic force application is mechanical deformation of the tooth-PDL-alveolar bone complex. The PDL experiences compression, tension, fluid movement, and changes in extracellular-matrix strain. Mechanical loading is sensed by cell-matrix adhesions, cytoskeletal structures, mechanosensitive ion channels, primary cilia-associated systems, and transcriptional mechanosensors [1,6].

Integrin and cytoskeletal signalling :

Integrins connect extracellular-matrix proteins to focal adhesion complexes and the actin cytoskeleton. Mechanical strain alters focal adhesion signaling and activates intracellular pathways including focal adhesion kinase and MAPK/ERK-related signaling. These pathways influence transcription of genes involved in inflammation, matrix turnover, proliferation, and differentiation [1,6].

Mechanosensitive ion channels

Piezo1/Piezo2 and TRPV-family channels have emerged as potential mechanosensors in periodontal ligament cells. Mechanical deformation can modify ion flux and downstream signaling, providing a rapid link between physical force and biochemical responses [6].

YAP/TAZ Mechanotransduction

YAP and TAZ are mechanosensitive transcriptional regulators that respond to changes in cytoskeletal tension and cell-matrix mechanics. A recent review identified YAP/TAZ as important mediators of periodontal mechanotransduction [7]. More recently, Deng et al. demonstrated that YAP activation during OTM was associated with NF- κ B p65 signaling and osteoclastogenesis. Their experimental data indicated that both compression and tension could activate early osteoclast recruitment, while inhibition of YAP delayed tooth movement [5]. These findings provide a direct molecular bridge between mechanical sensing and osteoclast-mediated remodeling.

VASCULAR CHANGE AND HYPOXIA

Orthodontic force changes PDL vascularity and interstitial fluid flow. Compression can reduce local perfusion and create a transient hypoxic environment, whereas subsequent vascular adaptation contributes to tissue recovery. Hypoxia influences cellular metabolism, inflammatory signaling, angiogenic responses, and cell survival. The hypoxic response should therefore be integrated with mechanotransduction rather than considered an independent event [1,8].

Recent work on autophagy further emphasizes the relationship among compression, tension, fluid shear stress, and hypoxia. Autophagy may help cells adapt to mechanical and metabolic stress and may influence both OTM and orthodontically induced inflammatory root resorption [9].

ASEPTIC INFLAMMATION AND OSTEOIMMUNOLOGY

Orthodontic force produces a controlled sterile inflammatory response rather than an infectious inflammatory process. Mechanical injury and changes in the local microenvironment activate periodontal and immune cells, resulting in secretion of IL-1 β , IL-6, TNF- α , IL-8, PGE2, chemokines, and growth factors [10]. These mediators recruit and activate leukocytes and modify osteoclast and osteoblast activity.

Macrophages have a central role because they can participate in tissue clearance, inflammatory signaling, osteoclastogenesis, angiogenesis, and resolution. Osteoimmunology studies emphasize the interaction between leukocytes and stromal/osteoblastic cells as a major mechanism linking mechanical loading to bone remodeling [10]. Recent experimental evidence also indicates that macrophage polarization can participate in resolution of orthodontically induced pulpal inflammation, demonstrating that immune-cell function extends beyond the alveolar bone compartment [11].

RANK/RANKL/OPG AND OSTEOCLASTOGENESIS

The RANK/RANKL/OPG axis is a central molecular regulator of osteoclastogenesis during OTM. RANKL is expressed by osteoblast-lineage cells, osteocytes, periodontal ligament cells, and activated immune cells. RANKL binds to RANK on osteoclast precursor cells and activates intracellular NF- κ B signaling, followed by NFATc1-dependent osteoclast differentiation. OPG acts as a soluble decoy receptor that limits RANKL-RANK interaction [12].

Recent reviews confirm that osteoclastogenesis is fundamental to orthodontic bone remodeling and that excessive activation can also contribute to orthodontically induced inflammatory root resorption [12]. Consequently, the local RANKL/OPG balance is more biologically informative than considering either molecule alone. Clinical and experimental studies have demonstrated increases in RANKL and changes in OPG during OTM, supporting their role in remodeling [12,13].

RANKL signaling also interacts with inflammatory cytokines and mechanotransduction pathways. IL-1 β , TNF- α , and PGE2 can enhance osteoclastogenic activity, while YAP-mediated NF- κ B signaling provides an additional link between mechanical loading and osteoclast differentiation [5,12]. This interconnected network explains why OTM cannot be attributed to a single molecular mediator.

CYTOKINE AND PROSTAGLANDIN NETWORK

IL-1 β , IL-6, TNF- α , IL-8, and PGE2 are among the best studied mediators of the early response to orthodontic force. Their concentrations can change rapidly after force application and are influenced by force magnitude, timing, biological age, sampling site, and appliance characteristics [13,14].

A recent systematic review and meta-analysis reported that proinflammatory cytokines tend to show early increases after orthodontic force, whereas anti-inflammatory mediators participate in later tissue repair. Although pooled clinical evidence remains heterogeneous, IL-1 β has been associated with the rate of OTM in several studies [14]. Thus, cytokines should be interpreted as dynamic regulators of the remodeling environment rather than isolated biomarkers with fixed diagnostic thresholds.

EXTRACELLULAR-MATRIX REMODELING: MMPs AND TIMPs

Matrix metalloproteinases participate in degradation and turnover of the PDL extracellular matrix during OTM. MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, MMP-12, MMP-13, and MMP-14 have been investigated in relation to mechanical loading. Their biological effects are regulated by tissue inhibitors of metalloproteinases (TIMPs), so the MMP/TIMP balance is more informative than an isolated MMP concentration [15].

Recent literature emphasizes that MMPs are not simply destructive enzymes. They participate in matrix turnover, cell migration, release or activation of signaling molecules, and tissue repair. Therefore, MMP elevation during OTM may indicate active remodeling rather than pathological destruction by itself [15].

OSTEOCLASTS, OSTEOBLASTS AND THE ANABOLIC RESPONSE

During the catabolic response, osteoclast precursors derived from the monocyte/macrophage lineage are recruited and differentiated under the influence of M-CSF and RANKL. Mature osteoclasts attach to mineralized surfaces and create resorption lacunae through acidification and proteolytic degradation of the extracellular matrix [12].

The anabolic response involves mesenchymal progenitor recruitment, osteoblast differentiation, extracellular-matrix deposition, and mineralization. Osteocytes act as important coordinators by releasing Wnts, prostaglandins, nitric oxide, sclerostin, RANKL, and other signals that regulate osteoblast and osteoclast activity [16].

Wnt/ β -catenin signaling is an important osteogenic pathway. Sclerostin, produced predominantly by osteocytes, suppresses Wnt signaling. Emerging evidence also implicates PTHrP in communication between periodontal ligament cells and osteocytes, potentially influencing sclerostin and osteogenic responses. These mechanisms may help explain the transition from early catabolism to later bone adaptation [16].

NEURAL REGULATION OF ORTHODONTIC TOOTH MOVEMENT

The neural component represents an important emerging dimension of OTM biology. Periodontal and paradental tissues are innervated by sensory and autonomic fibers that can release neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P. These mediators can influence vascular permeability, immune-cell activity, periodontal metabolism, and bone-cell function [17,18].

Recent reviews identify neural regulation as an expanding field in OTM, with sensory and autonomic systems interacting with periodontal tissues and alveolar bone [17]. Neuronal guidance molecules provide an additional molecular interface. Semaphorins, ephrins, and Eph receptors are expressed in periodontal and alveolar tissues and can be mechanically regulated. *Sema3A*, for example, has been linked to *Rac1* and β -catenin activation and osteogenic marker expression, suggesting a role in balancing osteoblast and osteoclast responses [18,19].

These findings indicate that the nervous system should not be considered a secondary contributor to OTM. Instead, neural, vascular, immune, and skeletal components form an interconnected signaling network that may influence both the rate of movement and tissue adaptation.

BIOMARKERS OF ORTHODONTIC TOOTH MOVEMENT

Biomarkers associated with OTM should be classified according to the biological process they represent. Importantly, many molecules participate in more than one pathway; therefore, a biomarker should not automatically be interpreted as a specific indicator of bone resorption or formation.

Biological category	Representative biomarkers	Principal interpretation	Current translational relevance
Inflammation	IL-1 β , IL-6, TNF- α , IL-8, PGE2	Early sterile inflammatory response and modulation of osteoclastogenesis	Potential monitoring markers; limited specificity and strong timing dependence [14]
Osteoclastogenesis / bone resorption	RANKL, OPG, RANKL/OPG, TRAP, DPD, PYD, NTX, OPN	Osteoclast differentiation and bone turnover	Mechanistically important; GCF patterns are promising but heterogeneous [13,20]
Matrix remodeling	MMP-1, MMP-2, MMP-8, MMP-9, MMP-13, TIMPs	PDL extracellular-matrix degradation and remodeling	Potential early indicators of active tissue remodeling [15,21]
Bone formation	ALP/BALP, osteocalcin, RUNX2, type I procollagen	Osteogenic differentiation, matrix deposition and mineralization	Useful research markers; not specific enough for stand-alone clinical prediction [20]
Root resorption	Dentin phosphoprotein, dentin sialoprotein, dentin sialophosphoprotein, fetuin-A, selected cytokines	Possible evidence of orthodontically induced root resorption	Promising non-invasive proxies; currently insufficient for routine diagnosis [22]
Neural / neurovascular	CGRP, substance P,	Neurogenic	Emerging mechanistic

	NGF-related and neuronal guidance signaling	inflammation, vascular modulation and bone-cell regulation	field; not established clinical tests [17-19]
Relapse / post-treatment stability	ALP, MMP-1 and remodeling-associated mediators	Bone formation/remodeling and periodontal adaptation after appliance removal	Preclinical evidence suggests potential for biological modulation [23,24]

Systematic evidence on GCF biomarkers demonstrates substantial variation in sampling, timing, force protocols, analytical methods, and study populations. Bone formation markers such as ALP and osteocalcin and resorption markers such as TRAP, DPD, PYD, NTX, and OPN have been investigated, but methodological heterogeneity limits direct comparison [20]. Similarly, recent systematic review evidence on salivary and GCF proteins suggests that dentin-related proteins and selected inflammatory markers may be promising proxies for root resorption, but larger standardized studies are required before clinical implementation [22].

BIOLOGICAL MODULATION OF OTM

Improved understanding of the molecular cascade has stimulated attempts to accelerate or control OTM through biological modulation. Candidate approaches include prostaglandins, vitamin derivatives, growth factors, RANKL-related interventions, PTH-related pathways, sclerostin modulation, herbal compounds, photobiomodulation, minimally invasive procedures, and biomaterial-based delivery systems [24].

Alhasyimi and Rosyida reported that cocoa administration accelerated OTM in rats and was associated with changes in RANKL and OPG, supporting the hypothesis that nutritional modulation may influence osteoclastogenesis [25]. However, this is preclinical animal evidence and should not be interpreted as evidence that cocoa is an established clinical accelerator of orthodontic tooth movement.

Lestia et al. investigated a carbonated hydroxyapatite-statin nanoemulsion during orthodontic relapse in rats and reported changes in alkaline phosphatase levels, suggesting enhanced osteogenic activity during the post-treatment remodeling phase [23]. More recent work has also examined statin-loaded carbonate hydroxyapatite systems for reduction of early relapse and modulation of MMP-1, further illustrating the potential of local biomaterial-based biological control [24].

These approaches should be interpreted cautiously because acceleration of osteoclastogenesis without adequate control may increase adverse remodeling. The translational goal should therefore be selective modulation of the remodeling process rather than indiscriminate stimulation of bone resorption.

ROOT RESORPTION AS AN ADVERSE MOLECULAR RESPONSE

Orthodontically induced inflammatory root resorption shares several inflammatory and osteoclastogenic pathways with physiological tooth movement. Excessive mechanical loading can increase inflammatory signaling and clastic-cell activity at the root surface [12,26]. Understanding the threshold between physiological remodeling and pathological resorption is therefore an important molecular research objective.

Recent systematic evidence indicates that proteins such as dentin phosphoprotein, dentin sialoprotein, dentin sialophosphoprotein, fetuin-A, and selected cytokines may have potential as salivary or GCF indicators of ongoing root resorption. At present, these biomarkers should be considered promising research tools rather than validated replacements for radiographic assessment [22].

RELAPSE AND POST-TREATMENT REMODELING

Relapse is also a biologically active process. Following removal of orthodontic appliances, periodontal fibers, alveolar bone, and remodeling-associated cells continue to adapt to the altered tooth position. The balance between osteoclast-mediated resorption, osteoblast-mediated formation, extracellular-matrix turnover, and fiber reorganization contributes to post-treatment stability.

The study by Lestia et al. provides a recent example of molecular intervention during relapse, demonstrating altered ALP activity following local carbonated hydroxyapatite-statin nanoemulsion administration in rats [23]. Additional preclinical work using simvastatin-loaded carbonate hydroxyapatite has reported suppression of MMP-1 and reduced early relapse, suggesting that modulation of matrix remodeling may be another strategy for improving post-treatment stability [24].

INTEGRATED MOLECULAR PATHWAY OF OTM

Mechanical orthodontic force

↓

PDL deformation + extracellular-matrix strain + fluid shear stress

↓

Mechanosensors: integrins / focal adhesions / Piezo-TRPV channels / YAP-TAZ / MAPK

↓

Vascular alteration + transient hypoxia + cellular stress

↓

Aseptic inflammation + neurovascular signaling

↓

IL-1 β / IL-6 / TNF- α / IL-8 / PGE2 / chemokines / growth factors / MMPs

↓

M-CSF + increased RANKL relative to OPG

↓

RANK $\rightarrow$ NF- κ B $\rightarrow$ NFATc1

↓

Osteoclast differentiation and activation

↓

Alveolar bone resorption $\rightarrow$ tooth displacement

↓

Inflammatory resolution + progenitor-cell recruitment

↓

Wnt/ β -catenin + PTHrP/sclerostin regulation + osteogenic differentiation

↓

Osteoblast activity $\rightarrow$ osteoid deposition $\rightarrow$ mineralization $\rightarrow$ alveolar adaptation

↓

Remodeling / retention / possible relapse depending on tissue adaptation

Importantly, recent evidence indicates that this pathway is temporally and spatially overlapping rather than strictly linear. Early osteoclast activity may occur at both compression and tension sites, while later osteogenic activity becomes more evident during tissue adaptation [5].

EMERGING SCIENCE AND FUTURE DIRECTIONS

Future research is moving beyond single-molecule explanations toward cell-specific and spatially resolved models of OTM. Important emerging areas include YAP/TAZ mechanotransduction, mechanosensitive ion channels, osteocyte signaling, macrophage phenotypes, neuronal guidance molecules, neuropeptide signaling, PTHrP-sclerostin communication, autophagy, and PDL stem-cell responses [5-9,16-19].

Single-cell RNA sequencing, spatial transcriptomics, proteomics, and advanced imaging may help identify which cells express specific mediators at defined time points and locations. Such approaches could clarify why individuals respond differently to similar orthodontic forces and may eventually enable personalized modulation of OTM while minimizing root resorption and relapse.

CONCLUSION

Orthodontic tooth movement is a coordinated mechanobiological process involving mechanical sensing, vascular and metabolic adaptation, sterile inflammation, immune-cell activity, neural signaling, osteoclastogenesis, extracellular-matrix remodeling, and osteoblast-mediated bone formation. The biphasic concept provides a useful temporal framework, whereas the RANKL/RANK/OPG axis, cytokine and prostaglandin networks, mechanotransduction pathways, hypoxia, MMP/TIMP activity, Wnt/ β -catenin signaling, PTHrP/sclerostin interactions, and neurovascular mechanisms provide molecular detail. Recent evidence demonstrates that compression and tension cannot be treated as biologically isolated compartments and that osteoclast and osteoblast responses overlap in time and space. GCF and salivary biomarkers are promising for monitoring biological activity, but methodological heterogeneity currently limits their use as definitive clinical predictors. Emerging biological and biomaterial approaches may allow selective modulation of OTM and relapse, but most remain preclinical. A deeper understanding of cell-specific and temporally coordinated signaling will be essential for developing safer, more predictable, and individualized orthodontic treatment.

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