RESEARCH PAPER

STEM CELLS IN ORTHODONTICS: CURRENT EVIDENCE, REGENERATIVE APPLICATIONS AND FUTURE CLINICAL DIRECTIONS

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Aim: To review the current evidence on stem cells in orthodontics, focusing on tooth movement, periodontal and alveolar regeneration, treatment acceleration, and emerging regenerative approaches.

Objectives: To summarize relevant stem-cell sources; describe their role in mechano-transduction and tissue remodeling; evaluate regenerative applications; assess cell-based and cell-free strategies; and identify translational and safety limitations.

Methods: This narrative review synthesizes experimental and human clinical evidence cited in the article on dental and craniofacial stem cells, orthodontic tooth movement, mechanobiology, periodontal and alveolar regeneration, tissue engineering, secretomes and extracellular vesicles. Systematic reviews, meta-analyses, feasibility studies and clinical reports were considered.

Results: Stem/progenitor cells may contribute to orthodontic remodeling through osteoclastogenesis, osteoblastogenesis, angiogenesis and periodontal tissue repair. Clinical evidence is more developed for selected periodontal and craniofacial bone-regeneration applications than for stem-cell-assisted acceleration of orthodontic tooth movement. Secretomes and extracellular vesicles are promising, but remain investigational.

Conclusion: Stem cells are an emerging regenerative option in orthodontics, with the most realistic near-term role in selective periodontal and alveolar tissue regeneration. Further standardized clinical trials are required before routine use for orthodontic tooth movement.

Keywords: stem cells; orthodontics; periodontal ligament stem cells; dental pulp stem cells; mesenchymal stem cells; tooth movement; mechanobiology; mechanotransduction; tissue engineering; periodontal regeneration; alveolar bone regeneration; regenerative orthodontics; orthodontic tooth movement; stem-cell therapy; extracellular vesicles; secretome; dental stem cells; craniofacial regeneration; biomaterials; personalized orthodontics.

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Introduction

Orthodontic tooth movement is a biologically regulated process in which controlled mechanical force produces a coordinated response involving periodontal ligament deformation, vascular changes, inflammatory mediators, osteoclast recruitment, osteoblast activity and remodeling of the surrounding alveolar bone. The clinical rate and quality of tooth movement therefore depend not only on appliance mechanics but also on the biological capacity of the periodontal tissues to remodel. Contemporary orthodontic research increasingly focuses on understanding this biological response and on identifying safe methods for improving treatment efficiency while maintaining periodontal health. Stem cells are undifferentiated or relatively immature cells capable of self-renewal and, depending on their source and microenvironment, differentiation toward multiple lineages. Dental and craniofacial tissues contain several populations of mesenchymal stem/stromal cells, including periodontal ligament stem cells (PDLSCs), dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHED), stem cells from the apical papilla (SCAPs), dental follicle progenitor cells and gingiva-derived mesenchymal stem cells. These populations have attracted considerable attention because they can participate in tissue repair and because they release bioactive molecules that influence immune cells, endothelial cells, fibroblasts and bone-forming cells.

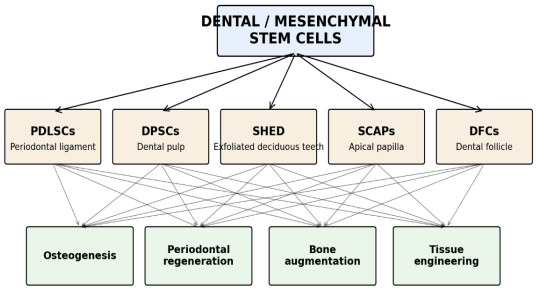


Figure 1. Major dental and craniofacial stem-cell sources and their potential regenerative applications.

1. Stem Cells Relevant to Orthodontics

2.1 Periodontal ligament stem cells

PDLSCs were characterized as a population of postnatal stem/progenitor cells within the periodontal ligament capable of clonogenic growth and multilineage differentiation. Their location is particularly relevant to orthodontics because the periodontal ligament is the principal tissue transmitting orthodontic force to alveolar bone. PDLSCs can contribute to fibroblastic, osteogenic and cementogenic phenotypes and can influence neighboring cells through paracrine signaling. Mechanical loading may alter their proliferation, migration, differentiation and secretion of inflammatory or osteogenic mediators.

2.2 Dental pulp stem cells

DPSCs were among the first human dental stem-cell populations to be extensively characterized. They demonstrate mesenchymal characteristics and can differentiate toward odontogenic, osteogenic and other lineages under appropriate conditions. Their major translational interest has been pulp-dentin regeneration, but their broader regenerative and immunomodulatory properties make them relevant to craniofacial tissue engineering.

2.3 SHED and other dental stem-cell populations

SHED are obtained from exfoliated deciduous teeth and are attractive because the source is relatively accessible and minimally invasive. SCAPs are associated with the apical papilla of immature permanent teeth and have demonstrated proliferative and differentiation potential. Dental follicle cells contribute to the formation of periodontal and supporting tissues. Gingiva-derived mesenchymal stem cells have also shown immunomodulatory and regenerative properties. Together, these populations provide a diverse biological resource for future dental tissue engineering.

2. Stem Cells and the Biology of Orthodontic Tooth Movement

Orthodontic tooth movement is classically described as a remodeling response to sustained mechanical loading. Compression of the periodontal ligament is associated with vascular and cellular changes and recruitment of osteoclasts, while tension promotes fibroblast activity and bone formation. Modern models emphasize that the response is not divided into completely separate compression and tension compartments; instead, mechanical strain, fluid movement, inflammatory mediators, hypoxia and cellular signaling interact continuously.

PDLSCs and other local progenitor cells may contribute to this response by sensing changes in their physical microenvironment and by communicating with osteoblasts, osteoclast precursors, endothelial cells and immune cells. Mechanosensitive pathways involving integrins, focal adhesions, cytoskeletal remodeling, ion channels and intracellular signaling systems can influence expression of cytokines, chemokines and osteogenic genes. These mechanisms provide a biological bridge between orthodontic force and remodeling of the periodontal tissues.

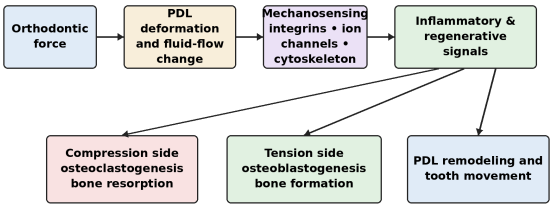


Figure 2. Schematic overview of proposed stem/progenitor-cell mechanobiology during orthodontic tooth movement.

3. Mechano-Transduction and Stem-Cell Responses

Mechano-transduction describes conversion of a physical stimulus into a biochemical and cellular response. In orthodontics, changes in stress and strain within the periodontal ligament can modify cell shape, membrane tension, extracellular-matrix interactions and intracellular signaling. Integrin-mediated adhesion, actin-cytoskeleton organization, calcium signaling and mechanosensitive ion channels are among the mechanisms proposed to translate force into gene-expression changes.

The inflammatory component of orthodontic tooth movement is part of the physiological response when appropriately regulated. Cytokines and chemokines facilitate recruitment and activation of osteoclast precursors and other cells. At the same time, osteoblast-lineage cells participate in new bone deposition on the tension side. Stem/progenitor cells may influence both phases through direct differentiation and paracrine communication. Consequently, manipulating stem-cell activity could theoretically change the speed or quality of tooth movement, but excessive stimulation may also increase risks such as root resorption, periodontal breakdown or uncontrolled bone remodeling.

The biological objective should therefore not be maximal cellular activation. A more clinically relevant objective is controlled modulation of the remodeling environment so that tooth movement occurs efficiently while periodontal support and root integrity are preserved.

4. Stem Cells in Periodontal and Alveolar Regeneration

Periodontal regeneration is one of the more clinically developed areas connecting dental stem-

cell biology with orthodontics, although protocols and long-term outcomes remain heterogeneous. Patients requiring orthodontic treatment may present with periodontal defects, thin alveolar housing, previous periodontal disease, recession or dehiscence. In selected situations, restoration of supporting tissues may be required before or alongside orthodontic movement. Stem-cell-based approaches have therefore been investigated as adjuncts to periodontal and alveolar bone regeneration.

Clinical studies and systematic reviews suggest that mesenchymal stem/stromal-cell-based approaches may improve selected periodontal outcomes, particularly when combined with suitable scaffolds or regenerative materials. However, differences in cell source, preparation, delivery vehicle, defect morphology, outcome definitions and follow-up limit comparisons among studies. These approaches should be considered investigational or used only within evidence-supported indications; they should not routinely replace established periodontal regenerative procedures.

5.1 Alveolar bone regeneration

Alveolar bone volume and morphology are central to orthodontic tooth movement because teeth can be moved only within biologically tolerable boundaries. Tissue-engineering approaches combining cells, scaffolds and signaling molecules have therefore been explored for reconstruction of deficient alveolar bone. Human feasibility studies have reported encouraging findings in craniofacial bone regeneration, but larger controlled studies with standardized long-term outcomes are required before these approaches can be incorporated routinely into orthodontic treatment planning.

5.2 Periodontal ligament regeneration

True periodontal regeneration requires restoration of multiple tissues, including cementum, periodontal ligament fibers and alveolar bone. Stem cells may support this process through differentiation and paracrine effects, including modulation of inflammation and angiogenesis. For orthodontic patients, successful regeneration could potentially enlarge the safe envelope for tooth movement, but this concept remains translational and should not be interpreted as evidence that stem-cell therapy permits movement beyond established periodontal limits.

5. Potential Role in Accelerating Orthodontic Tooth Movement

Acceleration of orthodontic treatment has traditionally been attempted through mechanical modification, surgical approaches, pharmacological modulation and adjunctive physical stimuli. Stem-cell biology introduces another theoretical pathway: enhancing the coordinated activity of progenitor cells involved in bone resorption and formation. Experimental findings suggest that local progenitor-cell populations respond to orthodontic loading and may contribute to the remodeling process.

Despite this promise, direct human evidence remains limited. Routine orthodontic treatment should not currently use stem-cell injections solely to accelerate movement outside approved research protocols. Dose-response relationships, optimal delivery routes, adverse-event profiles and long-term effects on roots and periodontal tissues remain insufficiently established.

6. Stem-Cell-Based Strategies for Orthodontically Relevant Tissue Damage

Orthodontic treatment may be associated with transient or, in susceptible individuals, clinically important periodontal and root changes. These include gingival recession, dehiscence, fenestration and external apical root resorption. Stem-cell-based regenerative concepts have been proposed to improve tissue repair, but evidence for prevention or treatment of orthodontically induced root resorption is considerably less mature than evidence for periodontal regeneration.

7. Biomaterials, Scaffolds and Cell-Free Approaches

Stem cells rarely function optimally in isolation. The local microenvironment strongly influences survival, differentiation and paracrine activity. Tissue-engineering strategies therefore combine cells with scaffolds that provide structural support and biochemical or mechanical cues. Hydrogels, collagen-based matrices, synthetic polymers, mineralized scaffolds and bioactive materials have all been investigated in dental regeneration.

An important development is the movement from whole-cell therapy toward cell-free regenerative medicine. Conditioned media, secretomes, extracellular vesicles and exosomes contain proteins, lipids, nucleic acids and other signaling molecules that may reproduce some beneficial effects of stem cells while reducing certain risks associated with transplantation. These approaches remain investigational, but they may ultimately be easier to standardize, store and regulate than living-cell products.

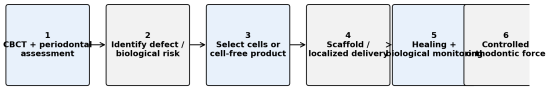


Figure 3. Proposed translational workflow for future stem-cell-assisted orthodontic care; this is a conceptual pathway, not a validated clinical protocol.

8. Clinical Applications and Translational Potential

A future regenerative orthodontic pathway could begin with comprehensive assessment of dental, periodontal and skeletal anatomy. Cone-beam computed tomography (CBCT) may help assess alveolar boundaries and defects when justified by the clinical indication. Periodontal phenotype, previous periodontal disease, tooth movement

requirements and biological risk could then be incorporated into treatment planning. A regenerative intervention might be considered only where a specific tissue deficiency exists and where evidence supports the chosen procedure.

9. Clinical Evidence: Current Status

Application	Current evidence	Clinical interpretation
Understanding tooth movement	Substantial experimental/mechanistic evidence	Stem/progenitor cells participate in remodeling; direct cell therapy is not established.
Periodontal regeneration	Human studies and systematic reviews	Promising adjunct in selected defects; heterogeneity remains substantial.
Alveolar/craniofacial bone regeneration	Early human feasibility/controlled studies	Potentially useful in selected defects; requires standardized protocols and long-term data.
Accelerating routine tooth movement	Limited direct human evidence	Experimental; should not be routine clinical care.
Root-resorption prevention/repair	Predominantly preclinical/early translational	Insufficient evidence for routine stem-cell treatment.
Secretome/extracellular-vesicle therapy	Preclinical/early translational	Promising cell-free direction; clinical protocols not established.

10. Limitations and Safety Considerations

The term "stem-cell therapy" covers biologically distinct products, and findings cannot be generalized across different cell sources or products. Autologous and allogeneic cells have different manufacturing and immunological considerations. Cell passage number, culture conditions, cryopreservation, viability, scaffold choice and delivery technique can influence biological behavior. In addition, stem-cell products may have effects beyond the intended site. Potential risks include infection, inappropriate differentiation, abnormal tissue formation, immune reactions, thrombosis or other procedure-related complications. For pluripotent-cell products, genetic instability and tumorigenicity are particularly important concerns. Even with adult mesenchymal cells, long-term safety and reproducibility must be demonstrated before widespread orthodontic application.

11. Future Directions

The future of regenerative orthodontics is likely to be biological and personalized rather than simply mechanical. Integration of CBCT-derived anatomy, periodontal phenotype, genetic or molecular biomarkers, digital treatment simulation and biological risk prediction may allow clinicians to estimate the remodeling capacity of individual patients. Stem-cell-derived signals could potentially be delivered locally to selected sites when a defined regenerative need is present.

Future clinical trials should use standardized cell characterization, clearly defined orthodontic outcomes, objective three-dimensional measurements, patient-reported outcomes and long-term periodontal and root-safety assessments. Multicenter randomized trials will be essential before biological acceleration strategies can be recommended as routine orthodontic treatment.

12. Conclusion

Stem cells represent an important emerging component of regenerative orthodontics. Dental and craniofacial stem/progenitor populations participate in periodontal homeostasis, mechanotransduction and tissue repair, making them biologically relevant to orthodontic tooth movement. Current clinical evidence is strongest for periodontal and alveolar regeneration, while direct stem-cell-assisted acceleration of routine orthodontic movement remains investigational. The most realistic near-term role of stem-cell technology is selective regeneration of deficient periodontal or alveolar tissues and development of cell-free biological products. Future advances in mechanobiology, biomaterials, extracellular vesicles, biomarkers and digital treatment planning may enable personalized biological modulation of orthodontic treatment. Until robust clinical evidence establishes safety, efficacy and reproducibility, stem-cell interventions should remain within appropriately regulated

clinical research or evidence-supported regenerative indications.

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