The effect of PDLSCs on orthodontic tooth movement – A review

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ABSTRACT

Background: Stem cells have been widely used in various fields of the health sector, one of which is dental health. Teeth with malocclusion require orthodontic treatment to achieve good function and aesthetics. Orthodontic tooth movement (OTM) occurs due to a bone remodeling process, namely deposition in areas of tension and resorption in areas of pressure. Differentiated stem cells are thought to influence OTM through several different mechanisms. Purpose: This narrative review seeks to explain how stem cells affect the mobility of orthodontic teeth. Review: OTM is aided by inflammatory mediators that are produced as a result of the induction of stem cells in the periodontal ligament. These mediators control osteoclast and osteoblast differentiation and proliferation, as well as bone remodeling. Periodontal ligament stem cells (PDLSCs) are important local immune response modulators in the inflammatory milieu and have an impact on a range of immune cells. Conclusion: PDLSCs, which are included in mesenchymal stem cells (MSCs), play a role in OTM through various mechanisms that can cause acceleration in OTM.

Keywords: malocclusion; stem cell; orthodontic tooth movement; bone remodelling; medicine

INTRODUCTION

Undifferentiated cells called stem cells have the capacity to self-renew and specialize into a variety of useful cell types. These cells can be widely applied to wounds to encourage tissue regeneration and healing.1–3 Bone marrow, umbilical cord, muscle, adipose tissue, teeth, periosteum, skin, blood, and synovial membrane have all been mentioned as potential sources for stem cells.4,5 Periodontal ligament stem cells (PDLSCs) have been identified as having traits in common with mesenchymal stem cells (MSCs) since they were first isolated in 2004.6 Dentofacial abnormalities and dental malocclusions are treated with orthodontic therapy. Achieving facial esthetics and enhancing oral health-related quality of life are the two main objectives of orthodontic treatment.7,8 To properly treat malocclusion with orthodontics, orthodontists still face significant difficulties. For instance, periodontitis patients’ teeth may be damaged by excessive orthodontic forces or regular forces. Orthodontic root resorption brought on by mechanical stress and relapse after treatment continue to be significant therapeutic difficulties. Bone remodeling results in a process known as orthodontic tooth movement (OTM). When a tooth is loaded mechanically, bone resorption takes place where there is stress, and new bone grows where there is tension.9 Complex bone metabolic processes are involved in this mechanism, which eventually causes tooth movement. OTM performance is closely linked to cellular and connective tissue responsiveness, tissue vitality, tooth structural integrity, and periodontal health. Due to their shared use of multiple cells and mediators, such as receptors, cytokines, and other signaling molecules, the immune and skeletal systems are two interrelated systems that have an impact on one another. This connection is exemplified by the intricate and highly coordinated non-infectious inflammatory periodontal tissue required for OTM.10

Depending on the pace of tooth displacement, Burstone split OTM into three distinct phases in 1962. This model was recently updated to include four clearly distinguishable phases (initial phase, lag phase, acceleration phase, and linear phase). The initial phase, which lasts for 24 to 48 hours after orthodontic force is applied, is stimulated immediately. A sudden movement of teeth within the alveolar socket is the defining feature of this phase. The periodontal ligament and surrounding tissues begin to show signs of necrosis and hyalinization, which causes the initial phase to be followed by a lag phase with little to no tooth movement. 20–30 days pass during the lag phase. After the necrotic and hyalinized tissue is completely removed by osteoclasts and phagocytes during a process known as
undermining resorption, the rate of tooth shift begins to gradually increase and then changes to continuous tooth movement during a linear phase (rapid OTM) as long as the mechanical stimulus endures.\textsuperscript{11,12}

PDLSCs are crucial for maintaining periodontal homeostasis because they have immunomodulatory properties, the capacity to proliferate, and the ability to produce cementum/periodontal ligament-like complexes.\textsuperscript{13} Additionally, during OTM, they play crucial roles in periodontal and osseous remodeling and are probably sensitive to mechanical loading. It may be possible to overcome the difficulties in orthodontic treatment by having a better understanding of the mechanical response of PDLSCs and the biological signaling system involved.

REVIEW

PDLSCs and OTM acceleration

Alveolar bone and periodontal ligament remodeling in response to mechanical pressure create OTM.\textsuperscript{14,15} Focal necrosis caused by the PDL microvasculature’s constriction ignites the first inflammatory response in the pressure area. Next, osteoclasts from the nearby marrow space are recruited.\textsuperscript{16} These osteoclasts are primarily produced by hematopoietic stem cells.\textsuperscript{17} As a result, stem cells can speed up OTM by supplying progenitor cells.

A study by Feng et al. (2016) stated that orthodontic force application resulted in an increase in PDL progenitor cells with suppressed type I collagen expression (Col-I), whereas force withdrawal resulted in an increase in Col-I expression. This demonstrates that PDLSCs can respond to mechanical forces during orthodontic treatment by suppressing collagen expression.\textsuperscript{18} In response to the strains of orthodontic treatment, stem cells have the ability to accelerate OTM. When orthodontic force is applied, tooth movement is restricted until the necrosis has disappeared, which produces a clinically apparent delay. Theoretically, rapid OTM might be achieved with stem cell transplantation in high-stress regions.

Mesenchymal stem cells (MSCs) generated from adipose are known to have a high capacity for osteogenic differentiation and PDL,\textsuperscript{19,20} and stem cells in PDL (PDLSCs), which have the characteristics of MSCs, are known to have an important role in periodontal and bone remodeling during OTM.\textsuperscript{21} The track markers of PDLSCs expanded on both the tension and pressure sides after 3 days of orthodontic force application, according to Zhang et al.\textsuperscript{22} Additionally, stem cell generation in PDL regulates osteoclast and osteoblast proliferation and differentiation, as well as bone remodeling, by producing inflammatory signals including interleukin-11 and Cox-2.\textsuperscript{23,25} By activating Cox-2, which is known to enhance osteoblastic markers and cementoblast-specific markers as well as boost bone sialoprotein production, IL-11 is known to enable MSCs to grow into osteoblasts or cementoblasts during tooth movement.\textsuperscript{26} Under these circumstances, it is conceivable that stimulation of PDLSCs by transplanted MSCs or direct MSC activity in PDL tissues could have an accelerating effect on OTM by expediting the process of bone remodeling through osteoblast-osteoclast turnover.\textsuperscript{27}

Additionally, PDLSCs increased collagen production following the cessation of orthodontic force application while decreasing collagen I expression during OTM. This process was previously thought to indicate that enhanced MSC would have the ability to accelerate OTM. Additionally, it is hypothesized that the transplantation of stem cells to pressure points will result in quicker OTM, which is predicated on the idea of avoiding the delay brought on by the elimination of hyaline necrotic tissue.\textsuperscript{28} The claim made by Huang et al. that stem cells in PDL have the potential to be employed to expedite orthodontic treatment operations because of their capacity for proliferation and differentiation also supports research findings regarding expedited OTM by adding MSCs to PDL.\textsuperscript{21}

As essential PDL mechanosensors, PDLSCs play a variety of roles in the orthodontic strength-induced remodeling of the alveolar bone and PDL that leads to OTM. The ability of PDLSCs to proliferate and differentiate into osteogenic tissue is altered by orthodontic pressure. They produce the receptor activator NF-B ligand (RANKL) and osteoprotegerin, which have an immediate impact on osteoclasts and osteogenesis (OPG).

Other regulatory chemicals that are produced by PDLSCs create signaling pathways with osteoblasts, osteoclasts, and osteocytes. Additionally, they release chemicals that are both anabolic and catabolic and that have a role in the remodeling of PDL’s extracellular matrix (ECM) during OTM.\textsuperscript{21,29} Furthermore, through secreting a variety of pro-inflammatory factors, PDLSCs seem to be the key players in causing orthodontic force-induced non-infectious inflammation.\textsuperscript{30,31}

Modulation of Immune Cells by PDLSCs in Different OTM Phases

It is postulated that the inflammatory response during OTM is very dynamic and particular to each phase of OTM.\textsuperscript{16} PDLSCs are essential local immune response modulators in the inflammatory milieu, having an impact on a range of immune cells including dendritic cells, T lymphocytes, B lymphocytes, granulocytes, and macrophages.\textsuperscript{32}

PDLSCs exert their immunomodulatory activity through a variety of mechanisms, including the expression of membrane-bound immunomediators like programmed cell death ligands 1 and 2, as well as soluble immunomediators like tumor necrosis factor-inducible gene 6 protein, indoleamine-2,3-dioxygenase-1, and prostaglandin E2. Since different cytokines, including TNF-, IL-1, and IFN-\alpha, induce the synthesis of immunomediators,\textsuperscript{33} the aseptic inflammatory milieu during OTM can modify the immunomodulatory features of PDLSCs, which affect immune cell activity and inflammatory responses.

Current research has shown that the immunomodulatory interaction between MSCs and immune cells is mediated via extracellular vesicles released by MSCs.\textsuperscript{34} The extent to which these immunomodulatory processes of PDLSCs

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may also alter aseptic inflammation is, however, not yet completely understood.

The substances transferring orthodontic force to PDLSCs

MicroRNAs, which are small non-coding RNAs that can be mechanically sensitive, are essential posttranscriptional regulators in the osteogenic differentiation of PDLSCs in response to orthodontic stress.\(^5\)\(^3\) 53 microRNAs, including hsa-miR-21, which was found to be important in strain-induced osteogenesis of PDLSCs in vitro, were differently expressed in PDLSCs following strain, according to microarray results.\(^3\)

Chen and colleagues found that miR-21 promoted force-induced alveolar bone production on the tension side during OTM in wild mice but was inhibited in miR-21 animals using a wild and miR-21-deficient (miR-21/+) mouse OTM paradigm.\(^3\) PDLSCs were also obtained for the first time from donors with or without OTM. In PDLSCs cultivated following OTM, miR-21 expression was raised along with an increase in osteogenesis, which was stopped by miR-21 suppression. Interestingly, enhanced osteogenesis in cultured PDLSCs persisted even after orthodontic force reduction, pointing to an epigenetic influence.

Recently, the activity of MSCs and the metabolism of bone have been linked to a gaseous transmitter termed H\(_2\)S.\(^3\) It has been established that nuclear factor-B/osteoprotegerin (RANKL/OPG) activator receptor ligand-regulated force-induced H\(_2\)S generation in PDLSCs affects the concentration of macrophages and osteoclastic and osteogenic activity in alveolar bone and subsequently controls the OTM process.\(^3\)

Applying orthodontic stresses increased H\(_2\)S generation and elevated cystathionine \(\beta\)-synthase (CBS) in PDL, according to Liu and colleagues’ research using a rat OTM model. Furthermore, CD90 is confined to the majority of the CBS expression (the MSC marker). Accordingly, alterations in CBS expression in PDLSCs were linked to compression-induced H\(_2\)S release in the supernatant of cultured PDLSCs. Additionally, by preventing endogenous H\(_2\)S production, the concentration of osteoblasts and macrophages caused by orthodontic force on the tension side and osteoclasts on the pressure side was reduced, as was the space between OTM. In order to transduce and react to orthodontic force stimulation, the study showed that PDLSCs produce H\(_2\)S.

CONCLUSION

Understanding the healing process during orthodontic tooth movement and the interaction between mechanical forces and stem cells would help orthodontists better manage orthodontic operations. A lighter force should be utilized during OTM, especially for patients with periodontitis, as it has been previously indicated that using too much force can harm the function of PDLSCs and other stem cells. PDLSCs have the potential to be employed for the repair of periodontal tissues, which could expedite orthodontic treatment operations because of their capacity for proliferation and differentiation. There are still a number of significant issues that require investigation, though.

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