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ROLE OF HEMATOPOETIC STEM CELL IN INFLAMMATORY RESPONSE DURING ORTHODONTIC TOOTH MOVEMENT : A NARRATIVE REVIEW

Dwi Rahmawati*, Alexander Patera Nugraha, I Gusti Aju Wahju Ardani, Ari Triwardhani and Ida Bagus Narmada

Department of Orthodontic, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.
*e-mail : dwi-rahmawati@fkg.unair.ac.id

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ABTRACT : The basic concept of Orthodontic Tooth Movement (OTM) for orthodontists is always interesting and important to know so that it can determine strategies to reduce orthodontic treatment time. The purpose of this narrative review is to describe the role of Hematopoietic Stem Cells (HSCs) in the inflammatory response during OTM as well as the blood circulation system during OTM. OTM can stimulate the biological response from periodontal tissue after orthodontic force is given. The resulting response during OTM was the remodelling of periodontal ligament and alveolar bone. OTM involves various chemical mediators including chemokines, cytokines, prostaglandins and bone cells such as osteoblasts and osteoclasts. HSCs are multipotent cells that play an important role during inflammation through the blood circulation system. OTM stimulates sterile inflammation that causes HSCs migration to injury area. HSCs are thought to have an important role during OTM by regulating inflammation so further research is needed on this matter.

Key words : Alveolar bone, hematopoietic stem cell, medicine, osteoclast, osteoblast.

INTRODUCTION

The orthodontic treatment involves the movement of teeth from a position to the desired position to get facial aesthetics and good stomatognathicsystem (Nugraha *et al*, 2020). The basic concept of orthodontic tooth movement (OTM) for orthodontists is always interesting to learn so that it can be used to determine strategies to reduce orthodontic treatment time. Various studies have been carried out using mechanical force from orthodontic appliance and also to understand cellular and molecular OTM (Sabane *et al*, 2016; Nugraha *et al*, 2019). The alveolar bone resorption and bone formation that resulted from the orthodontic force will facilitate the orthodontic tooth movement (Narmada *et al*, 2019). Osteoclast and osteoblast as bone cells play important role during bone remodelling (Rezkita *et al*, 2020). The initial phase, lag phase and post-lag phase were the three phases of OTM. Because of the orthodontic fore applied to the teeth, there will be compression and tensile in the periodontal ligament which will result in blood vessels extravasation, the inflammatory cells, osteoblastogenesis or osteoclastogenesis (Sitasari *et al*, 2020;).

Hematopoietic Stem Cells (HSCs) is a stem cell derived from blood in bone marrow. Blood cells produced by the proliferation and differentiation of a very small population of multipotent HSCs have the ability to differentiate and self-renewal. HSCs is a multipotent cell and is able to form and differentiate into all blood cells and immune cells (Rahmawati *et al*, 2019). Previous studies stated that HSCs was one of the main responses at injury. Pro-inflammatory cytokines would be released during infection or inflammation (King and Goodell, 2011). The purpose of this narrative review is to describe the role of HSCs in the inflammatory response during OTM as well as the blood circulation system during OTM.

Orthodontic Tooth movement

OTM is a biological response from orthodontic pressure, the resulting response being the remodelling of periodontal ligaments and alveolar bone (Hisham *et al*, 2019). OTM occurs due to cellular and molecular changes in periodontal tissue (Andrade *et al*, 2014). OTM consists of 3 phases: initial, lag, and postlag (Niklas *et al*, 2013). This initial phase occurs 24 to 48 hours after the use of orthodontic devices, which is characterized by the shifting of teeth into the periodontal ligament space with relatively fast movement (Ariffin *et al*, 2011). Cellular and tissue reactions in the initial phase begin to occur since they are powered by orthodontic devices. This reaction involves osteoblast progenitors, osteoclast progenitors, and inflammatory cells (Krishnan and Davidovitch, 2015).

Then, proceed with the lag phase that occurs for 20-30 days. In the lag phase the tooth movement that occurs is very minimal. This phase is characterized by the hyalinization of the periodontal ligament in the pressure region. Tooth movement will re-occur if necrotic tissue has been eliminated (Ariffin *et al*, 2011). This process involves phagocytic cells such as macrophages, foreign body giant cells, and osteoclasts to eliminate necrotic tissue, especially in pressure areas (Krishnan and Davidovitch, 2015). The post-lag phase will occur after the lag phase. In the post-lag phase, tooth movement increases again (Ariffin *et al*, 2011). OTM in the post-lag phase occurs due to alveolar bone remodeling by osteoclasts and osteoblasts. The periodontal tissue remodelling can occur due to the formation of new blood vessels mediated by hypoxia-inducible factor-1 (HIF-1), Vascular Endothelial Growth Factor (VEGF) and other biological agents such as Fibroblast Growth Factor (FGF), Tumor Necrosis Factor - alpha (TNF-α) and Transforming Growth Factor (TGF-β) (Feller *et al*, 2015; Inayati *et al*, 2020).

OTM is a complex biological process, orthodontic treatment will cause a local inflammation (Salomão *et al*, 2014). Inflammation that occurs is a physiological response from the load obtained by the periodontal tissue (d'Apuzzo *et al*, 2017). This inflammation is characterized by vasodilation of capillaries in periodontal tissue and migration of leukocytes from capillaries to periodontal tissue (Shintcovsk *et al*, 2014). These capillaries are biochemically induced to synthesize and secrete various pro-inflammatory cytokines and chemokines, growth factors, and enzymes (Di Domenico *et al*, 2012; Nareswari *et al*, 2019).

Orthodontic pressure will result in ischemia, vascular disorders, and hyaline zone formation in the periodontal ligament compression area. Whereas vasodilation of blood vessels will occur in periodontal ligament in the tensile region (Salomão *et al*, 2014). Changes in homeostasis and microcirculation of periodontal ligaments will result in the release of biological mediators such as cytokines, chemokines, growth factors, neurotransmitters, arachidonic acid metabolites, as well as several hormones that will stimulate bone resorption in areas of pressure and bone formation in the area of tensile (Andrade *et al*, 2014). Vascular, cellular and extracellular matrix changes that occur in the process of orthodontic tooth movement will trigger remodeling resulting in tooth movement (Salomão *et al*, 2014). Orthodontic treatment will lead to detection of bone resorption biomarkers such as Nuclear Factor of Activated T-cell 1 (NFATc1), Receptor activator of nuclear factor kappa-ligand (RANKL), and Sclerostin (Narmada *et al*, 2019; Hermawan *et al*, 2020). In the tensile area of OTM, bone formation marker will increase such as Runt-related transcription factor 2 (RUNX2), Osterix, Alkaline Phosphatase (ALP), Osteocalcin, Osteopontin, Osteonectin, and Osteoprotegerin (OPG) (Sitasari *et al*, 2020; Hisham *et al*, 2019)

Inflammation response in orthodontic tooth movement

In OTM, blood flow is reduced on compression side due to stressed PDL resulted cell apoptosis (Al-Ansari *et al*, 2015; Nareswari *et al*, 2019). Cell apoptosis also includes several osteocytes and osteoblasts in afflicted periodontal tissue. An acute inflammatory response will be occurred by releasing cytokines (Al-Ansari *et al*, 2015). Chemokine was secreted by monocytes during OTM such as monocyte chemo attract protein-1 (MCP-1) (Taddei *et al*, 2012). Osteoclast progenitor cells will differentiate intopre-osteoclasts and osteoclast into the bloodstream. At the firs hours of OTM, the inflammatory mediators, cytokines and cell will be secreted to the afflicted periodontal tissue (Al-Ansariet *et al*, 2015). Interleukin-1b (IL-b), tumor necrosis factor-alpha (TNF-α) were the cytokines that have important role during OTM (Garlet *et al*, 2007). IL-1benhance M-CSF and RANKL expression that help osteoclastogenesis. Meanwhile, prostaglandins E2 (PGE2) stimulate the osteoclast formation and activity through RANKL enhancement. OPG was secreted to control and regulated the osteoclast activity during bone resorption (Yasuda *et al*, 1998). Therefore, in order for OTMcan be done successfully, the OPG level must be less at the compression site (Al-Ansari *et al*, 2015).

Hematopoietic Stem Cell (HSCs)

Hematopoietic Stem Cells (HSCs) is a stem cell derived from blood in the bone marrow. Blood cells produced by the proliferation and differentiation of very small populations of multipotent HSCs have the ability to differentiate and self-renewal. Hematopoietic, consisting of many types of cells with special functions (Jos *et al*, 2006). Besides that HSCs is believed to only be able to proliferate and differentiate into Hematopoietic cell lineage. However, currently the concepts of HSC are developing and it has been reported by some researchers that HSC can also cause non-hematopoietic cell lineage such as osteogenic differentiation (Aggarwal, 2014; Rahmawati *et al*, 2019).

Inflammation: an important regulator of HSCs

Specific inflammatory signals such as cytokines and Toll-like receptors (TLRs) are important in determining HSCs role. Previous study conducted on mice and

zebrafish analysis have shown detailed mechanisms the inflammation can affect the proliferation, differentiation and self-renewal capacity of HSCs. HSCs will normally be in an inactive form through a combination of cell intrinsic transcription and epigenetic regulators together with IL-1 signalling to induce HSC proliferation (Pietras, 2017). In addition, Wnt / β-catenin signalling can regulate the osteoclastogenesis by RANKL transcription suppression and the enhancement of OPG expression (Spencer *et al*, 2006). The Frizzled related proteins suppress the Wnt and Frizzled ligands and Dickkopf (Dkks) and sclerostin proteins (Kobayashi *et al*, 2008; Kubota *et al*, 2008); Issack *et al*, 2008; Van Bezoojien *et al*, 2007).

Activation of specific transcription factors, especially Runx2 and activation of both Bone Morphogenic Protein (BMP) pathways and Wnt signaling together mediate endogenous mesenchymal stem cells (MSCs) to differentiate into osteogenic and induce osteoblastogenesis (Sari *et al*, 2019; Prahasanti *et al*, 2020). In turn, MSCs that differentiate into osteogenic will express the osteoblast marker such as osteocalcin, osteopontin, osteonectin, ALP, and type 1 collagen, and decrease aggrecan expression (Nugraha *et al*, 2018a-c; Nugraha *et al*, 2019b-c).

The mechanical loading in the bone during OTM can increase the canonical Wnt / β-catenin signaling through the activation of transcriptional osteogenic genes resulted the enhancement of differentiation of MSCs into osteogenic lineage and maturation of osteoblasts for bone formation (Robinson *et al*, 2006). Furthermore, in the context of OTM, the force exerted is transmitted through a matrix of tissue that is compressed to local cells in the periodontal ligament (PDL) and alveolar bone, increase pro-inflammatory cytokine and growth factors, in turn, triggers the remodelling of PDL and alveolar bone ultimately enabling OTM (Yamaguchi *et al*, 2007; Di Domenico *et al*, 2012).

CONCLUSION

From this narrative review can be concluded that, HSCs are multipotent cells that play an important role during inflammation through the blood circulation system. OTM stimulates sterile inflammation that causes HSCs migration to injury area. HSCs are thought to have an important role during OTM by regulating inflammation so further research is needed on this matter.

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