Digital Repository Universitas Jember

ISSN 0974-3618 (Print)
0974-360X (Online)
www.rjptonline.org
RJPT Research Journal of Pharmacy and Technology

RESEARCH ARTICLE

The Role of Stem Cell on Orthodontic Tooth Movement Induced-Alveolar Bone Remodeling

M. N. Amin[1]*, N. Permatasari[2]
[1]Department of Biomedical Science, Faculty of Dentistry, Jember University,
Kalimantan Street, No. 37, Jember, 68121, Indonesia.
[2]Pharmachology Department, Faculty of Medicine, Universitas Brawijaya,
Veteran Street, Malang, 65145, Indonesia.
*Corresponding Author E-mail: **m_nurul_amin.fkg@unej.ac.id**

ABSTRACT:
Alveolar bone tissue constantly undergoes remodeling through new bone formation and bone resorption. Osteoclasts originated from hematopoietic precursor cells and monocytes/macrophage lineage. In particular it will differentiate into mononuclear preosteoclasts and will merge into multinucleated osteoclast. Osteoblasts originated from undifferentiated mesenchymal stem cells. Osteoprogenitor cells evolved into preosteoblasts, and then into osteoblasts and osteocytes latter, which has the capability of bone mineralization and calcification. Orthodontic mechanical force responded directly by MSC to perform self-renewal and osteogenic differentiation, whereas HSC respond to mechanical force mediated by osteoblastic lineage cell in osteoclastic differentiation.

KEYWORDS: Stem cells, orthodontic tooth movement, alveolar bone remodeling.

INTRODUCTION:

The use of orthodontic appliances to correct malocclusion involves the process of alveolar bone remodeling. The process can be stimulated using a mechanical force obtained from the activation of appliance components applied to press the teeth and forwarded to the surrounding tooth tissues including gingiva, periodontal ligament and alveolar bone. Mechanical force causes the area around the teeth divided into two regions i.e. the compression area and tension area. In the compression area, the mechanical force will stimulate the osteoclast to perform alveolar bone resorption. On the other hand, in the tension area a new alveolar bone formation will be performed by osteoblasts[1].

Osteoclasts are giant cells with many cell nuclei found only in bone. Osteoclasts are originated from hematopoietic precursor cells, and are monocytes/macrophage lineages that will specifically form mononuclear preosteoclasts that will subsequently become multinucleated osteoclasts.

Received on 27.01.2022 Modified on 21.05.2022
Accepted on 03.11.2022 © RJPT All right reserved
Research J. Pharm. and Tech 2023; 16(1):123-128.
DOI: 10.52711/0974-360X.2023.00023

Osteoblasts are originated from undifferentiated MSCs. The osteoprogenitor cells develop into preosteoblasts, and subsequently become osteoblasts that have the ability to conduct mineralization and bone calcification. When bone formation process has been completed, the osteoblasts differentiate into osteocytes buried in bone[2]. Osteoclast precursor cells are identified as granulocyte macrophage colony forming units (CFU-GM), which develop into granulocytes, monocytes and osteoclasts CFU-GM derived cells differentiate into committed osteoclast precursors, which are postmitotic cells and combine to form multinucleated osteoclasts[3]. During the osteoclast differentiation process, the precursor cell expresses the c-Fms (M-CSF receptor) followed by RANK. M-CSF and RANKL produced by osteoblasts and play an important role in the osteoclast progenitors proliferation and differentiation[4]. Osteoblast is originated from Mesenchymal Stem Cells (MSC) in the bone marrow, differentiate into osteocytes and are immersed in calcified bone[5]. RANKL and RANK interactions will lead to osteoclast formation and differentiation stimulation through some osteoclastogenesis transcription factors activation[6].

Intercellular communication in bone remodeling processes requires modulation and formation of MSC

Digital Repository Universitas Jember

for osteoblasts, and hematopoietic stem cells (HSC) for osteoclasts. MSC is essential in improving bone and cartilage regeneration.[7,8] The optimal combination of MSCs with the right order improves the success of regeneration [9,10,11]. MSC culture expansion is needed to produce enough MSC and used as a framework for improving bone loss. Discerning selection of MSC sources will result in better quality of tissue repair[12]. On the other hand, HSC formation and propagation are strongly influenced by osteoclastic activity. Activated osteoclast activity inhibited by molecular and cellular interactions may lead to inhibition of HSC colonization. In addition, HSC may decrease in number due to selective osteoblasts reduction due to an increase in osteoblasts number related with an enlarged HSC pool size[13].

This study was aimed at explaining and understanding osteoclast and osteoblast stem cells in bone remodeling stimulated by the mechanical force of the orthodontic appliance.

Mesenchymal Stem Cells (MSC)

MSC is a multipotent stromal cell, can differentiate into several types of cells including chondrocytes, osteoblasts, myocytes, adipocytes and neurons. MSC has a small cell body with several long and thin cell extensions[14]. The cell body consists mostly of a round nucleus with a prominent nucleolus surrounded by flat scattered chromatin particles, thus it provides a clear appearance of the nucleus. Other parts of the cell body consist of small parts of the Golgi body, rough endoplasmic reticulum, mitochondria and polyribosome [15]. MSC resides in several places[16,17] i.e. developing tooth bud of the lower third molar, dentalpulp and gingiva[18,19,20], blood and umbilical cord tissue[21,22], amniotic fluid, and adipose tissue[23].

The International Society for Cellular Therapy (ISCT) has standards for the identification of MSC[24,25] as presented in following Table 1.

Table 1. Criteria for Identification of MSC [24]

1.	Adherence to plastic in standard culture conditions		
2.	Phenotype	Positive (≥ 95 % +)	Negative (≤2 % +)
		CD 105 CD 73 CD 90	CD 45 CD 34 CD 14 or CD 11b CD 79α or CD 19 HLA DR
3.	*In vitro* differentiation: osteoblast, chondroblast and adipocytes (demonstrated by staining of *in vitro* cel culture)		

Description:

CD34 (cluster of differentiation 34/Hematopoietic progenitor cell antigen CD34); SCA-1 (Stem cells antigen-1); CD59 (MAC-inhibitory protein (MAC-IP)/membrane inhibitor of reactive lysis (MIRL)/ protectin); Thy1 (Thymocyte differentiation antigen 1); CD38 (cluster of differentiation 38/cyclic ADP ribose hydrolase); C-kit (Mast/stem cell growth factor receptor (SCFR)/proto-oncogene c-Kit/tyrosine-protein kinase Kit/CD117); lin (lineage marker)

Hematopoietic Stem Cells (HSC):

HSC is a blood cell that produces all other blood cells and is originated from mesoderm. They reside in a red bone marrow contained in the middle on most of the bones. HSC is also defined as a cell with long-term and short-term regeneration capacities and is committed to multipotent, oligopotent, and unipotent progenitors[14]. HSC itself is a cell with a number 1: 10,000 in myeloid tissue. HSC produces blood cells from myeloid strains (macrophages, monocytes, neutrophils, basophiles, eosinophils, erythrocytes, megakaryocytes or platelets and dentriticcells) and lymphoid (B cells, T cells and natural killer cells)[26]. HSC microscopically has images like lymphocytes, i.e. non-adherent, spherical, spherical nucleus and low cytoplasm-to-nucleus ratio. HSC, at baseline/primitive conditions, cannot be separated as a pure cell population, making it impossible to identify on a microscope[27]. HSC is found in mature bone marrow, especially in the femur, pelvis and sternum. It is also found in small amounts of umbilical cord[21,22] and peripheral blood[27].

Some cell surface proteins in rats and humans can be used as markers for HSC identification when they are in undifferentiated state in vitro and in vivo[17]. When HSC begins to develop into cell lineages, these cell surface markers can no longer be used for identification[28]. These cell surface markers can be seen in Table 2.

Table 2. Cell Surface Markers in HSC Rat and Human[28]

Rat	Human
$CD34^{low/-}$	$CD34^{+}$
$SCA\text{-}1^{+}$	$CD59^{+}$
$Thy1^{+/low}$	$Thy1^{+}$
$CD38^{+}$	$CD38^{low/-}$
$C\text{-}kit^{+}$	$C\text{-}kit^{-/low}$
lin^{-}	lin^{-}

Description:

CD34 (cluster of differentiation 34/Hematopoietic progenitor cell antigen CD34); SCA-1 (Stem cells antigen-1); CD59 (MAC-inhibitory protein (MAC-IP)/membrane inhibitor of reactive lysis (MIRL)/ protectin); Thy1 (Thymocyte differentiation antigen 1); CD38 (cluster of differentiation 38/cyclic ADP ribose hydrolase); C-kit (Mast/stem cell growth factor receptor (SCFR)/proto-oncogene c-Kit/tyrosine-protein kinase Kit/CD117); lin (lineage marker)

DISCUSSION:

The mechanical forces generated by orthodontic

Digital Repository Universitas Jember

appliance activation imposed on teeth and periodontal tissues produce biophysical signals with different styles of force. Tension forces in alveolar bone and PDL have the ability to stimulate osteogenic gene expression required in the process of differentiating osteogenic progenitor cells becomes mature osteoblasts with osteoid precipitation occurring during mineralization. On the other hand, the compression forces on the PDL and alveolar bone stimulate RANK expression directly the action of IL-1β and prostaglandins, which initiate resorption by osteoclasts[29].

MSC Response to Mechanical force from Orthodontic Appliance:

The tension force on the MSC in the PDL will activate the signaling pathway mediated by the ERK protein kinase 1/2 (family of mitogen-activated protein kinase/MAPK molecules). The ERK 1/2 pathway activation causes the induction of the transcription factor Runx 2, which is an important regulator in osteogenic gene expression, triggering the osteogenic progenitor cells differentiation and maturation into osteoblasts, and then produce collagen type 1,alkaline phosphate and osteocalcin. In addition to the MAPK intracellular signaling pathway, c-JUN cascade N-terminal kinase (JNK) and p38 also play a role in osteoblasts[30,31].

In general, the mechanotransduction in MSC can be divided into several paths i.e. integral and Chaderin-mediated signaling focal adhesion (FA), signaling of soluble factors such as Wnt and TGF-β and Mechanosensitive Ion Channels (MIC). Several different signals include soluble-mediated factor transduction signal pathways, mechano-sensing cellular processes and unified mechano-transduction to activate intracellular intracellular signaling networks in an integrated and interactive manner regulating the fate of SC[32].

The mechanotransduction system through integrin signaling is played by focal adhesion kinase (FAK) and kinases of the Src family like fyn. The main downstream signaling pathway that follows the FAK/Src initiation is path of Ras-Raf-MEK-ERK, but the molecular mechanism by which integrins regulate MAPK remains unclear. Some possible pathways are integrin-(FAK)/(fyn-Shc)-Grb2-SOS-Ras or through an EGF receptor. Translocation of ERK into the nucleus can regulate gene expression through activating some required transcription factor[33,34].

The other racial downstream path is the PI3k/Akt path, can be initiated via integrin signaling. The pathway of PI3k/Akt is known to be important for SC self-renewal and differentiation. Paling et al[35] reports that PI3k signaling is activated through LIF and needed to maintain SC self-renewal, and one of the downstream signaling goals for PI3k/Akt is Nanog[36].

RhoA is the main molecular regulator of actinous cytoskeleton pressure and focal adhesion (FA) formation, often referred to as upstream regulator integrin, by the action of the Rho-kinase effectors (ROCK). Signaling RhoA/ROCK also acts as a downstream signaling target mediated by the activated FAT[37]. RhoA can be initiated by different cytokines and growth factors as well as biophysical signals from their cellular microenvironment. The functional role of RhoA /ROCK mediated by cytoskeleton contractility is required for lineage commitments from MSC. Activated RhoA triggers MSC osteogenesis through the regulation of Runx2 expression, when RhoA is inhibited causing MSC adipogenesis. In response to the activation of RhoA/ROCK signaling, an intact actin cytoskeleton structure is required for MSC differentiation in mechanoresponsiveness. RhoA/ROCK-mediated cytoskeletal contactivity may directly regulate multiple gene expression of the transcription factor (e.g. PPAR-γ and Sox-9) to affect differentiation of SC[38].

Dupont et al[39] explains that an alternative signaling pathway have an important role in determining the fate of SC is the Hippo pathway. The effector targets of this pathway are Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ), and like β-catenin also translocates into the nucleus and regulates gene expression. The YAP/TAZ pathway is essential for responding to changes in substrate stiffness and cell shape. This pathway is also known to be important in the process of osteogenic differentiation of human bone marrow from MSC derivates, by removing obstacles from the YAP and TAZ pathways, and normally will trigger osteogenic differentiation process.

The second signaling of mechanotransduction is the soluble-mediated signaling, including Wnt, TGF-β and other factors. Signaling Wnt / β-catenin can regulate the decision of the fate of SC. Expression, nuclear translocation and β-catenin accumulation on the Wn canonical path are regulated by Dvl. Wnt and integrin signaling interactions occur through two distinct pathways: integrin-linked kinase (ILK) and FAK. ILK plays a role for stabilizing and/or stimulating nuclear accumulation of β-catenin, whereas other pathways, Grb2 integrate with integrin signaling via FAK by Wnt signaling through Dvl and jnk, where Dvl and Jnk are downstream kinases of Grb2 and stimulate β-catenin to the nucleus translocation. β-catenin translocation will subsequently activate the Runx2 gene. In addition to SC levels, Wnt signaling generated by biophysical signals can directly regulate osteoblasts. When mechanical

Digital Repository Universitas Jember

forces are applied, Wnt signaling can decrease the expression of β-catenin even though it initially increases the β-catenin expression[40]. Other researchers mentioned that the osteogenic differentiation process of MSC, played by the cooperation between canonical Wnt and BMP. BMP, specifically BMP-2 induces p300-mediated acetylation Runx2 which results in increased Runx2 capability. This shows that there is cooperation between BMP and canonical Wnt in regulating Runx2[41].

TGF-β plays a major role in inhibiting cell proliferation, which is associated with maintaining SC in quiescent states[42], and several other studies suggest that TGF-β plays an important role in maintaining pluripotency of SCs through Smad2/3 signaling[43]. Besides playing an important role in signal transduction through the Smad2/3 signaling line, TGF-β can also activate other important signaling pathways e.g. PI3k, MAPK and Rho/ROCK[44]. Signaling linkages between integrin and TGF-β can be explained that integrins can directly regulate TGF-β activation through cellular attraction given by actin cytoskeleton and G-protein coupled receptors (GPCR). But integrins can indirectly control the TGF-β pathway by activating the release of TGF-β from ECM when there is a mechanical force from outside the cell. TGF-β may regulate the actin cytoskeleton via the RhoA/ROCK pathways[45].

The third signaling of mechanotransduction is MIC-mediated signaling. MIC may be related to the extracellular matrix and/or cytoskeleton, as well as the relative changes of the pathway associated with the extracellular matrix or cytoskeleton as the pathway opening response. Thus, MIC is directly initiated by external forces or intracellular cytoskeleton contactivity[45]. The main downstream effect of MIC activation is the change in cytoplasmic Ca2+ concentration corresponding to the size of the force. Some studies suggest that changes in Ca2+ concentrations observed in MSC act as indicators and regulators of MSC differentiation[46]. Kim et al[47] mentioned that changes in Ca2+ concentrations indicate mechanical forces have the important role to directly regulate the fate of SC through modulating calcium signals.

HSC Response to Mechanical Force from Orthodontic Appliance:

In the opposite area i.e. the compression area, alveolar bone resorption processes require modulation of endosteal HSC nerve formation. Regulation of alveolar bone resorption is preceded by the recruitment of osteoclast precursor cells, all of which are mediated by osteoblastic lineage cells. This cooperation requires cellular contact, cytokine production and the formation of factor coupling during the process[48]. Osteoblasts and other mesenchymal cells e.g. perivascular primitive mesenchymal cells, provide a niche in which HSC is exposed to molecular signals like cytokines, chemokines and growth factors, which control self-renewal, proliferation, apoptosis, differentiation, homing, quiescence, and others[49]. On selective removal of osteoblasts causes a reduction in the number of HSCs where osteoblast increase is associated with an increase in HSC pool size in bone marrow. The effects of osteoblasts are due to direct cell interactions with HSCs through Jagged 1 (Jag-1) osteoblast and Notch receptor signaling on HSC which leads to an increase in HSC pool and signaling through the stromal Angiopoietin 1 (Ang-1) and Tie-2 receptor on HSC causing preserved HSC quiescence in the niche[50].

The next stage in HSC or osteoclast precursor cells as a response of mechanical force is the mobilization of osteoclast precursors including the release of cells into the circulation of bone marrow and homing from the bloodstream to the tissues. This mobilization of osteoclast precursors requires a variety of molecules and includes cytokines like granulocyte-macrophage colony stimulating factor (GM-CSF), IL-1β, IL-7, IL-3, IL-12, stem cell factor (SCF) and flt-3 ligand (Flt-3L), chemokines include IL-8, macrophage inflammatory protein-1α (MIP-1α) and stromal cell-derived factor-1 (SDF-1)[51]. SDF-1 is the most important chemoattractant for SC, which is an SC survival factor and is also as an SC attachment regulator with ECM or with stromal cells. When SDF-1 binds to its receptor CXCR4 makes a strong retention signal for HSC and progenitor cells fixed in the niche[52]. Decreasing concentration of SDF-1 and CXCR4 expression by some factors including mechanical forces can cause cell release into the blood circulation towards the target tissue. In addition, there are three chemokines to draw osteoclast progenitor cells to the desired tissue of CK β-8, regulated upon activation of T-expressed and secreted (RANTES) and MIP-1α cells. These three chemokines are produced by osteoblasts, osteoclasts and T cells and bind to CCR1 and CCR5 receptors in osteoclast progenitor cells. Once in the tissue, the osteoclast progenitor cells will continue the process of differentiation into mature cells by the help of other cytokines[53].

The involvement of osteoblastic lineage cells is needed in affecting the fate of HSC. Osteoblastic lineage cells prove osteopontin (OPN) act as a negative regulator of HSC pool size inhibiting HSC proliferation, trigger HSC apoptosis and affecting Jag-1 and Ang-1 expression by stromal cells. Stromal-derived factor-1 (SDF-1) produced by mesenchymal cells and osteoblasts is a major chemoattractant as some hematopoietic progenitors, including HSC[54].

Digital Repository Universitas Jember

On the other hand, osteoclast is also involved in mobilizing HSC in response to stress and pharmacological treatment. Activation of osteoclasts in HSC stress-induced mobilization through the production of proteolytic enzymes required for the stability of HSC niches. Osteoclast inhibition also increases HSC mobilization and reduces the primitive amount of HSC in bone marrow[55]. Thus, the modulation of osteoclast activity will have an impact on HSC. In particular, in rats lacking osteoclast activity causes severe osteopetrosis associated with extramedullary hematopoiesis. This suggests that osteoclasts play a role not only in regulating or preserving but also in the early formation of HSC niches[56].

CONCLUSION:

It can be concluded that the mechanical force received by the mechanically induced alveolar bone remodeling process is responded directly by the MSC through several mechanisms to differentiate into osteoblasts, whereas HSCs cannot response directly to differentiate into osteoclasts but it is mediated by cells osteoblastic lineage including MSC.

CONFLICT OF INTEREST:

The authors declare no conflict of interest.

REFERENCES:

1. Krishnan V. Davidovitch Z. On A Path to Unfolding The Biological Mechanisms of Orthodontic Tooth Movement. Journal of Dental Research. 2009; 88: 597 – 608.https://doi.org/10.1177/0022034509338914
2. Senba M. KawaiK. Mori N. Pathogenesis of Metastatic Calcification and Acute Pancreatitis in Adult T-Cell Leukemia under Hypercalcemic State. Leukemia Research and Treatment2012: 1- 10.https://doi.org/10.1155/2012/128617
3. Menaa C. KuriharaN.RoodmanGD. CFU-GM derived cells form osteoclasts at a very high efficiency. Biochemical and Biophysical Research Communications.2000; 267(3): 943–946. https://doi.org/10.1006/bbrc.1999.2042
4. Lacey DL. TimmsE. Tan HL. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell. 1998; 93(2): 165–176. https://doi.org/10.1016/s0092-8674(00)81569-x
5. Suda, MJATTakahashi N. Contributions to osteoclast biology from Japan. Proc JpnAcad Ser B Phys Biol Sci. 2008 Dec; 84(10): 419–438.
1. https://doi.org/10.2183/pjab/84.419
6. Blair JM. Zheng Y. DunstanCR. RANK ligand. Int J Biochem Cell Biol. 2007;39(6):1077-81. https://doi.org/10.1016/j.biocel.2006.11.008
7. Selvi ST. Stem Cell Therapy. Int. J. Adv. Nur. Management. 2017; 5(4): 361-364. https://doi.org/ 10.5958/2454-2652.2017.00077.4
8. Ramadhani NF.Nugraha AP. Ihsan IS. Agung YO.Rantam FA.Ernawati DS.Rini RidwanD. Narmada IB.AnsoriANM.HayazaS. NoorTNEBTA. Gingival Medicinal Signaling Cells Conditioned Medium effect on the Osteoclast and Osteoblast number in Lipopolysaccharide-induced Calvaria Bone Resorption in Wistar Rats' (Rattus novergicus). Research Journal of Pharmacy and Technology. 2021; 14(10):5232-7. https://doi.org/10.52711/0974-360X.2021.00911
9. Arthur A.Zannettino A.Gronthos S. The Therapeutic Applications of Multipotential Mesenchymal/Stromal Stem Cells in Skeletal Tissue Repair. J Cell Physiol. 2009 Feb;218(2):237-45. https://doi.org/10.1002/jcp.21592
10. Kumar RK. Research J. Pharm. and Tech 2018; 11(4): 1530-1534. https://doi.org/10.5958/0974-360X.2018.00285.8
11. DikshaSP. Role of Stem Cells in treatment of different Diseases. Research J. Pharm. and Tech 2018; 11(8): 3667-3678. https://doi.org/10.5958/0974-360X.2018.00674.1
12. Jones E. Yang X. Mesenchymal stem cells and bone regeneration: current status. Injury. 2011 Jun;42(6):562-8. https://doi.org/10.1016/j.injury.2011.03.030
13. Mansour A.Abou-Ezzi G.Sitnicka E. Jacobsen SE.Wakkach A. Blin-Wakkach C. Osteoclasts promote the formation of hematopoietic stem cell niches in the bone marrow. J Exp Med. 2012 Mar 12;209(3):537-49. https://doi.org/10.1084/jem.20110994
14. KumariR. Stem Cell. Int. J. Nur. Edu. and Research. 2018; 6(4):443-446. https://doi.org/10.5958/2454-2660.2018.00107.2
15. Salazar KD. Lankford SM. Brody AR. Mesenchymal stem cells produce Wnt isoforms and TGF-beta1 that mediate proliferation and procollagen expression by lung fibroblasts. Am J Physiol Lung Cell Mol Physiol. 2009 Nov;297(5):L1002-11. https://doi.org/10.1152/ajplung.90347.2008
16. Wei X. Yang X. Han ZP. Qu FF. Shao L. Shi YF. Mesenchymal stem cells: a new trend for cell therapy. Acta Pharmacol Sin. 2013 Jun;34(6):747-54. https://doi.org/10.1038/aps.2013.50
17. Manjusha P. Yeole, Shailju G. Gurunani, Yogesh N. Gholse. Stem Cell Techniques. Research J. Pharm. and Tech. 6(3): March 2013; Page 304-306.
18. Septiana P. Suciadi, Alexander P. Nugraha, Diah S. Ernawati5, Nurina F. Ayuningtyas5, Ida B. Narmada, Chiquita Prahasanti, AristikaDinaryanti, IgoSyaiful Ihsan, Eryk Hendrinto, Helen Susilowati, Fedik Abdul Rantam. The Efficacy of Human Dental Pulp Stem Cells in regenerating Submandibular Gland Defects in Diabetic Wistar Rats (Rattus novergicus). Research J. Pharm. and Tech. 2019; 12(4):1573-1579. https://doi.org10.5958/0974-360X.2019.00261.0
19. Timothy CN.Samyuktha PS. BrundhaMP. Dental pulp Stem Cells in Regenerative Medicine – A Literature Review. Research J. Pharm. and Tech 2019; 12(8):4052-4056. https://doi.org/10.5958/0974-360X.2019.00698.
20. NugrahaAP.RezkitaF.PuspitaningrumMS.LuthfimaidahMS. NarmadaIB.PrahasantiC.ErnawatiDS.RantamFA. Gingival Mesenchymal Stem Cells and Chitosan Scaffold to Accelerate Alveolar Bone Remodelling in Periodontitis: A Narrative Review. Research J. Pharm. and Tech 2020; 13(5):2502-2506. https://doi/10.5958/0974-360X.2020.00446.1
21. Balaji S. Umbilical cord blood as a source of stem cells. Research J. Pharm. and Tech. August, 2015; 8(8):1093-1095. https://doi.org/10.5958/0974-360X.2015.00190.0
22. AzeemS. RajS. KajalK. ThiagarajanP. Umbilical Cord Stem Cells: A Review. Research J. Pharm. and Tech 2018; 11(6): 2709-2714. https://doi.org/10.5958/0974-360X.2018.00500.0
23. Fedik AR.NugrahaAP.FerdiansyahF.Purwati P.Bumi C.SusilowatiH.HendriantoE.NovembriD.SurotoUH.SumartonoC.SetiawatiR.PrakoeswaCR.IndramayaDM. A Potential Differentiation of Adipose and Hair Follicle-derived Mesenchymal Stem Cells to Generate Neurons Induced with EGF, FGF, PDGF and Forskolin. Research J. Pharm. and Tech. 2020; 13(1): 275-281.https://doi.org/10.5958/0974-360X.2020.00056.6
24. Dominici M. Le Blanc K. Mueller I.Slaper-Cortenbach I. Marini F. Krause D. Deans R. Keating A.ProckopDj. Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;8(4):315-7. https://doi.org/10.1080/14653240600855905
25. Lv FJ. Tuan RS. Cheung KM. Leung VY. Concise review: the surface markers and identity of human mesenchymal stem cells. Stem Cells. 2014 Jun;32(6):1408-19. https://doi.org/10.1002/stem
26. Eaves CJ. Hematopoietic stem cells: concepts, definitions, and the

Digital Repository Universitas Jember

new reality. Blood. 2015 Apr 23;125(17):2605-13. https://doi.org/10.1182/blood-2014-12-570200

27. Dzierzak E. Speck NA. Of lineage and legacy: the development of mammalian hematopoietic stem cells. Nat Immunol. 2008 Feb;9(2):129-36. https://doi.org/10.1038/ni1560
28. Krause DS.Theise ND. Collector MI.Henegariu O. Hwang S. Gardner R.Neutzel S.Sharkis SJ. Multi-organ, multi-lineage engraftment by a single bone marrow-derived stem cell. Cell. 2001 May 4;105(3):369-77. https://doi.org/10.1016/s0092-8674(01)00328-2
29. Feller L.Khammissa RA. Schechter I.Thomadakis G. Fourie J.Lemmer J. Biological Events in Periodontal Ligament and Alveolar Bone Associated with Application of Orthodontic Forces. ScientificWorldJournal. 2015;2015:876509. doi: 10.1155/2015/876509
30. Zhang P. Wu Y. Jiang Z. Jiang L. Fang B. Osteogenic response of mesenchymal stem cells to continuous mechanical strain is dependent on ERK1/2-Runx2 signaling. Int J Mol Med. 2012 Jun;29(6):1083-9. https://doi.org/10.3892/ijmm.2012.934
31. Zhu J. Zhang X. Wang C. Peng X. Zhang X. Different magnitudes of tensile strain induce human osteoblasts differentiation associated with the activation of ERK1/2 phosphorylation. Int J Mol Sci. 2008 Dec;9(12):2322-2332. Httpdz;//doi.org/10.3390/ijms9122322
32. Sun Y. Chen CS. Fu J. Forcing stem cells to behave: a biophysical perspective of the cellular microenvironment. Annu Rev Biophys. 2012;41:519-42. https://doi.org/10.1146/annurev-biophys-042910-155306
33. Parsons JT. Focal adhesion kinase: the first ten years. J Cell Sci. 2003 Apr 15;116(Pt 8):1409-16. https://doi.org/10.1242/jcs.00373
34. Webb DJ.Donais K. Whitmore LA. Thomas SM. Turner CE. Parsons JT. Horwitz AF. FAK-Srcsignalling through paxillin, ERK and MLCK regulates adhesion disassembly. Nat Cell Biol. 2004 Feb;6(2):154-61. https://doi.org/10.1038/ncb1094
35. Paling NR.Wheadon H. Bone HK. Welham MJ. Regulation of embryonic stem cell self-renewal by phosphoinositide 3-kinase-dependent signaling. J Biol Chem. 2004 Nov 12;279(46):48063-70. https://doi.org/10.1074/jbc.M406467200
36. Storm MP. Bone HK. Beck CG.Bourillot PY. Schreiber V. Damiano T. Nelson A.Savatier P. Welham MJ. Regulation of Nanog expression by phosphoinositide 3-kinase-dependent signaling in murine embryonic stem cells. J Biol Chem. 2007 Mar 2;282(9):6265-73. https://doi.org/10.1074/jbc.M610906200
37. DuFort CC.Paszek MJ. Weaver VM. Balancing forces: architectural control of mechanotransduction. Nat Rev Mol Cell Biol. 2011 May;12(5):308-19. https://doi.org/10.1038/nrm3112
38. Arnsdorf EJ.Tummala P. Kwon RY. Jacobs CR. Mechanically induced osteogenic differentiation--the role of RhoA, ROCKII and cytoskeletal dynamics. J Cell Sci. 2009 Feb 15;122(Pt 4):546-53. https://doi.org/10.1242/jcs.036293
39. Dupont S. Morsut, L. Aragona M. et al. Role of YAP/TAZ in mechanotransduction. Nature. 2011; 474:179–183. https://doi.org/10.1038/nature10137
40. Crampton SP. WuB. ParkEJ. Jai-Hyun K. Solomon C. WatermanML. HughesCCW. Integration of the β-catenin-dependent wnt pathway with integrin signaling through the adaptor molecule grb2. PLoS One. 2009; 4(11): e7841.https://doi.org/10.1371/journal.pone.0007841
41. Kolf CM. Cho E, Tuan RS. Mesenchymal stromal cells. Biology of adult mesenchymal stem cells: regulation of niche, self-renewal and differentiation. Arthritis Res Ther. 2007;9(1):204. https://doi.org/10.1186/ar2116
42. Blank U. Karlsson G. Karlsson S. Signaling pathways governing stem-cell fate. Blood. 2008 Jan 15;111(2):492-503. https://doi.org/10.1182/blood-2007-07-075168
43. James D. Levine AJ. Besser D.Hemmati-Brivanlou A. TGFbeta/activin/nodal signaling is necessary for the maintenance of pluripotency in human embryonic stem cells. Development. 2005 Mar;132(6):1273-82. https://doi.org/10.1242/dev.01706
44. Moustakas A.Heldin CH. Non-Smad TGF-beta signals. J Cell Sci. 2005 Aug 15;118(Pt 16):3573-84. https://doi.org/10.1242/jcs.02554
45. Hayakawa K. Tatsumi H.Sokabe M. Actin stress fibers transmit and focus force to activate mechanosensitive channels. J Cell Sci (2008) 121 (4): 496–503.https://doi.org/10.1242/jcs.022053.
46. Maeda T. Sakabe T. Sunaga A. Sakai K. Rivera AL. Keene DR. Sasaki T. Stavnezer E. Iannotti J. Schweitzer R. Ilic D. Baskaran H. Sakai T. Conversion of mechanical force into tgf-β-mediated biochemical signals. Curr Biol. 2011 Jun 7;21(11):933-41. https://doi.org/10.1016/j.cub.2011.04.007.
47. Sun, S. Liu YM. Lipsky S. Cho M. Physical manipulation of calcium oscillations facilitates osteodifferentiation of human mesenchymal stem cells. FASEB J. 2007 May;21(7):1472-80. doi: 10.1096/fj.06-7153com
48. Kim TJ.Seong JH. Ouyang MX. Sun J. Lu SY. et al. Substrate rigidity regulates ca2+ oscillation via rhoa pathway in stem cells. J Cell Physiol. 2009 Feb; 218(2): 285–293. https://doi.org/10.1002/jcp.21598.
49. Martin TJ. Sims NA. Osteoclast-derived activity in the coupling of bone formation to resorption. Trends Mol Med. 2005 Feb;11(2):76-81. https://doi.org/10.1016/j.molmed.2004.12.004.
50. Méndez-Ferrer S. Michurina T. Ferraro F. et al. Mesenchymal and haematopoietic stem cells form a unique bone marrow niche. Nature 466, 829–834 (2010). https://doi.org/10.1038/nature09262
51. ZhongJ. RajagopalanS. Dipeptidyl peptidase-4 regulation of SDF-1/CXCR4 axis: implications for cardiovascular disease.Front Immunol. 2015; 6: 477. https://doi.org/10.3389/fimmu.2015.00477
52. Arai F. HiraoA. OhmuraM. SatoH. Matsuoka S. TakuboK. Ito K. KohGY.SudaT. Tie2/angiopoietin-1 signaling regulates hematopoietic stem cell quiescence in the bone marrow niche. Cell. 2004 Jul 23;118(2):149-61. https://doi.org/10.1016/j.cell.2004.07.004
53. Soysa NS. AllesN. AokiK.OhyaK. Osteoclast Formation and Differentitation: An Overview. J Med Dent Sci. 2012 Nov 8;59(3):65-74. PMID: 23897045.
54. Dar A. KolletO. LapidotT. Mutual, reciprocal SDF-1/CXCR4 interactions between hematopoietic and bone marrow stromal cells regulate human stem cell migration and development in NOD/SCID chimeric mice. Exp Hematol. 2006 Aug;34(8):967-75. https://doi.org/10.1016/j.exphem.2006.04.002
55. Lymperi, S. ErsekA. FerraroF. DazziF. HorwoodNJ. Inhibition of osteoclast function reduces hematopoietic stem cell numbers in vivo. Blood. 2011 Feb 3;117(5):1540-9. https://doi.org/10.1182/blood-2010-05-282855.
56. Blin-Wakkach C. WakkachA. Rochet N. Carle GF. Characterization of a novel bipotent hematopoietic progenitor population in normal and osteopetrotic mouse. J Bone Miner Res. 2004 Jul;19(7):1137-43. https://doi.org/10.1359/JBMR.040318