AJDS LAZHAR Al-Azhar Journal of Dental Science Vol. 21- No. 5- 433:441- December 2018
Record 1110-2624 | the ISSN Portal portal.issn.org

STEM CELLS IN ORTHODONTICS : A REVIEW

Yasser Mohammad El-Sayed Hassouna*, Ashraf Atia Ali El-Bedwehi**, Aldany Atwa Mohamed***, Wael Abo-Elkhair Mostafa****, Mohamed Abdel-Akher Mohamad Omar*****

ABSTRACT

Stem cells SCs are undifferentiated cells capable of self-renewal and differentiation into multiple functional cell types .This review article provided a new insights into understanding the role of stem cells in orthodontics. Stem cells therapy, Characteristics and types of stem cells especially dental pulp stem cells is discussed. Isolation and differentiation of dental pulp stem cells This article gave an idea about Biomaterials used in craniofacial tissue regeneration and the applications of dental pulp stem cells DPSCs as well as future advantages of stem cells therapy in orthodontics.

INTRODUCTION

Stem cells SCs are undifferentiated cells capable of self-renewal and differentiation into multiple functional cell types. These cells can widely be used in wounds to promote repair and tissue regeneration.[1–3] All stem cells, regardless of their source, have three general properties, which make them different from other cells in the body:

a. Stem cells are unspecialized/ undifferentiated and such character is one of their essential properties.

b. Unspecialized stem cells can give rise to specialized cell types through differentiation process.

c. Stem cells are able to divide and renew themselves- unlike muscle cells, blood cells or nerve cells, which normally do not replicate themselves, stem cells may duplicate many times. If the resulting stem cells continue to be unspecialized, like the parent stem cells, the cells are said to be capable of long term self-renewal.[1–3]

Stem cells therapy:

Stem cells therapy represents a branch of a wider base which is known by tissue engineering that contains different approaches such as cell injection, cell induction and cell seeded scaffold. These approaches depend on the use of one or more key elements e.g., cells, growth factors and matrix to guide tissue regeneration.[4]Cell-based therapy is a promising approach in tissue regeneration. However, a purely cellular treatment cannot be always applied so there is an increased interest in using a combination of cells, matrix and other bioactive agents.[5]

Characteristics of stem cells:

Stem cells classified according to characteristics to:

1. **Totipotency**: Is the ability of definite type of cells to Produce all types of cells as well as germ cells or Embryonic Stem Cells ESCs, which also named omnipotent.

* Orthodontist Maadi Military Hospital Cairo, Egypt.
** Professor of Orthodontics Vice president for girls branch Al-Azhar University Egypt.
*** Professor of Orthodontics, Orthodontic Department, Faculty of Dental Medicine (Boys), Al-Azhar University, Cairo, Egypt.
**** Professor of Microbiology and Immunology, Military Medical Academy Egypt.
***** Professor of oral and Maxillofacial Surgery, Dean of Faculty of Dental Medicine (Boys),Al-Azhar University, Cairo Egypt.

2. **pluripotency**: Is the ability of Producing all types of cells apart from cells of the embryonic membrane.
3. **Multipotency**: Is the ability to distinguish into more than one adult cell type such as Mesenchymal Stem Cells MSCs.
4. **Unipotency**: And called also dedicated progenitors: produce one particular cell type.[6]

Types of stem cells:

Human stem cells can be categorized into three main categories embryonic, germinal and somatic:

1. Embryonic stem cells ESCs originate from the inner cell mass of the blastocyst. ESCs are omnipotent having unlimited power of division and have indefinite replicative life span.[2,7]
2. Germinal stem cells GSCs are derived from primary germinal layers of embryo. They differentiate into progenitor cells to produce specific organ cells.[2]
3. Somatic/adult stem cells are progenitor cells as they are less totipotent i.e. less replicative life span than ESCs. They exist in mature tissues such as hematopoietic, neural, gastrointestinal and Mesenchymal tissues.[2]

Dental pulp stem cells DPSCs:

The existence of stem cells within tooth was reported for the first time in the new millennium after isolation of cells with high proliferative potential for self-renewal from adult human dental pulp that were capable to develop into multiple cell lineages in vitro.[2,8] So far five different human dental-tissue- derived stem/progenitor cells have been isolated and characterized.[2,9]

The dental pulp tissues containing cell reach zone which is the source of Dental pulp stem cells DPSCs, is thought to be derived from migrating neural crest cells during development. A cell type of mesenchymal origin showing high proliferation and plasticity, represented an emerging source of adult stem cells offering fascinating features in consideration of potential applications in regenerative medicine.[10]

Dental Pulp tissue is extracted from the teeth removed during routine dental procedure throughout the life and these teeth are the most convenient and valuable source of DPSCs which are well characterized as a Mesenchymal Stem Cells MSCs.[11]Routine Extraction of teeth is a non invasive process of gaining MSCs from dental pulp tissue. DPSCs can be cryopreserved and revived whenever; they are needed for future regenerative therapies.[11,12]

Some of the diseases which are being cured by DPSCs include type 1 diabetes, neurological diseases, Immunodeficiency diseases and diseases of bone and cartilages.[8,11–14]

Sources of Dental Stem Cells DSCs:

DPSCs were obtained from human permanent and primary teeth[11,15], human wisdom teeth which were evaluated and their rate of impaction was discussed[16–19], human exfoliated deciduous teeth SHEDs, and apical papilla.[11,155] Other sources of dental stem cells are the periodontal ligament, which houses Periodontal Ligament Stem Cells PDLSCs, and the dental follicle, which contains Dental Follicle Progenitor Cells DFPCs .[16,20]

Stem Cells from Apical Papilla SCAP are the cells which are found at the tooth root apex. They have higher proliferation rates more over have a differentiation property in vitro similar to DPSCs. They are capable of differentiating into odontoblast cells and produce dentin in vivo. Due to their higher proliferative potential, SCAPs are also suitable for cell-based therapy for formation of apex roots. Human periodontal ligament stem cells DLSCs can differentiate into cementoblast-like cells. They also have a capacity to form connective tissue which is rich in collagen I fibers.[6,16]

DPSCs or stem cells from human exfoliated deciduous teeth SHED cells require a longer time for initial colony formation than other somatic cells.[21] Also It has been reported that DPSCs can be differentiated by modulation with growth factors, transcriptional factors, extracellular matrix proteins and receptor molecules into different cell types include odontoblast, osteoblast, chondrocyte, cardiomyocytes, neuron cells, adipocyte, corneal epithelial cell, melanoma cell and insulin secreting Beta cells.[11,16]

Isolation of dental pulp stem cells DPSCs:

In order to extract the pulp tissues the extracted teeth were grooved using dental fissure burs without exposing the pulp chamber and cut into two-halves using a dental cutter. The pulp tissues were extracted using a barbed broach (size 10).[22] Study of the HDPSCs was performed in vitro through laboratory investigations and in vivo in laboratory animals.[8]

The isolated DPSCs was cultured and expanded to increase their number in appropriate cultures in a process called passaging, in such media the cells have better differentiation, gene expression, response to stimulation, drug metabolism, and an overall level of functioning; they are closer to the in vivo state and have high viability.[23] The differentiation capacity of these DPSCs changes during cell passaging, and DPSCs at the 9th passage restrict their differentiation potential to the osteoblast lineage in vivo.[24]

The same concept was done in one of many studies proving the characters of HDPSCs. Vascularity of tissue engineered bone using HDPSCs and Bioglass scaffolds was tested in vitro using monocellular layer medium and in vivo through implantation of stem cells in laboratory mices. the study suggested that the combination of HDPSCs with Bioglass scaffolds offers a promising strategy for regenerating vascularized bone grafts.[25]

Isolation of stem cells from human dental pulp could be performed through several methods based on many experiments and investigations. Some of these methods were explained through comparing between the following techniques:

a. Dental pulp tissues were digested with collagenase or dispase enzyme and isolated trypsinised cells are plated in culture dishes.

b. Dental pulp tissues were explanted undigested dental pulp small tissue pieces directly to petridishes.

c. Dental pulp tissues were initially trypsinised and then small tissue pieces were explanted to petridishes for their outgrowth. [26]

They have grown these cultures in Minimum Essential Medium MEM supplemented with 20% Fetal Bovine Serum FBS at 37˚C with 5% CO_2 and 90% humidity in CO_2 incubator. They Resulted that the third method gave better cell outgrowth with achieving confluency at 60% within 2 days of culture. They have recommended the use of the third method for isolation of DPSCs from human dental pulp tissues. [19,26]

Isolation of human DPSCs from extracted teeth was to freeze and then to store at –196˚C for 24h. During freezing, the cells were suspended in freezing media containing 10% dimethyl sulfoxide DMSO. This method resulted an increase of the survival rates of revived DPSCs by 2 to 2.5 folds.[11,16,27]

A different method of isolation was through studying 4 human deciduous whole teeth, cryopreserved by making micro-channels into the tooth with the help of laser beam and then these cells were preserve at –80˚C. This method resulted saving the time in isolating DPSCs before cryopreservation and thus the initial costs and workload of tooth banking was reduced. The DPSCs cells have shown normal morphology, cell viability and proliferation rate as well as maintain

normal mesenchymal phenotype, similar to those of cells isolated from fresh non-cryopreserved teeth. They have further shown that DPSCs isolated without laser piercing have significant loss of cell viability and proliferation rate as compared to teeth cryopreserved by leaser piercing.[10,11,16,27]

Differentiation of Dental Pulp Stem Cells DPSCs:

DPSC represent a rapidly proliferating cell population that readily differentiates into the osteoblastic, neural, myocytic, and hepatocytic lineages. This multi-lineage capacity of these DPSC suggests that they may have a more broad therapeutic application than lineage-restricted adult stem cell populations.[16,28]DPSCs multi-potency has been compared to those of Bone Marrow Stem Cells BMSCs. It has been demonstrated that proliferation, availability, and cell number of DPSCs are greater than BMSC.[16,29]

Applications of dental pulp stem cells DPSCs:

Suitable stem cells for tissue engineering should be able to differentiate into the target tissue/organ and should be easily collected and prepared to provide a further benefit to ensure patient safety. DPSCs hold great future clinical potential due to their differentiation capacity and easy accessibility.[16]

1. Pulp regeneration what time the entire pulp tissue is lost, regeneration requires the new creation of pulp. In order to do such clinical application, several issues must be considered: first, regenerated blood supply is essential to pulp tissue, even through the blood supply occurs only from the apical foramen; second, newly differentiated odontoblasts should form on the existing dentinal wall of the root canal space; and finally, newly formed dentin must be produced by the differentiated odontoblasts on the existing dentin.[30]

2. Tooth reconstruction according to considerate of tooth formation, the stem cell niche and regenerative mechanisms extends, keep it possible to generate a method to biologically replace lost teeth. A hypothesis of functional biological replacement tooth must include generation of a root and periodontal ligament with nerve and blood supplies.[31]

3. In the Neurology field Dental pulp cells in laboratory animal study have also been projected as a treatment for peripheral nerve injury. Initially, dental pulp cells were transplanted into collagen gels and infused within a tube, which was positioned within a gap in the buccal branch of rat facial nerve. It has been shown that the transplanted dental pulp cells formed blood vessels and myelinating like tissues and contributed to the promotion of normal nerve regeneration. A degradable poly dl-lactide- co-glycolide PLGA tube was developed to avoid the need for a potential second operation to remove the silicon tube.[32]The neurological potentiality of dental pulp cells are very similar to that of bone marrow cells.[33]

4. Angiogenesis and vasculogenesis Stem cells and endothelial progenitor cells EPCs can be used to stimulate vasculogenesis as a potential treatment for ischaemic disease. Correspondingly therapeutic benefits of injection of bone marrow or adipose- derived MSCs after myocardial infarction MI and other heart diseases have also been reported. The potential of DPSCs and sub-fractions of DPSCs as modes of treatment for MI and ischaemia have been proved.[34]

5. Endocrinology Cell therapy treatments for liver disease require effective stem cell derived hepatocytes. DPSCs have been differentiated to produce Hepatocyte Like Cells HLCs with acquired hepatocyte functions, such as glycogen storage and urea production. Recently, hepatic differentiation of DPSCs was undertaken using cryopreserved dental pulp tissue from teeth with disease. Differentiated cells possessed a polygonal shape and normal karyo- type and

expressed hepatic metabolic function genes and liver-specific genes. Hepatocyte-like cells HLCs were nearly close to normal function like Glycogen storage and urea production, such results indicated that the differentiated hDPSCs were functionally close to the target. Although research into hepatic differentiation of DPSCs is at an early stage, the use of cryopreserved tissue to generate HLCs provides a promising alternative for the treatment of liver diseases.[35–38]

Biomaterials used in craniofacial tissue regeneration:

The use of bone grafts combined with guided tissue regeneration can serve as a scaffold for clot formation and stabilization. Biomaterials had a critical role in tissue engineering and though stem cells therapy.Such materials for constructing scaffolds can be natural/synthetic and rigid/non rigid. Natural biomaterials offer good cellular compatibility through supporting cell vitality and function. Their disadvantages include origin variability, immunogenicity, limited range of mechanical properties and lack of control over porosity . Unlike natural biomaterials, synthetic biomaterials can be manufactured in unrestricted supply under controlled conditions, being of lesser cost and can be customized to obtain desired shape, cell differentiation properties and mechanical and chemical properties especially the strength, pore characteristics and degradation rate suited for intended applications. However, synthetic biomaterials lack cell adhesion sites and require chemical modifications to improve cell adhesion.[155]Various kinds of 3D scaffolds have been designed to mimic the biological spontaneous bone formation characteristics by providing a suitable microenvironment for Osteogenesis.[39]

Stem cells therapy in orthodontics:

In Orthodontics, Stem Cells SCs can provide a step ahead in the field of craniofacial research and development.[40]

The applications of Stem Cells in Orthodontics in the future could be like the following:

1. Alveolar bone defect repair :

Orthodontic treatment includes extraction of premolars for correction of malocclusion. During surgical removal of teeth, accidentally buccal plates could be lost leading to alveolar bone defect. Such defects can be filled with stem cells to avoid the risk of dehiscence and periodontal damage after the spaces have been closed by retraction. Alveolar cleft osteoplasty can be successfully done with stem cells.[40]

A study was accomplished autologous bone regeneration in humans. It was obtained through the use of a biocomplex of dental pulp stem/progenitor cells from extracted wisdoms seeded onto a collagen-based scaffold. The area treated with such complex was significantly better than the control side treated with scaffold only The study gave evidence that the procedure described using Autologous DPCs were a new tool for bone tissue engineering resulted in optimal bone repair.[41]

2. Oral tissues remodeling and regenerating:

Remodelling of the alveolar bones is important in regenerating tissues.

Stem cells play an essential role in controlling this phenomenon coupled by local signaling/growth factors and systemic hormones.[42]

3. Distraction Osteogenesis:

Stem cells can induce mobilization of osteoblastic and osteoclastic cells. Stem cells can also accelerate bone regeneration in the distraction gap and enhance bony tissue consolidation .Such application was carried on through many studies started by experimental studies[43–45] and have been finalized by a clinical trial on the human being.[41]

4. Temporo-mandibular joint disorders and Defects:

Degenerative bone diseases including temporo-mandibular joint TMJ defects can be bioengineered

with stem cells.[46,47] Cells from various sources like articular cartilage cells, fibroblasts, mesenchymal stem cells have been used to reconstruct TMJ.[48–50]

5. Root bio- Engineering:

Stem cells from apical papilla SCAP and Periodontal ligament stem cells (PDLSCs) could be used if amalgamated together in construction of tooth. This hypothetical process is mentioned by root bio-engineering.[40]

Future advantages of stem cells therapy in orthodontics:

1. The least treatment time:

Embryonic stem cells have been proved to differentiae into cartilage cells and have been implanted on artificially created cranial osseous defects.[51] Mesenchymal stem cells MSCs express and secrete various factors and other cytokines that are important for angiogenesis. Various bioactive factors are secreted by the stem cells that suppress the local immune system, inhibit fibrosis, stimulate mitosis. Thus, by increasing the rate of healing and regeneration, treatment time hopefully could to be reduced. [52]

2. Periodontal health concern:

The success of orthodontic treatment is related to the health of periodontium is without any signs of diseases and defects.[53] Human PDLSCs get attached to the surfaces of the alveolar bone and tooth root when integrated into the PDL tissue.[40] Dental pulp stem cells DPSCs have the highest osteogenic potential among bone marrow mesenchymal stem cells BMMSCs and periosteal cells.[54]

3. Reduction of root resorption risk :

External apical root resorption is the most common and undesirable sequelae of Orthodontic treatment. Various derivatives of stem cells may be used prior to the treatment, May prevent root resorption or post treatment to repair the damage.[54–56]

4. Accelerated wound healing:

Bone marrow mesenchymal stem cell BMMSCs treated wounds exhibit significantly accelerated wound closure, with increased re-epithelialization, cellularity, and angiogenesis.[57]

Future Perspectives of Stem Cells Therapy:

1. Periodontal Regeneration:

Periodontium can be regenerated successfully by transplantation of ex vivo prolonged autologous MSCs. It is also confirmed, that periodontal defects can be managed by reimplantation of these cells. Dental Pulp Stem Cells DPSCs can form ectopic dentin and related pulp tissue.[58]

2. Tooth regeneration:

Three key elements are involved in tooth regeneration which include: Inductive morphogenes, Stem cells and Scaffold.[40,59,60]

Regeneration of tooth hypothesis can be carried out throughout many steps. The adult stem cells are harvested and are arranged into a scaffold that provides optimized environment. Cells are instructed with targeted soluble molecular signals spatially and gene expression is read. Finally, the above mentioned mixture is incubated into a suitable conditions till the final product is produced. [59,60]

3. Reimplantation and Transplantation of teeth can be carried out via stem cell therapy through enhanced tissue healing processes.[59]

4. Bioengineered Teeth:

A method has been developed to regenerate tooth buds in a single procedure by combining dental pulp and bone marrow on a scaffold and implanting this into surgically created defects. After a number of months, the construct led to organized dentin, enamel, pulp, cementum, and periodontal ligament surrounded by regenerated alveolar bone, suggesting a method that could translate directly to humans.[40]

5. Stem Cell Banking:

Cryopreservation or banking of stem cells maintains the viability of cells indefinitely. "During cryopreservation, the cells are put to sleep through a process called vitrification, in which the tissue is placed in liquid nitrogen at a temperature of -196 degrees Celsius. The cryopreservation process stops all cellular metabolism involving both cell growth and cell death. The cells preserved today can be applied to future regenerative therapies.[61,62]

SUMMARY

From this review article it has been summarized that suitable stem cells for tissue engineering were able to differentiate into the target tissue/organ and be easily collected and prepared to provide a further benefit to ensure patient safety and treatment success.

REFERENCES

1. Ramalho-santos M, Willenbring H. Commentary On the Origin of the Term Stem Cell.Cell Press . 2007;7:1:35-38
2. Kabir R, Gupta M, Aggarwal A, Sharma D, Sarin A, Kola M. Imperative role of dental pulp stem cells in regenerative therapies: A systematic review. Niger J Surg. 2014;20:1:1-8.
3. Potten C, Loeffler M. Stem cells: attributes, cycles, spirals, pitfalls and uncertainties. Lessons for and from the crypt. Development. 1990;110:4:1001-20.
4. Abou Neel E, Chrzanowski W, Salih V, Kim H, Knowles J. Tissue engineering in dentistry. Vol. 42, Journal of Dentistry. Elsevier Ltd; 2014. p. 915-28.
5. Chatzistavrou X, Rao R, Caldwell D, Peterson A, McAlpin B, Wang Y, et al. Collagen/fibrin microbeads as a delivery system for Ag-doped bioactive glass and DPSCs for potential applications in dentistry. J Non Cryst Solids. 2016;432:143-9.
6. Singh H, Bhaskar D, Rehman R, Jain C, Khan M. Stem Cells : An Emerging Future in Dentistry. Int J Adv Heal Sci. 2014;1:2:17-23.
7. Wang X, Hu J, Tan Y, Cui J, Wang G, Mrsny R, et al. Cancer stem cell marker Musashi-1 rs2522137 genotype is associated with an increased risk of lung cancer. PLoS One. 2014;9:5:e95915.
8. Gronthos S, Mankani M, Brahim J, Robey PG, Shi S. Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. Proc Natl Acad Sci U S A. 2000;97:25:13625-30.
9. Telles P, Machado M, Sakai V, Nör J. Pulp tissue from primary teeth: new source of stem cells. J Appl Oral Sci. 2011;19:3:189-94.
10. Gioventù S, Andriolo G, Bonino F, Frasca S, Lazzari L, Montelatici E, et al. A novel method for banking dental pulp stem cells. Transfus Apher Sci. 2012;47:2:199-206.
11. Potdar P, Jethmalani Y. Human dental pulp stem cells: Applications in future regenerative medicine. World J Stem Cells. 2015;7:5:839-51.
12. Potdar P. Establishment and molecular characterization of breast cancer mesenchymal stem cell line derived from human non-metastasis breast cancer tumor. Stem Cell Discov. 2011;1:2:21-8.
13. Davila J, Cezar G, Thiede M, Strom S, Miki T, Trosko J. Use and application of stem cells in toxicology. Toxicol Sci. 2004;79:2:214-23.
14. Bobis S, Jarocha D, Majka M. Mesenchymal stem cells: characteristics and clinical applications. Folia Histochem Cytobiol / Polish Acad Sci Polish Histochem Cytochem Soc Bobis, S, Jarocha, D Majka, M Mesenchymal stem cells Charact Clin Appl Folia Histochem Cytobiol. 2006;44:4:215-30.
15. Arthur A, Rychkov G, Shi S, Koblar S, Gronthos S. Adult human dental pulp stem cells differentiate toward functionally active neurons under appropriate environmental cues. Stem Cells. 2008;26:7:1787-95.
16. Aljamie M, Alessa L, Noah R, Elsayed L. Dental Pulp Stem Cells, a New Era in Regenerative Medicine : A Literature Review. 2016;:June:155-63.
17. Akinbami B, Didia B. Analysis of body mass index, the mandible, and dental alveolar arch factors in prediction of mandibular third molar impaction: A pilot study. J Contemp Dent Pract. 2010;11:6:41-8.
18. Bishara S. Third molars: a dilemma! Or is it? Am J Orthod Dentofacial Orthop. 1999;115:6:628-33.
19. Chang Y, Li W, Twu N, Li H, Lo W, Chang Y, et al. Induction of dental pulp-derived induced pluripotent stem cells in the absence of c-Myc for differentiation into neuron-like cells. J Chinese Med Assoc. 2014;77:12:618-25.
20. Chatzivasileiou K, Lux C, Steinhoff G, Lang H .Dental follicle progenitor cells responses to Porphyromonas gingivalis LPS J. Cell. Mol. Med. 2013; 17:6: 766-773.

21. Gazarian K, Ramírez-García L. Human deciduous teeth stem cells (SHED) display neural crest signature characters. PLoS One. 2017;12(1):1-14.
22. Abdul Wahab R, Zainal Ariffin S, Yeen W, Ahmad N, Senafi S. Molecular markers of dental pulp tissue during orthodontic tooth movement: a pilot study. Sci W J. 2012;236427:1-4.
23. Lee J, Cuddihy M, Kotov N. Three-Dimensional Cell Culture Matrices: State of the Art. Tissue Eng Part B Rev 2008;14:1:61–86.
24. Yu J, He H, Tang C, Zhang G, Li Y, Wang R, et al. Differentiation potential of STRO-1(+) dental pulp stem cells changes during cell passaging. Bio Med Cen Cell Biol. 2010;11.32;1-7
25. El-Gendy R, Kirkham J, Newby P, Mohanram Y, Boccaccini AR, Yang XB. Investigating the Vascularization of Tissue-Engineered Bone Constructs Using Dental Pulp Cells and 45S5 Bioglass ® Scaffolds. Tissue Eng Part A. 2015;21:13-14:2034-43.
26. Raoof M, Yaghoobi M. A modified efficient method for dental pulp stem cell isolation. Dent Res J. 2014;11:2: 244-50.
27. Conde M, Chisini L, Grazioli G, Francia A, de Carvalho R, Alcazr J, et al. Does cryopreservation affect the biological properties of stem cells from dental tissues? A systematic review. Braz Dent J. 2016;27:6:633-40.
28. Ghobadi F, Mehrabani D, Mehrabani G. Regenerative potential of endometrial stem cells: a mini review. World J Plast Surg. 2015;4:1:3-8.
29. Akpancar S, Tatar O, Turgut H, Akyildiz F, Ekinci S. The Current Perspectives of Stem Cell Therapy in Orthopedic Surgery. Arch trauma Res. 2016;5:4:e37976.
30. Huang G. Dental pulp and dentin tissue engineering and regeneration: advancement and challenge. Front Biosci (Elite Ed). 2011;3:788-800.
31. Volponi A, Pang Y, Sharpe P. Stem cell-based biological tooth repair and regeneration. Trends Cell Biol. 2010;20:12:715-22.
32. Ellis K, O Carroll D, Lewis M, Rychkov G, Koblar S a. Neurogenic potential of dental pulp stem cells isolated from murine incisors. Stem Cell Res Ther. 2014;5:1:30.
33. Mohammad M, Yaseen N, Al-Joubory A, Abdullah R, Mahmood N, Ahmed AA, et al. Production of Neural Progenitors from Bone Marrow Mesenchymal Stem Cells. Stem Cell Discov.2016;6:1:1-12.
34. Iohara K, Zheng L, Wake H, Ito M, Nabekura J, Wakita H, et al. A Novel Stem Cell Source for Vasculogenesis in Ischemia: Subfraction of Side Population Cells from Dental Pulp. Stem Cells. 2008;26:2408-18.
35. Hadjizadeh A, Doillon C. Directional migration of endothelial cells towards angiogenesis using polymer fibres in a 3D co-culture system. J Tissue Eng Regen Med. 2010;4:7:524-31.
36. Akpinar G, Kasap M, Aksoy A, Duruksu G, Gacar G, Karaoz E. Phenotypic and proteomic characteristics of human dental pulp derived mesenchymal stem cells from a natal, an exfoliated deciduous, and an impacted third molar tooth. Stem Cells Int. 2014;457059:1-19.
37. Boss M, Pacifici A, Carbone D, Tenore G, Ierardo G, Pacifici L, et al. Today prospects for tissue engineering therapeutic approach in dentistry. Sci World J. 2014;151252: 1-9.
38. Da Silva A, Da Silva D, Grotta R, Gordón-Núñez M, Agripino G. Biotechnology of Tissues and Materials in Dentistry - Future Prospects. Curr Concepts Dent Implantol.Intech Pub 2015; 3:59-75.
39. Wu H, Wang T, Sun J, Lee Y, Shen M, Tsai Z, et al. Development and characterization of a bioinspired bone matrix with aligned nanocrystalline hydroxyapatite on collagen nanofibers. Materials. 2016;9:198:1-11.
40. Mishra S. Stem Cells: A Step Ahead in Regenerative Dentistry with Accent on Orthodontics. Br J Med Med Res. 2016;14:12:1-7.
41. D'Aquino R, De Rosa A, Lanza V, Tirino V, Laino L, Graziano A, et al. Human mandible bone defect repair by the grafting of dental pulp stem/progenitor cells and collagen sponge biocomplexes. Eur Cells Mater. 2009;18:75–83.
42. Jang B, Byeon Y, Lim J, Ryu H, Kim W, Koyama Y, et al. Implantation of canine umbilical cord blood-derived mesenchymal stem cells mixed with beta-tricalcium phosphate enhances osteogenesis in bone defect model dogs. J Vet Sci . 2008;9:4:387-93.
43. Wu B, Kou X, Zhang C, Zhang Y, Cui Z, Wang X, et al. Stretch force guides finger-like pattern of bone formation in Suture. PLoS One. 2017;12:5:1-15.
44. Walvekar A, Nair D, John P, Rajan P. Distraction Osteogenesis. Distraction Osteogenes NJIRM. 2015;6:4:99-104.
45. Zigdon-Giladi H, Rudich U, Michaeli Geller G, Evron A. Recent advances in bone regeneration using adult stem cells. World J Stem Cells. 2015;7:3:630-40.

46. Ferreira F, Cunali R, Bonotto D, Farias AC de, Cunali PA. Total temporomandibular joint alloplastic reconstruction. Rev dor. 2014;15:3:211-4.

47. Guevara G, Arturo H, Kelly M, Luiz L. Temporomandibular Joint Total Replacement Stock Prostheses- Current Available Knowledge A Literature Review. J Surg Transplant Sci. 2013;1:1-6.

48. Detamore M. Human umbilical cord mesenchymal stromal cells in regenerative medicine. Stem Cell Res Ther. 2013;4:6:5-7.

49. Naujoks C, Meyer U, Wiesmann H, Jäsche-Meyer J, Hohoff A, Depprich R, et al. Principles of cartilage tissue engineering in TMJ reconstruction. Head Face Med. 2008;4:3:1-7

50. Yang Y, Lin S, Wang B, Gu W, Li G. Stem cell therapy for enhancement of bone consolidation in distraction osteogenesis. Bone Jt Res. 2017;6:6:385-90.

51. Horwitz E, Prockop D, Fitzpatrick L, Koo W, Gordon P, Neel M, et al. Transplantability and therapeutic effects of bone marrow-derived mesenchymal cells in children with osteogenesis imperfecta. Nat Med. 1999;5:3:309-13.

52. Caplan A. Mesenchymal stem cells: Time to change the name! Stem Cells Transl Med. 2017;6:6:1445–51.

53. Vizitiu T, Ionescu E. Microbiological Changes in Orthodontically Treated Patients. Ther Pharmacol Clin Toxicol. 2010;14:4:283-6.

54. Nayak B, Wiltshire W, Ganss B, Tenenbaum H, McCulloch C a G, Lekic C. Healing of periodontal tissues following transplantation of cells in a rat orthodontic tooth movement model. Angle Orthod. 2008;78:5:826-31.

55. McNab S, Battistutta D, Taverne A, Symons A. External Apical Root Resorption Following Orthodontic Treatment. Angle Orthod. 2000;70:3:227-32.

56. Marques L, Martins-Júnior P. Root Resorption in Orthodontics: An Evidence-Based Approach. Orthod - Basic Asp Clin Considerations. Intech Pub.2012;19:429-66

57. Wu Y, Chen L, Scott P, Tredget E. Mesenchymal Stem Cells Enhance Wound Healing Through Differentiation and Angiogenesis. Stem Cells. 2007;25:10:2648-59.

58. Giordano G, La Monaca G, Annibali S, Cicconetti A, Ottolenghi L. Stem cells from oral niches: a review. Ann Stomatol Roma. 2011;2:1-2:3-8.

59. Kabir R, Gupta M, Aggarwal A, Sharma D, Sarin A, Kola M. Imperative role of dental pulp stem cells in regenerative therapies: a systematic review. Niger J Surg Off Publ Niger Surg Res Soc. 2014;20:1:1-8.

60. Honda M, Sumita Y, Kagami H, Ueda M. Histological and immunohistochemical studies of tissue engineered odontogenesis. Arch histol cytol. 2005;68:3: 89-101.

61. Hughes D, Song B. Dental and nondental stem cell based regeneration of the craniofacial region: A tissue based approach. Stem Cells Int. 2016;830195:1-20.

62. Kanaparthy R, Kanaparthy A. The changing face of dentistry: nanotechnology. Int J Nanomedicine. 2011;6:2799-804.