International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Stem Cells in Periodontal Regenerations - A Review

Dr. Arunagiri Karunanithi[1], Dr. Arulvizhi M[2], Dr. Srinivasan K[3]

[1]Assistant Professor, Department of Periodontology, Mahatma Gandhi Post Graduate Institute of Dental Sciences, Gorimedu, Puducherry
Corresponding Author Email: *giriarun133[at]gmail.com*
Contact Number: +91 9486767181

[2]Assistant Professor, Department of Oral and Maxillofacial Pathologist, Mahatma Gandhi Post Graduate Institute of Dental Sciences, Gorimedu, Puducherry
Email: *arulvizhiparthibane[at]gmail.com*
Contact Number: +91 8289827055

[3]Assistant Professor, Department of Periodontology, Mahatma Gandhi Post Graduate Institute of Dental Sciences, Gorimedu, Puducherry
Email: *srinivasan201094[at]gmail.com*
Contact Number: +91 9500205297

Abstract: ***The regeneration of periodontal tissues is considered a promising strategy.Stem cells have remarkable properties, such as immunomodulatory potential, proliferation, migration, and multilineage differentiation. Thus, they can be used to repair tissue damage andreduce inflammation, potentially leading to periodontal regeneration. Among the stem cells used forperiodontal regeneration, we studied dental mesenchymal stem cells (DMSCs), non-dental stem cells,and induced pluripotent stem cells (IPSCs). Although these cells have well-documented importantphysiological characteristics, their use in contemporary practice to repair the affected periodontiumis still a challenge.Periodontal tissue stem cells, which play a crucial role in maintaining the homeostasis of periodontal tissues,are found in the periodontal ligament (PDL). These cells have long been referred to as mesenchymalstem/stromal cells (MSCs), and their clinical applications have been extensively studied.***

Keywords: Stem cells; periodontal regeneration; dental mesenchymal stem cells;non-dental stem cells; induced pluripotent stem cells.

1. Introduction

The oral cavity is a gateway to the external world and is closely linked to systemic immunity and nutrient sensing, and the distinct symbiotic relationship between microbiota and oral tissues renders the bacteria influential to oral health. For example, periodontal homeostasis is susceptible to overwhelmed bacteria–immune responses, which may dramatically call for theconstruction of chronic infection. Contemporary investigations based on stem cells refer to tissue engineering methods aiming to regenerate periodontal tissues, which include the regenerative processes that can occur at the level of the periodontium and the entire tooth (dental pulp, root, dentine, and alveolar bone). [1, 2]

Over the past decades, mesenchymal stromal cells (MSCs) have journeyed from discovery to mechanistic studies and periodontal regenerative applications. For example, several studies reported the excellent capacity of transplanted periodontal ligament stem cells (PDLSCs) or adipose-derived stem cells (ADSCs) for repairing multiple periodontal lesions in animal models. Interestingly, PDLSCs appear to be better candidates for regenerative periodontal therapy than other types of MSCs because of their easy accessibility in the oral maxillofacial region. [3] Furthermore, PDLSCs exhibited preferable self-renewal capacity than bone marrow MSCs and superior differentiation potential compared with other orofacial MSCs like gingival MSCs under a conditioned medium. Inspired by the excellent therapeutic potential of PDLSCs, several preclinical and clinical studies applying PDLSCs for oral regeneration have been performed. However, the results of a recent clinical trial using autologous PDLSCs derived from the impacted tooth are not satisfactory, because there is no significant advantage to restoring the defective periodontium by transplanting PDLSCs, as the control group (cell-free group) had comparable tissue reconstruction. These observations appear to support the assumption that the living environment might be the primary reason affecting the regenerative process. Specifically, the endogenous stem cells in animal models may shape a healthy stem cell niche and possess a periodontal regenerative property but are impaired in periodontitis patients, which may explain the parallel mandibular defect regeneration in rabbits between the autologous bone graft group and the ADSC-containing group. Further, the artificial defects in animal models may not suffer from some decisive pathogenic factors, such as prolonged inflammatory stimuli and influences from systemic diseases. Therefore, mitigating host factors and recreating a beneficial microenvironment could be a promising approach for improving stem cell-based periodontal regeneration. Here, we summarize limitations from the host and coping strategies that influence resident or transplanted stem cell-mediated periodontal regeneration, such as the management of local microbial–host responses and rejuvenation of endogenous PDLSCs. [4,5] More importantly, we recommend that active treatments for systemic diseases would also assist in recovering the limited stem cell function based on amelioration of the inflammatory periodontal microenvironment.

Stem cell populations in periodontal tissue [6]

They are defined as clonogenic cells, which are capable of both self-renewal and multi-lineage differentiation. According to their origin and differentiation potential, stem cells are classified as:

- Embryonic stem cells
- Adult stem cells
- Induced pluripotent stem cells

Dental Stem Cells (Figure 1) [7]

- Dental pulp stem cells (DPSC)
- Periodontal ligament stem cells (PDLSC)
- Dental follicle stem cells (DFSC)
- Stem cells from apical papilla (SCAP)
- Stem cells from exfoliated deciduous teeth (SHED)
- Gingival mesenchymal stem cells (GMSC)
- Epithelial cell rests of Malassez (ECRM)

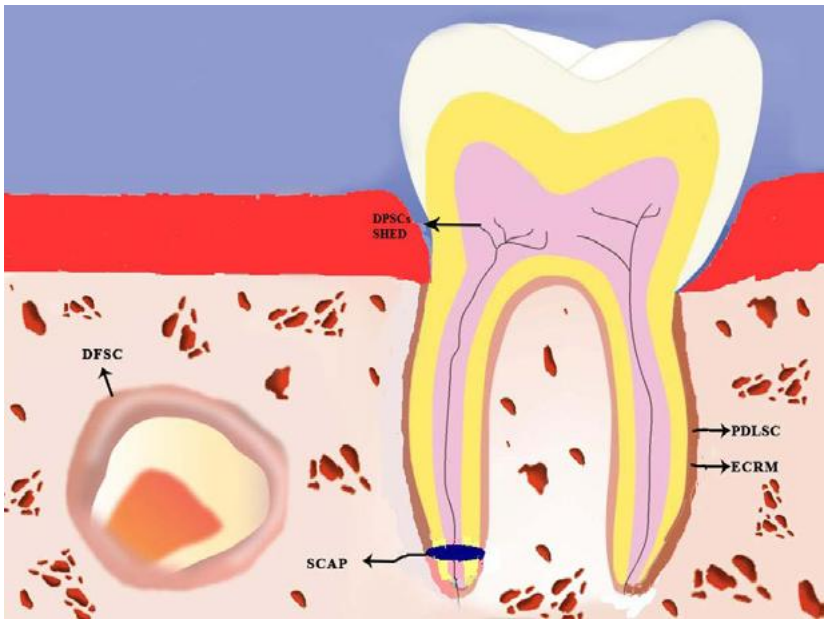

Figure 1: Schematic representation showing the location of dental mesenchymal stem cells [7]

Dental pulp stem cells (DPSCs): In an investigation, Gronthos, et al. [8] isolated from adult human dental pulp a clonogenic, rapidly proliferative population of cells which were found to be similar to BMSCs. In vitro characterization reveals mesenchymal stem cell markers such as STRO-1, CD31 and CD146 and also embryonic stem cell markers. They also express a mesenchymal marker vimentin. Human-derived DPSCs along with hydroxyapatite or beta tricalcium phosphate have been reported to be capable of forming bone and cementum. However, some authors are sceptical about the role of these cells in periodontal regeneration. Carinci and coworkers isolated a subpopulation within the DPSC with osteogenic potential. The osteoblasts obtained from these DPSC were compared with normal osteoblasts and numerous variations were found which might be responsible for the difference in bony tissue produced by these cells. Also, the effect of these stem cells on periodontal regeneration has been inconsistent based on numerous studies done in beagle dogs to date. [9]

Periodontal Ligament stem cell (PDLSC): The periodontal ligament is a specialized connective tissue that connects the cementum and alveolar bone, to maintain and hence support the teeth in sight and also preserve tissue homeostasis. Multipotent stem cells from human periodontal ligament were isolated for the first time by Seo, et al. [10]. He reported that PDLSCs exhibited some characteristic features similar to BMMSCs [56]. The peculiar features were multipotency, clonogenic ability, high proliferation and expression of putative stem cell markers such as STRO-1 and perivascular cell marker CD 146. Like the BMMSCs, they also express CD44, CD90, CD105, CD166. Scleraxis which is a transcription factor specific to the tendon was found to be highly expressed by PDLSCs as compared to BMMSCs and DPSCs. Hence it was concluded that periodontal ligament-derived MSCs are one of the most effective sources for periodontal regeneration. [11]

Dental Follicle Stem Cells (DFSC): A dental follicle is an ectomesenchyme-derived loose connective tissue sac surrounding the developing tooth bud from which arises the alveolar bone, cementum and periodontal ligament. DFSCs are relatively easy to harvest as can be procured from the follicles of unerupted third molars. [13] In vitro characterization reveals stem cell markers Nestin, Notch-1 and STRO-1. They express vimentin (mesenchymal marker) and cementoblast markers (Cementum protein-23, Cementum attachment protein). Guo, et al. [12] have reported that DFSCs have the potential to regenerate the entire root of the teeth.

Stem cells from apical papilla (SCAP): The apical papilla is the soft tissue present at the apices of developing roots of permanent teeth. It is responsible for the formation of the radicular pulp hence SCAP resemble DPSCs however, they are comparatively more immature and hence superior for tissue regeneration. They are isolated from tips of developing roots and hence can be harvested easily during extraction of impacted third molars. [14] In vitro, characterization reveals MSC markers STRO-1, CD146 and CD24 which seem to be a unique feature of these cells. They have been incorporated along with periodontal ligament stem cells in extraction sockets of miniature pigs, resulting in the successful formation of root and supporting periodontal structures. They have been considered crucial in root formation which might be partly because SCAP are the source of primary odontoblasts responsible for the formation of root dentin. [15]

Stem cells from Human Exfoliated Deciduous teeth (SHED):
Fu et al. [16] investigated the role of allogeneic SHED in the swine periodontitis model and found that they resulted in predictable periodontal regeneration similar to PDLSCs. SHED have been found to elevate regulatory T cells and downregulate T-helper 17 cells, hence have significant immunomodulatory capacity. Also, Yamada, et al. used SHED obtained from puppies and placed them in mandibular osseous defects created in parent canines. At 8 weeks the defect was filled with mature bone. Hence SHED derived from a child can be successfully used as a graft in the parent. [17]

Gingival Mesenchymal stem cells (GMSC*)*: Oral MSCs derived from human gingiva (GMSCs) also have been considered as a promising alternative cell source for periodontal regeneration. In addition to the physical characteristics of gingival fibroblasts, they exhibit adherence to plastic and multi-lineage differentiation potential. In vitro, characterization reveals cell surface markers CD44, CD73, CD90 and CD105 also stem cell markers such as SSEA-4, STRO-1, CD146, CD166, CD271 and vimentin which is a mesenchymal marker. In a canine model with class III furcation defects, the transplanted GMSCs significantly enhanced the regeneration of the damaged periodontal tissue, including the alveolar bone, cementum, and functional periodontal ligament. [18]

Epithelial Cell Rests of Malassez (ECRM): These are remnants of Hertwig's epithelial root sheath from which arise, all the periodontal structures. Since ECRM is normally present within the periodontium, studies have been carried out to research the stemness of ECRM. They express MSC markers CD29, CD44, HSP-90β also embryonic stem cell markers Oct-4, Nanog and SSEA-4. Also, Xiong J, et al. [19] have reported their capacity to carry out epithelial mesenchymal interactions. Following which numerous studies by the same authors have revealed that ECRM can differentiate into bone, cementum and periodontal ligament.

Non-Dental Stem Cells
Non-dental stem cells are classified into
- BMSC,
- Adipose-derived stem cells (ASCs), and
- Embryonic stem cells (ESCs).

Bone Marrow-Derived Mesenchymal Stem/Stromal Cells (BMSCs):
The recognition of the properties of marrow stromal cells has changed the perception of them, especially from a therapeutic perspective. BMSCs can differentiate into chondrocytes, osteoblasts, adipocytes, and muscle cells. BMSCs are classified according to the surface marker types (CD 29, CD 44, CD73, CD90, CD105, CD146, and STRO-1) and do not express CD14, CD34, or CD45. BMSCs can generate alveolar bone, Sharpey'sfibres, and cementum; hence, they can regenerate periodontal defects. BMSCs can stimulate the expression of odontogenic genes and differentiate into osteoblasts and fibroblasts after systemic or local transplantation. Another important characteristic of BMSCs is represented by their role in anti-inflammatory and immunosuppressive functions. BMSCs mediate T cell proliferation by regulating immunomodulation. [20] BMSCs inhibit inflammatory markers such as IL-1 and TNF, indicating that their use in the treatment of periodontitis could be feasible. Although remarkable improvements in periodontal parameters have been observed, clinical studies are needed to determine the role of BMSCs and their capacity to modulate inflammation and immunity before they become an option in the regenerative medicine/therapy of periodontitis. [21]

Adipose-Derived Stem Cells (ASCs)
ASCs are cells derived from adipose tissues and express markers similar to BMSCs, such as CD29, CD44, CD73, CD90, CD105, and CD166. However, ASCs do not express some markers specific to hematopoietic cells, such as CD31, CD34, and CD45. ASCs can improve the cementum and periodontal vessel regeneration and differentiate into adipocytes,osteocytes, and myogenic and neurogenic cells [22]. In comparison with BMSCs, ASCs have superior efficiency due to the easy harvesting process and the few notable complications at the donor site level. More importantly, ASCs, together with cytokines TNF-, IFN-, and IL-6, drive the expression of immunosuppressive factors IL-1RA and GBP4. Previous work has shown that ASCs represent a potential candidate for periodontal treatment and regeneration. ASCs secrete growth factors such as insulin-like growth factor binding protein-6, which enable the differentiation of ASCs in the periodontium. An animal model study in which allogeneic ASCs were transplanted to the affected periodontal tissue showed the proliferation of novel PDL fibres, cementum, and alveolar bone. [23]

Embryonic stem cells (ESCs)
They are derived from the inner cell mass of the blastocyst stage of embryonic development, before implantation in the uterine wall. They are pluripotent stem cells, which implies that they are capable of giving rise to cells of all three germ layers. They are responsible for the formation of an individual from anembryo and they disappear by the time adulthood is attained. Hence embryonic stem cells are the best source of cells for periodontal regeneration due to their high pluripotency. A bioengineered tooth was developed by Nakao, et al. using murine embryonic stem cells derived from epithelium and mesenchyme, which was able to erupt from the oral cavity of the mouse and develop into a fully functional tooth. Embryonic stem cells are ideal for periodontal regeneration. However, their use in clinical therapy has been hampered by ethical concerns. Another important disadvantage is that their implantation in the human body has been associated with the occurrence of rare cancers. [24]

Interaction between Stem Cells and the Periodontal Inflammatory Environment
Understanding the interaction mechanisms between stem cells and inflammation in periodontal disease is crucial for their subsequent use in periodontal regeneration. For example, interactions between stem cells and immune cells are different in inflamed tissue during the regeneration process compared with healthy tissue. Thus, it is important to recognize that stem cells have important immunomodulatory properties in inflamed periodontal

tissues and that these properties are derived from inflamed tissue. [25]

Stem Cells in the Inflammatory Environment

Among stem cells, DMSCs derived from inflamed tissue possess certain advantages, namely, that they are more easily accessible and, from an ethical point of view, there are fewer complications. Although PDLSCs are currently considered an ideal cell source for periodontal tissue regeneration compared with other DMSCs, obtaining these cells from healthy donors poses some challenges. PDLSCs derived from inflamed periodontal tissues are considered iPDLSCs. Compared with PDLSCs, iPDLSCs have higher migratory and proliferative capacities. However, iPDLSCs are responsible for modifying the signalling pathways related to osteogenesis; for this reason, they show a lower osteogenic differentiation capacity. These cells also have a decreased immunosuppressive potential and a reduced inhibitory capacity on T cell reproduction, PBMC proliferation, and Th17 differentiation compared with healthy tissue cells. iPDLSCs secrete more TNF, IFN, IL-2, and IDO, and less IL-10. When collagen sponges were combined with iPDLSCs isolated from inflamed human periodontal tissue in immunodeficient rats, this resulted in the formation of new collagen fibres, bone, and PDL-like tissue. Although the regeneration was not complete, important repair of the periodontal defects was still observed. Compared with normal DPSCs, infected tissue-derived DPSCs (iDPSCs) show similar surface marker expression, proliferative properties, and multilineage differentiation potential. [26] The use of DPSCs derived from infected human tissue as a graft at the level of root furcation revealed novel alveolar bone formation. These results may have important applications in periodontal regeneration with DMSCs obtained from inflammatory tissues. To obtain optimal results in terms of periodontal regeneration, the implantation of DMSCs obtained from infected tissue should be carried out, avoiding the onset of periodontal pathological processes on healthy tissues as much as possible.

Nevertheless, future studies are needed before applying this procedure as a standard protocol in a clinical setting. For example, the quality and quantity of stem cells depend on the source of the inflamed stem cells, the inflammatory state, and the experimental design. In addition, inclusion and exclusion criteria, as well as the procedure for the isolation and grafting of inflamed stem cells, must be established and standardized. This way, the effects of inflamed stem cells in the periodontium can be monitored and evaluated in the long term through in vivo and in vitro experiments. [27]

Infected Microenvironment and Its Influence on Stem Cells

The result of periodontal regeneration also depends on the interaction of stem cellswith the adjacent infected environment, and the immunomodulatory activity of these cellsis determined by the release of inflammatory cytokines into the circulation. Therefore, understandingthe effects that inflammatory cytokines exert on stem cells is a very importantaspect of optimizing and implementing clinical approaches mediated by stem cells.Among the most effective inflammatory cytokines during the periodontal inflammatoryprocess are TNF-α , IL-1, IL-6, and IFN- γ, and they exert their effects by attenuatingthe immunosuppressive properties of stem cells. Low levels of IFN- γ, enhance the antigen presentation function of stem cells and thus reduce their lysis, whereas high levelshave the opposite effect. For example, an infected microenvironment produced by Porfiromonasgingivalis LPS led to significant improvement in the cell proliferationof DMSCs. In addition, the co-culture of PDLSCs with IL-1 / TNF-α increased theproliferation rate of PDLSCs. This differentiation potential of DMSCs is mediated by pro-inflammatory cytokines and microbial pathogens. Specifically, Porfiromonasgingivalis LPS and Escherichia coli LPS inhibit the osteoblastic differentiationof PDLSCs, whereas IL-1 / TNF-α levels in the microenvironment can determine theinhibition of the osteogenesis process. [28]

In addition, other stem cells play an important role by exertingimportant effects at the level of the infected microenvironment, such as BMSCs that requireIFN- γto cause immunosuppression on T lymphocyte proliferation. The transplantation of BMSCs in a culture medium stimulated by LPS inhibited the production of inflammatory cytokines reduced the destruction of the inflammatory tissue and obtained tissue regeneration. Recent data have shown the regenerative potential of stem cells when used in an inflammatory environment. This is due to their capacity for proliferation, migration, multiple cell differentiation and immunosuppressive and anti-inflammatory properties in the inflamed microenvironment. Although still debatable, it seems that the use of stem cells in periodontal therapy provides the best results after controlling the inflammation through non-surgical and surgical treatments. [29]

Fate of transplanted MSCs

Several clinical studies have been conducted to evaluate the efficacy and safety of stem/progenitor cell transplantation for periodontal tissue regeneration. Transplanted stem cells are considered PDL-MSCs because they are expanded in vitro before transplantation, and no rigorous in vivo analysis has been conducted to prove their stemness and clonality. There has been a recent advancement in our understanding of the fate of transplanted cells. Initially, it was thought that the transplanted cells differentiate into mature cells and regenerate the tissue through a cell-autonomous mechanism. However, the transplanted cells were often undetectable within a few days, regardless of their administration. [30]

It has been reported that transplanted cells do not differentiate during their survival, but they secrete various cytokines; in particular, the paracrine factor is important. For example, Ozasa et al. demonstrated that autologous transplantation of adipose tissue-derived multi-lineage progenitor cells (ADMPCs) into alveolar bone defects enhances periodontal tissue regeneration. Interestingly, ADPMCs release trophic factors, including insulin-like growth factor binding protein 6, and stimulate the differentiation of PDLSCs into osteoblasts and cementoblasts. Other secreted factors from MSCs are extracellular vesicles, such as exosomes, which are used for cell communication, and MSC-derived exosomes have been studied extensively. Recently, it has become clear that transplanted MSCs undergo apoptosis and are phagocytosed

by macrophages, thereby activating anti-inflammatory and other pathways and inducing appropriate tissue regeneration. Thus, MSCs have been shown to have therapeutic effects following transplantation, but their function may be different from that of endogenous PDLSCs. In bone tissue, human SSCs have recently been classified as PDPN+CD146-CD73 +CD164 + cells, and their stemness has been proven in serial transplantation experiments. SSCs, like hematopoietic stem cells, withstand long-term follow-up of donor cells after transplantation. These features were not observed in MSCs. [31]

2. Future Perspectives & Conclusion

Recent studies have suggested that PDL-MSCs and PDLSCs are fundamentally different cell types, although there may be some overlap. PDLSCs have not yet been rigorously analyzed, and in vivo, analysis using modern techniques is required. As in other tissues, genetic lineage tracing, identification of label-retaining cells, and single-cell transcriptome analysis will be useful, but reliable evidence will not be established without the use of PDL-specific mice and efficient isolation methods. Combining the results of these analyses with the accumulated results of MSC research will lead to the identification of a stem cell population that sustains periodontal tissue and contributes to its regeneration. Elucidating the molecular mechanism of stem cell differentiation can lead to the development of new periodontal tissue regeneration therapies.

References

[1] Zhang Z, Deng M, Hao M, Tang J. Stem Cell Therapy in Chronic Periodontitis: Host Limitations and Strategies. Frontiers in Dental Medicine. 2022 Jan 24;2:833033.
[2] Deng ZL, Szafranski SP, arek M, Bhuju S, Wagner-Dobler I. Dysbiosis in chronic periodontitis: key microbial players and interactions with the human host. Sci Rep. (2017) 7:3703.
[3] Zhang Z, Deng M, Hao M, Tang J. Periodontal ligament stem cells in the periodontitis niche: inseparable interactions and mechanisms. J Leukoc Biol. (2021) 110:565–76.
[4] Kantarci A, Hasturk H, Van Dyke TE. Animal models for periodontal regeneration and peri-implant responses. Periodontol (2000). (2015) 68:66–82.
[5] Lu H, Zhao Y, Feng X, He L, Meng H. Microbiome in maintained periodontitis and its shift over a single maintenance interval of 3 months. J ClinPeriodontol. (2019) 46:1094–104.
[6] Mehta DS, Jyothy TM, Kumar T. Stem Cells in dentofacial research-At the Cross Roads. J Indian SocPeriodontol 2005; 9:91-108.
[7] Thomas George V, Thomas NG, John S, Ittycheria PG. The scope of stem cells in periodontal regeneration. Tissue Eng. 2015;1:13-21.
[8] Gronthos S, Brahim J, Li W, Fisher LW, Cherman N, Boyde A, et al. Stem cell properties of human dental pulp stem cells. J Dent Res. 2002; 81(8):531-5.
[9] Ponnaiyan D, Bhat KM, Bhat GS. Comparison of immuno-phenotypes of stem cells from human dental pulp and periodontal ligament. Int J Immunopathol Pharmacol. 2012; 25(1):127-34.
[10] Seo BM, Miura M, Sonoyama W, Coppe C, Stanyon R, Shi S. Recovery of stem cells from cryopreserved periodontal ligament. J Dent Res 2005; 84(10):907-912.
[11] Trubiani O1, Di Primio R, Traini T, Pizzicannella J, Scarano A, Piattelli A, et al. Morphological and cytofluorimetric analysis of adult mesenchymal stem cells expanded ex vivo from periodontal ligament. Int J Immunopatholol Pharmacol 2005; 18(2):213-221.
[12] Guo W, He Y, Zhang X, Lu W, Wang C, Yu H, et al. The use of dentin matrix scaffold and dental follicle cells for dentin regeneration. Biomaterials 2009; 30(35):6708-6723.
[13] Xiang L, Chen M, He L, Cai B, Du Y, Zhang X, et al. Wnt5a regulates dental follicle stem/progenitor cells of the periodontium. Stem Cell Res Ther. 2014; 5(6):135.
[14] Huang J, Gronthos S, Shi S. Mesenchymal stem cells derived from dental tissues vs those from other sources: their biology and role in regenerative medicine. J Dent Res 2009; 88(9):792-806.
[15] Sonoyama W, Liu Y, Yamaza T, Tuan RS, Wang S, Shi S, et al. Characterization of the apical papilla and its residing stem cells from human immature permanent teeth: a pilot study. J Endod. 2008; 34(2):166-71.
[16] Fu X, Jin L, Ma P, Fan Z, Wang S. Allogenic stem cells from deciduous teeth in treatment for periodontitis in miniature swine. J Periodontol 2014; 85(6):845-851.
[17] Yamada Y, Ito K, Nakamura S, Ueda M, Nagasaka T. Promising cell-based therapy for bone regeneration using stem cells from deciduous teeth, dental pulp and bone marrow. Cell Transplant 2011; 20(7):1003-1013.
[18] Yu X, Ge S, Chen S, Xu Q, Zhang J, Guo H, et al. Human gingiva-derived mesenchymal stromal cells contribute to periodontal regeneration in beagle dogs. Cells Tissue Organs. 2013; 198(6):428-37.
[19] Xiong J, Mrozik KM, Gronthos S, Bartold PM. Epithelial cell rests of malassez contain unique stem cell populations capable of undergoing epithelial-mesenchymal transition. Stem Cells Dev 2012; 21(11):2012- 2025.
[20] Du, J.; Shan, Z.; Ma, P.; Wang, S.; Fan, Z. Allogeneic Bone Marrow Mesenchymal Stem Cell Transplantation for Periodontal Regeneration. J. Dent. Res. 2014, 93, 183–188.
[21] Paknejad, M.; Eslaminejad, M.B.; Ghaedi, B.; Rokn, A.-R.; Khorsand, A.; Etemad-Moghadam, S.; Alaeddini, M.; Dehghan, M.M.; Moslemi, N.; Nowzari, H. Isolation and Assessment of Mesenchymal Stem Cells Derived from Bone Marrow: Histologic and Histomorphometric Study in a Canine Periodontal Defect. J. Oral Implantol. 2015, 41, 284–291.
[22] Huang, G.T.-J.; Gronthos, S.; Shi, S. Mesenchymal Stem Cells Derived from Dental Tissues vs. Those from Other Sources: Their Biology and Role in Regenerative Medicine. J. Dent. Res. 2009, 88, 792–806.
[23] Venkataiah, V.S.; Handa, K.; Njuguna, M.M.; Hasegawa, T.; Maruyama, K.; Nemoto, E.; Yamada,

S.; Sugawara, S.; Lu, L.; Takedachi, M.; et al. Periodontal Regeneration by Allogeneic Transplantation of Adipose Tissue-Derived Multi-Lineage Progenitor Stem Cells in Vivo. Sci. Rep. 2019, 9, 921.

[24] Mehta DS, Jyothy TM, Kumar T. Stem Cells in dentofacial research-At the Cross Roads. J Indian SocPeriodontol 2005; 9:91-108.

[25] Fawzy-El-Sayed, K.; Mekhemar, M.; Adam-Klages, S.; Kabelitz, D.; Dörfer, C. TlR Expression Profile of Human Gingival Margin-Derived Stem Progenitor Cells. Med. Oral Patol. Oral Cir. Bucal 2016, 21, e30–e38.

[26] Alongi, D.J.; Yamaza, T.; Song, Y.; Fouad, A.F.; Romberg, E.E.; Shi, S.; Tuan, R.S.; Huang, G.T.-J. Stem/Progenitor Cells from Inflamed Human Dental Pulp Retain Tissue Regeneration Potential. Regen. Med. 2010, 5, 617–631.

[27] Andrukhov, O.; Behm, C.; Blufstein, A.; Rausch-Fan, X. Immunomodulatory Properties of Dental Tissue-Derived Mesenchymal Stem Cells: Implication in Disease and Tissue Regeneration. World J. Stem Cells 2019, 11, 604–617.

[28] Tassi, S.A.; Sergio, N.Z.; Misawa, M.Y.O.; Villar, C.C. Efficacy of Stem Cells on Periodontal Regeneration: Systematic Review of Pre-Clinical Studies. J. Periodontal Res. 2017, 52, 793–812.

[29] Bindal, P.; Ramasamy, T.S.; Kasim, N.H.A.; Gnanasegaran, N.; Chai, W.L. Immune Responses of Human Dental Pulp Stem Cells in Lipopolysaccharide-Induced Microenvironment. Cell Biol. Int. 2018, 42, 832–840.

[30] Novello S, Debouche A, Philippe M, Naudet F, Jeanne S. Clinical application of mesenchymal stem cells in periodontal regeneration: a systematic review and meta-analysis. J Periodontal Res 2020;55:1–12.

[31] Ozasa M, Sawada K, Iwayama T, Yamamoto S, Morimoto C, Okura H, et al. Periodontal tissue regeneration by transplantation of adipose tissue-derived multi-lineage progenitor cells. Inflamm Regen 2014;34:109–16.