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Stem Cells - Paving Pathway Towards Periodontal Regeneration

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Abstract:
Periodontal disease is a prevalent and chronic oral health condition that poses significant challenges in its treatment and management. Traditional approaches often fail to achieve complete periodontal tissue regeneration, leaving patients with compromised oral health and function. In recent years, stem cell-based therapies have emerged as promising tools for periodontal regeneration, offering potential solutions to this complex problem. This review article explores the current state of knowledge regarding the use of stem cells in periodontal regeneration. We delve into the various types of stem cells, including mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and embryonic stem cells (ESCs), and their respective roles in regenerating the diverse tissues that constitute the periodontium. Furthermore, we discuss the mechanisms through which stem cells contribute to periodontal regeneration, such as their differentiation capabilities and immunomodulatory/anti-inflammatory effects. Overall, this review underscores the tremendous potential of stem cells in advancing the field of periodontal regeneration, offering a more effective and holistic approach to restoring the integrity of the periodontium. Through a comprehensive evaluation of the latest research and clinical developments, we aim to shed light on the promise of stem cell-based therapies for improving the quality of life for individuals affected by periodontal disease.

Keywords: *Stem cells, Periodontal regeneration, Dental stem cells, Non-dental stem cells, Mesenchymal stem cells*

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I. INTRODUCTION

For a successful periodontal regeneration, number of techniques have been tried, including the use of growth factors, guided tissue regeneration, root surface conditioning agents, and bone grafts [1]. With current trends in periodontal therapy even with the astute clinical skills of the operator, obtaining an optimum clinical outcome is still questionable.

The 19th century saw the first use of the term "stem cell" in literature. A clonogenic, undifferentiated cell with the capacity for self-renewal and multi-lineage differentiation is referred to as a "stem cell" [2]. In other words, a stem cell can multiply and produce new stem cells, and some of its offspring can differentiate and decide to mature along several lineages, giving rise to a variety of specialized cell types [3]. This potential of differentiation into several lineages lays the foundation for its implication in periodontal regeneration. Dental stem cells have the potential to be used in medical procedures such as cardiac treatments, brain tissue regeneration, treatments for muscular dystrophy, and pulpal regeneration [4]. There is limited evidence to the use of stem cells in periodontal regeneration. This paper aims to present the evolution of stem cells, its current clinical applications, and future directions of research in periodontal regeneration.

II. CHARACTERISTICS OF STEM CELLS

Stem cells form the foundation cells of the human body. A stem cell has two distinct characteristics:

(i) The capacity for endless self-renewal, producing new stem cells.
(ii) The capacity to differentiate into a variety of cells with diverse functions.

If a stem cell divides asymmetrically, one of the two daughter cells will continue to function as a stem cell while the other will eventuallyspecialize under certain circumstances [6].

Any cell population regardless of the tissue source that satisfies the following criteria is referred to as a mesenchymal stem cell (MSC):

- Morphologically: They resemble fibroblasts.
- Functionally: They are capable of self-renew and can differentiate into cells of the mesenchymal lineage (osteocyte, chondrocyte, and adipocyte), as well as into cells of the endoderm (hepatocytes), and ectoderm (neurons), under the right cell culture conditions.
- Phenotypically: More than 95% of the population exhibits the surface antigens CD105, CD73, and CD90, while less than 2% of the population exhibits the pan leukocyte marker CD45, the primitive hematopoietic progenitor and endothelial cell marker CD34, the monocyte and macrophage markers CD14 and CD11, the B cell markers CD79 and CD19, or HLA class II [7].

III. CLASSIFICATION OF STEM CELLS

Based on origin stem cells are classified as follows;

Based on their potency to differentiate into a variety of cells, stem cells are categorized as totipotent, multipotent, pluripotent,oligopotent, and unipotent

1. Totipotent: Stem cells that have the capacity to differentiate into all possible types of cells including extra embryonic types.Example: A fertilized egg.
2. Pluripotent: This has the ability to turn into all cell types with the exception of extra embryonic tissues. Example: Embryonicstem cells.
3. Multipotent: This has the capacity to differentiate into multiple but limited cell types. -Example: Mesenchymal stem cells
4. Oligopotent: This can differentiate into very few cell types. Example: Myeloid stem cells
5. Unipotent: This can differentiate into only one cell type. Example: Skin [8]

IV. EMBRYONIC STEM CELLS (ESCs)

Blastocysts, or embryos that are between 2-11 days old, are the source of ESCs. Given their ability to reproduce and endure endlessly in an undivided state, they are believed to be immortal. They are totipotent in nature and have the highest ability to heal and restore affected tissue and organs. It is morally and ethically challenging as extraction of ESCs may itself destroy the embryos. Additionally, it is challenging to manage the differentiation and proliferative potential of ESCs, which increases the risk of tumorigenicity and teratoma formation [5].

V. ADULT STEM CELLS

Some cells in the primary germ layers can develop into several cell types, but to a lesser extent than ESCs. These cells are the progenitors of adult stem cells. As the embryo develops, these precursor cells specialize further and commit to certain lineages. They are multipotent in nature. Adult stem cells, despite their limited capacity, are essential for tissue maintenance, repair, and regeneration throughout an organism's existence [5].

VI. DENTAL MESENCHYMAL STEM CELLS (DMSCs)

DMSCs are said to be multipotent as they can replenish and differentiate into a variety of cell types. The activity of many immune- related cell types is modulated by DMSCs. Numerous inflammatory substances released by immune-related cells serve as the foundation for DMSCs' immunological potential [9]. It includes DFSCs, DPSCs, PLSCs, SCAPs, GMSCs, SHEDs.

VII. DENTAL FOLLICLE STEM CELLS (DFSCs)

DFSCs were first isolated from human dental follicles of impacted third molars by Morsczeck et al., 2005. DFSCs are neural crest-derived cells that are found in the dental follicle of the tooth germ. DFSCs can differentiate into bone cells, adipocytes, chondrocytes, neurons, and cardiomyocytes under specific environmental conditions. Recent evidence has stated that these cells may transform into ductal and salivary gland cells [10]. DFSCs are renowned for forming the periodontium by migrating around the tooth bud and differentiating into PDLs, osteoblasts, and cementoblasts [11].

Immunomodulatory / Anti-inflammatory characteristics:

- The immunosuppressive effects are associated with the expression of TLR2/TLR4 (Toll-like receptors) in the membrane of DFSCs which are stimulated by Fusobacterium nucleatum and Porphyromonas gingivalis, controls the proliferation ofperipheral blood mononuclear cells (PBMCs) [12].
- Suppresses inflammation by stimulating anti-inflammatory cytokine IL-10 secretion and inhibiting pro-inflammatory markers (IL-4, IL-8, and IFN-γ) that affect bacterial adherence simultaneously.
- DFSCs prevent bone degradation by modifying phagocytic and chemotactic activity, and driving

macrophage polarizationto M2 phenotype [13].

VIII. DENTAL PULP STEM CELLS (DPSCs)

A distinct population of cells called dental pulp stem cells (DPSCs) entrenched within the pulp cavity of impacted third molars were first extracted and characterized by Gronthos et al. in 2000 [14]. These cells have phenotypic and functional traits that are strikingly comparable to mesenchymal stem cells that are produced from bone marrow. DPSCs can differentiate into osteoblasts, chondrocytes, adipocytes, odontoblasts, or neurogenic cells [15].

Dental pulp stem cells (DPSC) are known to have immunomodulatory (both innate and acquired immune responses) and anti- inflammatory effects by interacting with T cells, B lymphocytes, macrophages, and natural killer (NK) cells [16].

Immunological / Anti-inflammatory characteristics:

- DPSCs influence the TH17/Treg ratio by suppressing T cells, boosting anti-inflammatory factor production (IFN-γ), and lowering pro-inflammatory factor secretion (IL-17).
- DPSCs suppress B lymphocyte activity and decrease IgG and IgM production, resulting in immunological tolerance.
- DPSCs have an inhibitory influence on dendritic cells (DCs) and NK cells, which help to regulate the body's immune activity.
- The exosomes secreted by DPSCs can convert pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophagessubstantiating the immunomodulation favouring anti-inflammatory effects.
- DPSCs inhibit lipopolysaccharide (LPS)-induced macrophage secretion of tumor necrosis factor (TNF-α) via an indoleamine-2,3-dioxygenase (IDO)-dependent mechanism and suppress allogeneic T lymphocyte activation utilizing Fas/FasL interaction and Treg apoptosis.
- Programmed cell death (PD-L1) present on DPSCs interacts with the PD-1 receptor on activated T cells, suppressing immune mechanisms by counteracting T cell activation signals.
- When DPSCs were exposed to LPS, they increased the expression of TLR-4 and enhanced Wnt5a production via the TLR4/MyD88/PI3-kinase/AKT pathway [17–19].

IX. STEM CELLS FROM THE APICAL PAPILLA (SCAPs)

In 2006, Sonoyama et al. were the first to discover and extract SCAP from the apical papillae of immature (developing) permanent third molars. SCAP is known for its high proliferative capacity, self-renewability, and low immunogenicity [20]. A large body of evidence suggests that SCAPs can give rise to a variety of cell lineages, including osteogenic, odontogenic, neurogenic, adipogenic, chondrogenic, and hepatogenic cells [20–23]. It has been claimed that SCAPs constitute a promising source for periodontal repair based onthese properties.

Immunological characteristics:

Immunologically one of the key functions of SCAPs is suppression of T lymphocyte proliferation via an apoptosis-independentmechanism [24].

X. GINGIVA-DERIVED MESENCHYMAL STEM CELLS (GMSCs)

Zhang et al. isolated human GMSCs for the first time in 2009 from clinically healthy gingival tissues (lamina propria) that were retrieved as remnants or discarded during routine dental procedures with no history of periodontal disease and a relatively healthy periodontium. GMSCs are a great source in regenerative medicine as they are widely distributed, easy to access and extract with minimally invasive surgical procedures leaving no scars behind [25].

GMSCs are currently a sufficient cell source in the treatment and engineering of periodontal tissues, owing to their exceptional self-renewal, regeneration, and multilineage differentiation capacities. The immunomodulatory characteristics and accessibility of GMSCs have gained interest in cell therapy in recent years [26].

Immunomodulatory / Anti-inflammatory characteristics:

- TLRs 1, 2, 3, 4, 5, 6, 7, and 10 are expressed by GMSCs, which interact with the inflammatory environment and affect theirimmunological characteristics.
- PGE2, IL-10, or IL-6 produced by human GMSCs can decrease the activity of M1 macrophages.
- Additionally, GMSCs drastically lower DC activation and maturation via a PGE2-associated mechanism, which inhibits DCs'ability to deliver antigens and significantly lowers the inflammatory response.

- IDO and IL-10 are two immunosuppressive molecules that human GMSCs upregulate to prevent T-cell activation [27].

XI. STEM CELLS FROM HUMAN EXFOLIATED DECIDUOUS TEETH (SHEDs)

SHEDs were initially identified and isolated from the human dental pulp of exfoliated deciduous teeth by Miura et al. in 2003.

SHEDs demonstrate bone and dentin-like tissue regeneration with a high osteoinductive capability and proliferation rate [28].

Immunomodulatory / Anti-inflammatory characteristics:

- Through mediating T cell activation, maturation, and differentiation, SHEDs exhibit immunomodulatory properties.
- Additional immunosuppressive effects of SHEDs include suppression of Th17 cells and activation of regulatory T cells(Tregs)[29].
- Also, SHEDs can promote DC to increase the production of IL-10, an anti-inflammatory cytokine, and block the secretion ofinflammatory markers like IL-2, TNF-α, and IFN-γ [30].
- SHEDs cause bone marrow-derived macrophages to become M2 polarised, which has anti-inflammatory effects on periodontaltissues and aids in the regeneration of the periodontium [31].

XII. PERIODONTAL LIGAMENT STEM CELLS (PDLSCs)

The PDL is a type of connective tissue that secures the link between the tooth root and the surrounding alveolar bone. PDLSCs were first isolated from impacted third molars by Seo et al in 2004 [32]. PDLs, alveolar bone, cementum, blood vessels, and peripheral nerves can all be produced by PDLSCs. These cells also possess an excellent proliferation potential and a propensity for self-renewal[33].

PDLSCs have recently been suggested as prospective cell sources for the restoration of certain bone abnormalities brought on by periodontitis owing to their immunomodulatory qualities.

Immunological / Anti-inflammatory characteristics:

- PBMCs that have been activated release interferon (IFN-γ), which prompts PDLSCs to release soluble growth factors like TGF-β (transforming growth factor), IDO-1, and HGF (hepatocyte growth factor) that consequently, in part inhibit PBMC proliferation[34].
- Another innate immunological response by PDLSCs is the upregulation of neutrophil proliferation and the downregulation ofneutrophil death [35].
- The major histocompatibility complex glycoprotein 1b (GP1b) and prostaglandin E2 (PGE2) secreted by DCs are also significantly reduced by PDLSCs, which further restrict T cell proliferation [36].
- PDLSCs also decrease pro-inflammatory Th1/Th2/Th17 cells while enhancing the proliferation of anti-inflammatory Treg cells [37].
- In addition, PDLSCs also contribute to immunosuppression by preventing B cells from proliferating, migrating, and differentiating.
- The expression of programmed cell death protein 1 (PD-1) and its ligand (PD-L1) is fostered to produce these characteristicsin PDLSCs [38].
- PDLSCs promote the polarisation of the anti-inflammatory phenotype (M2 phenotype) by upregulating IL-10, CD163, andArg- (Arg-) 1, while downregulating TNF-α [35].

XIII. NON-ODONTOGENIC STEM CELLS

There are 3 types of non-odontogenic stem cells namely: Bone marrow-derived mesenchymal stem cells (BMSCs), adipose- derived stem cells (ASCs), and embryonic stem cells (ESCs).

XIV. BONE MARROW-DERIVED MESENCHYMAL STEM/STROMAL CELLS (BMSCs)

In 1967, Friedenstein et al. published the first description of MSC generated from bone marrow [39]. BMSCs can develop into muscle, adipocyte, chondrocyte, and osteoblast cells thereby giving rise to the alveolar bone, sharpey's fibres, and cementum, leading to regeneration of the periodontium [40]. Following systemic or local transplantation, BMSCs can promote the expression of genes related to tooth development and can eventually differentiate into osteoblasts and fibroblasts [41].

Immunomodulatory/ Anti-inflammatory characteristics:

- The activity of BMSCs in suppressing immune and inflammatory responses is another crucial trait [42].
- T cell proliferation is mediated by BMSCs through immunomodulation.

- BMSCs reduce inflammatory indicators including IL-1 and TNF- α, implying that they could be used to treat periodontitis.

Although considerable improvements in periodontal parameters have been reported, more clinical investigations are required to clarify the role of BMSCs and their ability to influence inflammation and immunity before their application in treating periodontitis by regenerative medicine/therapy [43].

XV. ADIPOSE-DERIVED STEM CELLS (ASCs)

Zuk and colleagues first identified and defined ADSCs as mesenchymal stem cells (MSCs) recovered from processed lipoaspirate in 2001. ASCs have similar properties to BMSCs and can differentiate into osteoblasts, adipocytes, chondrocytes, myogenic, and neurogenic cells. ASCs are more advantageous than BMSCs in yielding, with fewer significant donor site ailments [44].

Immunomodulatory/ Anti-inflammatory characteristics:

- ASCs in combination with cytokines like TNF-α, IFN-γ, and IL-6 can increase the production of immune suppressivemolecules such as GBP4 and IL-1RA [45].

XVI. INDUCED PLURIPOTENT STEM CELLS (iPSCs)

Yamanaka et al in 2007 successfully demonstrated the generation of iPSC from adult human dermal fibroblasts with the use of four transcriptional factors: Oct3/4, Sox2, Klf4, and c-Myc [46].

iPSCs mimicking pluripotent stem cells have the capacity to develop into iPS-derived MSCs (iPSC-MSCs) which can differentiate into multilineage cells that aid in the regeneration of cementum, alveolar bone, and inflammatory tissue in periodontitis

[47]. Dental tissue stem cells, such as PDLs, buccal mucosa fibroblasts, gingival, apical papilla, and dental pulp, offer benefits for theproduction of iPSCs [48].

Immunological characteristics:

Additionally, iPSC-MSCs can suppress Th1/Th2/Th17 cells and increase the levels of Treg cells, thereby decreasing leukocyteproduction and alveolar bone resorption [49].

XVII.APPLICATION OF STEM CELLS IN PERIODONTAL REGENERATION

Research has shown that Mesenchymal stem cells (MSCs), embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs) play a significant role in the revival of periodontal tissues. Among these MSCs are chosen over ESCs to avoid ethical concerns involved in it. BMSCs have been found to aid in periodontal regeneration when placed into bone deficiencies but due to the pain involved in cell harvesting and the amount of cells harvested being very low, they have not proven to be advantageous. Hence, DMSCs have become the choice of cells by several researchers[50].

Aimetti et al. (2018) published a 1-year follow-up case series on using autologous DPSCs in treating intra-bony defects and concluded that the application of DPSCs significantly improved clinical (PD, CAL) and radiographic parameters (BF) of periodontal regeneration[51]. Nerea et al. (2020) conducted studies to evaluate the safety and efficacy of autologous periodontal ligament-derived mesenchymal stem cells (PDL-MSCs) embedded in a xenogeneic bone substitute (XBS) for the regenerative treatment of intra-bony periodontal defects and found it to be safe and resulted in low postoperative morbidity and appropriate healing[52]. Abdal Wahab et al. (2020) in their study assessed the efficacy of gingival fibroblasts (GF) and their associated mesenchymal stem cells (GMSC) in the treatment of intrabony periodontal defects and found significant reduction in pocket depth (PD) and CAL gain [53]. Danae et al. (2021) in their studies to assess the safety/efficacy of tissue–engineered bio-complex in periodontal reconstruction found that there is radiographic evidence of bone fill is enhanced in autologous clinical-grade alveolar Bone-Marrow Mesenchymal-Stem-Cells (a-BMMSCs), seeded into collagen scaffolds, enriched with autologous fibrin/platelet lysate (aFPL) [54]. Ma et al.(2022) demonstrated that the migration, proliferation, and osteogenic differentiation of PDLSCs were improved by the implantation of DFSCs-sEVs (cell-derived small extracellular vesicles) type cells in a periodontal defect. Therefore, there may be a lot of potential for using DFSCs- sEVs for periodontal regeneration [55].

XVIII.CHALLENGES IN THE APPLICATION OF STEM CELLS

There are three main challenges in the application of stem cells in human trials: Biological, technical, and clinical. Biologically, the exact molecular-level mechanisms that guide and control the growth and specialization of various stem cells are still unclear. Technically, it is imperative to devise an ideal culture medium for stem cell culture, overcome the limited life expectancy of MSCs, and find the perfect biocompatible scaffold and transport system is yet to be identified. Clinically, the integration of the human stem cell derivatives with the recipient tissue and their ability to carry out the desired functions in humans is still under speculation.

XIX. FUTURE DIRECTIONS AND CONCLUSION

The future direction of stem cells in periodontal regeneration holds great promise. Researchers are exploring various avenues to enhance the efficacy of stem cell-based therapies for periodontal regeneration. Some potential directions include:

1. Personalized Medicine: Tailoring stem cell therapies to individual patients based on their genetic and physiological profiles toimprove treatment outcomes.
2. Combination Therapies: Investigating the synergistic effects of combining stem cells with other regenerative approaches, suchas growth factors or biomaterials, to optimize tissue regeneration.
3. Biomaterial Development: Advancing the development of biomaterials that can serve as scaffolds for stem cell growth anddifferentiation, promoting tissue regeneration.
4. Clinical Trials: Conducting large-scale clinical trials to further evaluate the safety and long-term effectiveness of stem celltherapies for periodontal regeneration.
5. Immune Modulation: Research in modulating the immune response to prevent rejection of transplanted stem cells and promotetissue integration.
6. Non-Invasive Approaches: Exploring non-invasive methods of delivering stem cells to periodontal tissues, such as usingnanoparticles or aerosols.

In conclusion, stem cells are paving the way for exciting developments in periodontal regeneration. While there's still much research to be done and challenges to overcome, the potential benefits for patients, including improved oral health, enhanced aesthetics, and reduced tooth loss, make this field of study highly promising. With ongoing research and technological advancements, stem cell- based therapies may become an integral part of periodontal care in the future.

References

[1]. Pejcic A, Kojovic D, Mirkovic D, Minic I. Stem Cells For Periodontal Regeneration. Balk J Med Genet. 2013;16(1):7-12. Doi:10.2478/Bjmg-2013-0012

[2]. Smith A. A Glossary For Stem-Cell Biology. Nature. 2006;441(7097):1060. Doi:10.1038/Nature04954

[3]. Lin NH, Gronthos S, Bartold PM. Stem Cells And Periodontal Regeneration. Aust Dent J. 2008;53(2):108-121. Doi:10.1111/J.1834-7819.2008.00019.X

[4]. Yamada Y, Nakamura-Yamada S, Kusano K, Baba S. Clinical Potential And Current Progress Of Dental Pulp Stem Cells For Various Systemic Diseases InRegenerative Medicine: A Concise Review. Int J Mol Sci. 2019;20(5). Doi:10.3390/Ijms20051132

[5]. Sivaram GMDS, Devi RSN. Stem Cells In Periodontal Regeneration. 2014;13(9):31-40.

[6]. Biehl JK, Russell B. Introduction To Stem Cell Therapy. J Cardiovasc Nurs. 2009;24(2):98-103. Doi:10.1097/JCN.0b013e318197a6a5

[7]. Rodríguez-Lozano FJ, Insausti CL, Iniesta F, Et Al. Mesenchymal Dental Stem Cells In Regenerative Dentistry. Med Oral Patol Oral Cir Bucal.2012;17(6):1062-1067. Doi:10.4317/Medoral.17925

[8]. Hynes K, Menicanin D, Gronthos S, Bartold PM. Clinical Utility Of Stem Cells For Periodontal Regeneration. Periodontol 2000. 2012;59(1):203-227.Doi:10.1111/J.1600-0757.2012.00443.X

[9]. Wang M, Xie J, Wang C, Zhong D, Xie L, Fang H. Immunomodulatory Properties Of Stem Cells In Periodontitis: Current Status And Future Prospective.
Stem Cells Int. 2020;2020. Doi:10.1155/2020/9836518

[10]. Xu QL, Furuhashi A, Zhang QZ, Jiang CM, Chang TH, Le AD. Induction Of Salivary Gland-Like Cells From Dental Follicle Epithelial Cells. J Dent Res.2017;96(9):1035-1043. Doi:10.1177/0022034517711146

[11]. Zhou T, Pan J, Wu P, Et Al. Dental Follicle Cells: Roles In Development And Beyond. Stem Cells Int. 2019;2019. Doi:10.1155/2019/9159605

[12]. Liu J, Wang L, Liu W, Li Q, Jin Z, Jin Y. Dental Follicle Cells Rescue The Regenerative Capacity Of Periodontal Ligament Stem Cells In An InflammatoryMicroenvironment. Plos One. 2014;9(10). Doi:10.1371/Journal.Pone.0108752

[13]. Chen X, Yang B, Tian J, Et Al. Dental Follicle Stem Cells Ameliorate Lipopolysaccharide-Induced Inflammation By Secreting TGF-B3 And TSP-1 To ElicitMacrophage M2 Polarization. Cell Physiol Biochem. 2018;51(5):2290-2308. Doi:10.1159/000495873

[14]. 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):13625-13630. Doi:10.1073/Pnas.240309797

[15]. Fernandes TL, Cortez De Santanna JP, Frisene I, Et Al. Systematic Review Of Human Dental Pulp Stem Cells For Cartilage Regeneration. Tissue Eng - Part BRev. 2020;26(1):1-12. Doi:10.1089/Ten.Teb.2019.0140

[16]. Ji L, Bao L, Gu Z, Et Al. Comparison Of Immunomodulatory Properties Of Exosomes Derived From Bone Marrow Mesenchymal Stem Cells And Dental Pulp StemCells. Immunol Res. 2019;67(4-5):432-442. Doi:10.1007/S12026-019-09088-6

[17]. Maioli M, Basoli V, Santaniello S, Et Al. Osteogenesis From Dental Pulp Derived Stem Cells: A Novel Conditioned Medium Including Melatonin Within AMixture Of Hyaluronic, Butyric, And Retinoic Acids. Stem Cells Int. 2016;2016. Doi:10.1155/2016/2056416

[18]. Lee S, Zhang QZ, Karabucak B, Le AD. Dpscs From Inflamed Pulp Modulate Macrophage Function Via The TNF-A/IDO Axis. J Dent Res. 2016;95(11):1274-1281. Doi:10.1177/0022034516657817

[19]. Min Q, Yang L, Tian H, Tang L, Xiao Z, Shen J. Immunomodulatory Mechanism And Potential Application Of Dental Pulp-Derived Stem Cells In Immune-Mediated Diseases. Int J Mol Sci. 2023;24(9). Doi:10.3390/Ijms24098068

[20]. Sonoyama W, Liu Y, Fang D, Et Al. Mesenchymal Stem Cell-Mediated Functional Tooth Regeneration In Swine. Plos One. 2006;1(1):1-8.Doi:10.1371/Journal.Pone.0000079

[21]. Sonoyama W, Liu Y, Yamaza T, Et Al. Characterization Of The Apical Papilla And Its Residing Stem Cells From Human Immature Permanent Teeth: A PilotStudy. J Endod. 2008;34(2):166-171. Doi:10.1016/J.Joen.2007.11.021

[22]. Dong R, Yao R, Du J, Wang S, Fan Z. Depletion Of Histone Demethylase KDM2A Enhanced The Adipogenic And Chondrogenic Differentiation Potentials OfStem Cells From Apical Papilla. Exp Cell Res. 2013;319(18):2874-2882. Doi:10.1016/J.Yexcr.2013.07.008

[23]. Patil R, Kumar BM, Lee WJ, Et Al. Multilineage Potential And Proteomic Profiling Of Human Dental Stem Cells Derived From A Single Donor. Exp Cell Res.2014;320(1):92-107. Doi:10.1016/J.Yexcr.2013.10.005

[24]. Ding G, Liu Y, An Y, Et Al. Suppression Of T Cell Proliferation By Root Apical Papilla Stem Cells In Vitro. Cells Tissues Organs. 2010;191(5):357-364.Doi:10.1159/000276589

[25]. Zhang Q, Shi S, Liu Y, Et Al. Mesenchymal Stem Cells Derived From Human Gingiva Are Capable Of Immunomodulatory Functions And Ameliorate Inflammation-Related Tissue Destruction In Experimental Colitis. J Immunol. 2009;183(12):7787-7798. Doi:10.4049/Jimmunol.0902318

[26]. Fawzy El-Sayed KM, Dörfer CE. Gingival Mesenchymal Stem/Progenitor Cells: A Unique Tissue Engineering Gem. Stem Cells Int. 2016;2016.Doi:10.1155/2016/7154327

[27]. Zhang QZ, Nguyen AL, Yu WH, Le AD. Human Oral Mucosa And Gingiva: A Unique Reservoir For Mesenchymal Stem Cells. J Dent Res. 2012;91(11):1011-1018. Doi:10.1177/0022034512461016

[28]. Miura M, Gronthos S, Zhao M, Et Al. SHED: Stem Cells From Human Exfoliated Deciduous Teeth. Proc Natl Acad Sci U S A. 2003;100(10):5807-5812.Doi:10.1073/Pnas.0937635100

[29]. Yildirim S, Zibandeh N, Genc D, Ozcan EM, Goker K, Akkoc T. The Comparison Of The Immunologic Properties Of Stem Cells Isolated From Human Exfoliated Deciduous Teeth, Dental Pulp, And Dental Follicles. Stem Cells Int. 2016;2016:11-13. Doi:10.1155/2016/4682875

[30]. De Sá Silva F, Ramos RN, De Almeida DC, Et Al. Mesenchymal Stem Cells Derived From Human Exfoliated Deciduous Teeth (Sheds) Induce ImmuneModulatory Profile In Monocyte-Derived Dendritic Cells. Plos One. 2014;9(5):1-13. Doi:10.1371/Journal.Pone.0098050

[31]. Li Z, Jiang CM, An S, Et Al. Immunomodulatory Properties Of Dental Tissue-Derived Mesenchymal Stem Cells. Oral Dis. 2014;20(1):25-34.Doi:10.1111/Odi.12086

[32]. Seo BM, Miura M, Gronthos S, Et Al. Investigation Of Multipotent Postnatal Stem Cells From Human Periodontal Ligament. Lancet. 2004;364(9429):149-155.Doi:10.1016/S0140-6736(04)16627-0

[33]. Tomokiyo A, Yoshida S, Hamano S, Hasegawa D, Sugii H, Maeda H. Detection, Characterization, And Clinical Application Of Mesenchymal Stem Cells InPeriodontal Ligament Tissue. Stem Cells Int. 2018;2018. Doi:10.1155/2018/5450768

[34]. Andrukhov O, Hong JSA, Andrukhova O, Blufstein A, Moritz A, Rausch-Fan X. Response Of Human Periodontal Ligament Stem Cells To IFN-Γ And TLR-Agonists. Sci Rep. 2017;7(1):2-9. Doi:10.1038/S41598-017-12480-7

[35]. Liu J, Chen B, Bao J, Zhang Y, Lei L, Yan F. Macrophage Polarization In Periodontal Ligament Stem Cells Enhanced Periodontal Regeneration. Stem Cell ResTher. 2019;10(1):1-11. Doi:10.1186/S13287-019-1409-4

[36]. Shin C, Kim M, Han JA, Et Al. Human Periodontal Ligament Stem Cells Suppress T-Cell Proliferation Via Down-Regulation Of Non-Classical Major Histocompatibility Complex-Like Glycoprotein CD1b On Dendritic Cells. J Periodontal Res. 2017;52(1):135-146. Doi:10.1111/Jre.12378

[37]. Ng J, Hynes K, White G, Et Al. Immunomodulatory Properties Of Induced Pluripotent Stem Cell-Derived Mesenchymal Cells. J Cell Biochem.2016;10(May):2844-2853. Doi:10.1002/Jcb.25596

[38]. Liu O, Xu J, Ding G, Et Al. Periodontal Ligament Stem Cells Regulate B Lymphocyte Function Via Programmed Cell Death Protein 1. Stem Cells. 2013;31(7):1371-1382. Doi:10.1002/Stem.1387

[39]. Drela K, Stanaszek L, Snioch K, Et Al. Bone Marrow-Derived From The Human Femoral Shaft As A New Source Of Mesenchymal Stem/Stromal Cells: An Alternative Cell Material For Banking And Clinical Transplantation. Stem Cell Res Ther. 2020;11(1):1-13. Doi:10.1186/S13287-020-01697-5

[40]. Paknejad M, Eslaminejad MB, Ghaedi B, Et Al. 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(3):284-291. Doi:10.1563/AAID-JOI-D-13-00220

[41]. Hasegawa N, Kawaguchi H, Hirachi A, Et Al. Behavior Of Transplanted Bone Marrow–Derived Mesenchymal Stem Cells In Periodontal Defects. JPeriodontol. 2006;77(6):1003-1007. Doi:10.1902/Jop.2006.050341

[42]. 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(2):183-188. Doi:10.1177/0022034513513026

[43]. Xiao L, Zhou Y, Zhu L, Et Al. SPHK1-S1PR1-RANKL Axis Regulates The Interactions Between Macrophages And Bmscs In Inflammatory Bone Loss. JBone Miner Res. 2018;33(6):1090-1104. Doi:10.1002/Jbmr.3396

[44]. Huang GTJ, Gronthos S, Shi S. Critical Reviews In Oral Biology & Medicine: 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. Doi:10.1177/0022034509340867

[45]. Venkataiah VS, Handa K, Njuguna MM, Et Al. Periodontal Regeneration By Allogeneic Transplantation Of Adipose Tissue Derived Multi-Lineage ProgenitorStem Cells In Vivo. Sci Rep. 2019;9(1):1-12. Doi:10.1038/S41598-018-37528-0

[46]. Takahashi K, Tanabe K, Ohnuki M, Et Al. Induction Of Pluripotent Stem Cells From Adult Human Fibroblasts By Defined Factors. Cell. 2007;131(5):861-872.Doi:10.1016/J.Cell.2007.11.019

[47]. Revilla A, González C, Iriondo A, Et Al. Current Advances In The Generation Of Human Ips Cells: Implications In Cell-Based Regenerative Medicine. J Tissue Eng Regen Med. 2016;10(11):893-907. Doi:10.1002/Term.2021

[48]. Malhotra N. Induced Pluripotent Stem (Ips) Cells In Dentistry: A Review. Int J Stem Cells. 2016;9(2):176-185. Doi:10.15283/Ijsc16029

[49]. Hynes K, Bright R, Marino V, Et Al. Potential Of Ipsc-Derived Mesenchymal Stromal Cells For Treating Periodontal Disease. Stem Cells Int. 2018;2018.Doi:10.1155/2018/2601945

[50]. Goriuc A, Foia L, Cojocaru K, Diaconu-Popa D, Sandu D, Luchian I. The Role And Involvement Of Stem Cells In Periodontology. Biomedicines.2023;11(2):1-16. Doi:10.3390/Biomedicines11020387

[51]. Aimetti M, Ferrarotti F, Gamba M, Giraudi M, Romano F. Regenerative Treatment Of Periodontal Intrabony Defects Using Autologous Dental Pulp Stem Cells: A 1-Year Follow-Up Case Series. Int J Periodontics Restorative Dent. 2018;38(1):51-58. Doi:10.11607/Prd.3425

[52]. Sánchez N, Fierravanti L, Núñez J, Et Al. Periodontal Regeneration Using A Xenogeneic Bone Substitute Seeded With Autologous Periodontal Ligament-Derived Mesenchymal Stem Cells: A 12-Month Quasi-Randomized Controlled Pilot Clinical Trial. J Clin Periodontol. 2020;47(11):1391-1402. Doi:10.1111/Jcpe.13368

[53]. Abdal-Wahab M, Abdel Ghaffar KA, Ezzatt OM, Hassan AAA, El Ansary MMS, Gamal AY. Regenerative Potential Of Cultured Gingival Fibroblasts In Treatment Of Periodontal Intrabony Defects (Randomized Clinical And Biochemical Trial). J Periodontal Res. 2020;55(3):441-452. Doi:10.1111/Jre.12728