Annals of Medicine Research and Public Health
Research Article (ISSN: 2995-5955)

A New Future: A Look into How Stem Cell Therapy Can Transform Treating Periodontitis

Sara Prodan, Vincent S Gallicchio*
Department of Biological Sciences, College of Science, Clemson University, Clemson, USA

Citation: *Sara Prodan, Vincent S Gallicchio. A New Future: A Look into How Stem Cell Therapy Can Transform Treating Periodontitis. Ann Med Res Pub Health. 2026;5(1):1-8.*

Received Date: 29 July, 2026**; Accepted Date:** 03 August, 2026**; Published Date:** 05 August, 2026

***Corresponding author:** Dr. Vincent S. Gallicchio, Department of Biological Sciences, College of Science, Clemson University, Clemson, South Carolina, 29636 USA

ABSTRACT
The use of stem cell therapy to treat previously deemed incurable diseases has become more prevalent as technology continues to advance. It provides a level of treatment that focuses on regenerating damaged structures to support the longevity of a patient's health, rather than just treating symptoms, as other common treatments do. In the dental field, a new treatment for periodontitis has been the emphasis of stem cell research, as the prevalence of the disease is only increasing, while current prognosis offers only palliative treatments. Both mesenchymal stem cells and dental tissue–derived stem cells are currently being investigated for their ability to regenerate dental structures damaged because of periodontitis. This review aims to examine the regenerative potential of various stem cell types that can be used in tissue engineering to develop a more suitable treatment for periodontitis.

Keywords: Periodontitis; Stem cell therapy; Regenerative dentistry; Tissue engineering; Dental stem cells

INTRODUCTION
Regenerative dentistry is an advanced branch of bioengineering aimed at replacing lost or injured tissues in the mouth using stem cells and other biomaterials. Current dental restoration treatments focus on repairing damaged tissues, while regenerative dentistry aims to biologically restore the function of teeth and their components for long–term sustainability. For regenerative dentistry to become more widely integrated into practices, there needs to be further developments in stem cell technology, biomaterial optimization, and individualized treatment methods.[1]

Tissue engineering combines stem cells, scaffolds, and signaling molecules to produce functional tissues that restore, maintain, and improve damaged tissues or organs.[2] Scaffolds provide the structural support for cell attachment and tissue development. They are designed out of polymeric biomaterials to mimic the functions of the native extracellular matrix in tissues, as cells in human tissues are anchorage dependent.[3] Scaffolds are rich in growth–factor signaling molecules that promote chemotaxis, proliferation, differentiation, neovascularization, and protein and extracellular matrix synthesis.[4] Cell sheet engineering is a scaffold–free tissue engineering technology that maximizes the function of stem cells while reducing rejection frequency and toxic side effects of traditional scaffolds. The main component of cell sheets is the extracellular matrix, as it is a dynamic reservoir of signaling biological molecules and has a variety of biological functions.[5]

The periodontium is a highly hierarchically organized organ made up of the gingiva, alveolar bone, periodontal ligament, and root cementum.[6] Its main functions are support of the tooth and protection of the tooth, nerve, and blood vessels from injury.[2] Periodontitis leads to the destruction of hard and soft tissues, which causes degradation in the teeth's supporting apparatus, tooth loss, and systemic complications.[6] It is caused by the buildup of plaque bacteria in biofilms within the subgingival. The clinical signs of periodontitis are the result of the immune–inflammatory response in the gingival and periodontal tissues due to the presence of plaque bacteria, causing the

destruction of structural components of the periodontium.[7] An individual's ability to form a specific antibody response to periodontopathogenic organisms indicates their susceptibility to disease as well as their likelihood of responding to treatment. Factors such as smoking, medical conditions, genetics, plaque control, and local factors may influence the host immune response and thus an individual's predisposition to periodontitis. Susceptibility to periodontitis may be correlated with plasma cells predominating the tissues or site because of dental plaque. The ability of an individual or site to form an extensive plasma cell infiltrate has been linked to indicating an inadequate defense against periodontal bacteria, leading to an increased risk of periodontitis.[8] Severe periodontitis affects about 10–15% of the population, while most people have mild periodontitis.[7] Severity of periodontitis is correlated with the appearance of oral squamous cell carcinoma, which suggests that people with periodontal disease have an increased risk of developing oral cancer.[9] Furthermore, data from the National Health and Nutrition Examination Survey 2009/2010 and 2011/2012 cycles indicated that 62.3% of adults 65 years of age or older exhibited some degree of periodontitis; by the year 2040 it is expected that this number will have increased by about 50%.[10]

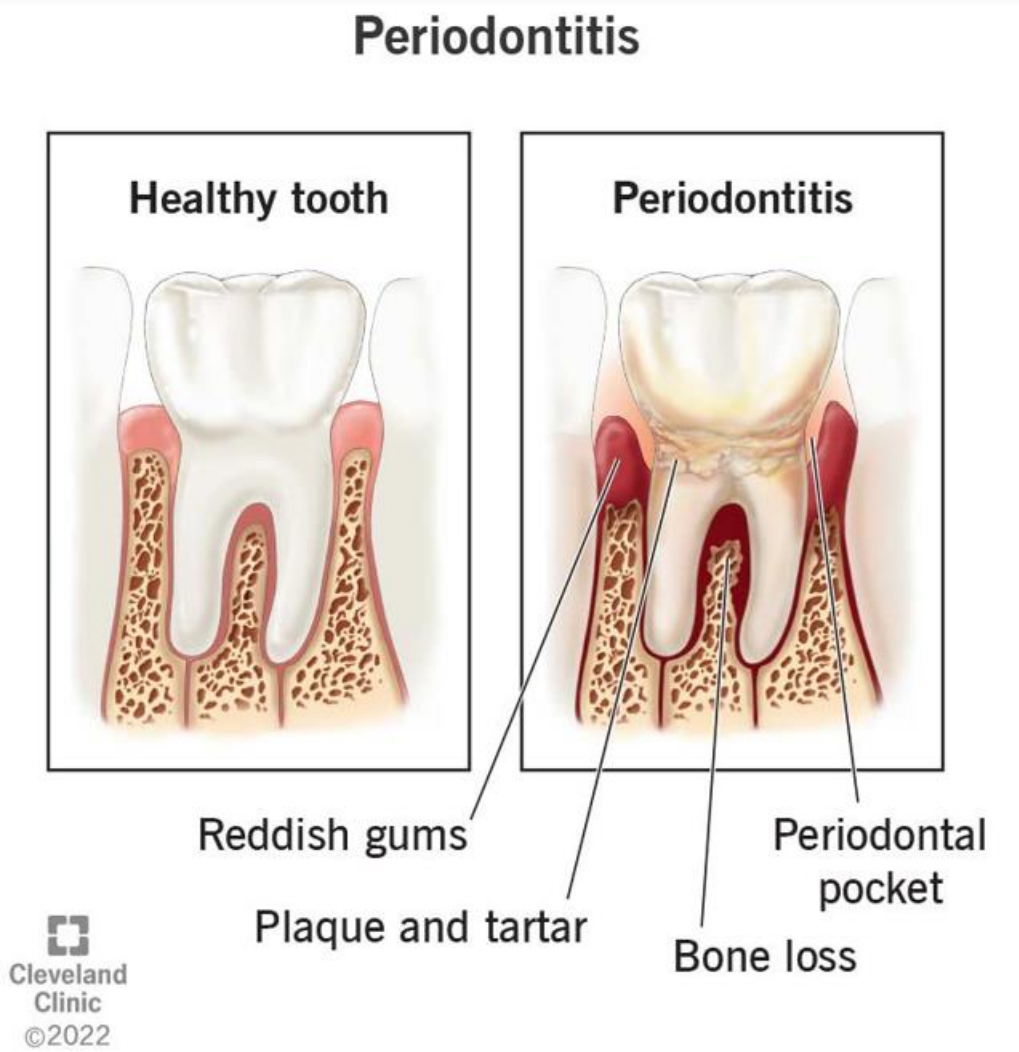

Figure 1: Visual representation of the hallmark symptoms of periodontitis in comparison to a non–diseased tooth.[11]

Current treatment for periodontitis focuses on preventing further disease progression to reduce the risk of tooth loss, minimize symptoms, and educate on maintaining a healthy periodontium. This includes individually tailored oral hygiene instructions, dietary changes, subgingival instrumentation to remove plaque and calculus, local and systemic pharmacotherapy, and various types of surgery. No treatment option has proven to be better than another, and all types appear to work best with adjunctive antimicrobial chemotherapy.[12] The big issue with these treatments

is that they are only palliative, so they have limitations in achieving comprehensive periodontal tissue regeneration. Consequently, the goal of periodontitis treatment needs to be restoration of the disrupted periodontium to its original shape and function.[2] The way to achieve this is using stem cells. Stem cell therapy can revolutionize periodontal regeneration by offering more effective, patient–tailored treatments while addressing the systemic health implications of periodontitis. The regenerative potential of stem cells can aid in the reconstruction of periodontal structures, allowing for the possibility of addressing the root cause of periodontitis.[13]

DISCUSSION

Stem cells are any unspecialized cells that are capable of long–term self–renewal through cell division and can be induced to differentiate into specialized, functional cells.[14] When a stem cell divides, the resulting two daughter cells can be both stem cells, a stem cell and a more differentiated cell, or both more differentiated cells.[15] Stem cells are generally classified into two groups: embryonic stem cells and adult stem cells.[14] Embryonic stem cells are pluripotent, so they can differentiate into almost any cell type in the human body. However, they are derived from the inner cell mass of early–stage embryos, making them both an ethical and practical concern for clinical use.[13] Adult stem cells can be harvested from many differentiated tissues in the body, like bone marrow, bone, fat, and muscle. They are multipotent, meaning they can differentiate into some but not all tissue types. Mesenchymal stem cells are a category of adult stem cells typically used in stem cell therapy.[14] Their multipotency is crucial for periodontal regeneration because it allows for the creation of cell types essential for repairing damaged structures within the periodontium.[13] Additionally, stem cells are present in most tissues in the craniofacial complex, sparking interest in dental applications. Every oral tissue except enamel, dentin, and cementum contains self–renewal stem cells that have the capacity to replace terminally differentiated cells or facilitate wound healing.[16] Dental pulp stem cells, stem cells isolated from human pulp of exfoliated deciduous teeth, periodontal ligament stem cells, stem cells from apical papilla, and dental follicle cells are some of the numerous types of stem cells that have been isolated from dental tissue with the potential to regenerate the tissue of teeth.[17] Dental tissue–derived stem cells have the potential to generate precise dental cell lineages, which can be used for tissue healing and regeneration.[1] Also, dental stem cells have immunomodulatory properties that have been demonstrated to have therapeutic effects on several systemic inflammatory diseases.[18] As a result, stem cell banks now offer cryopreservation services for dental stem cells.[16]

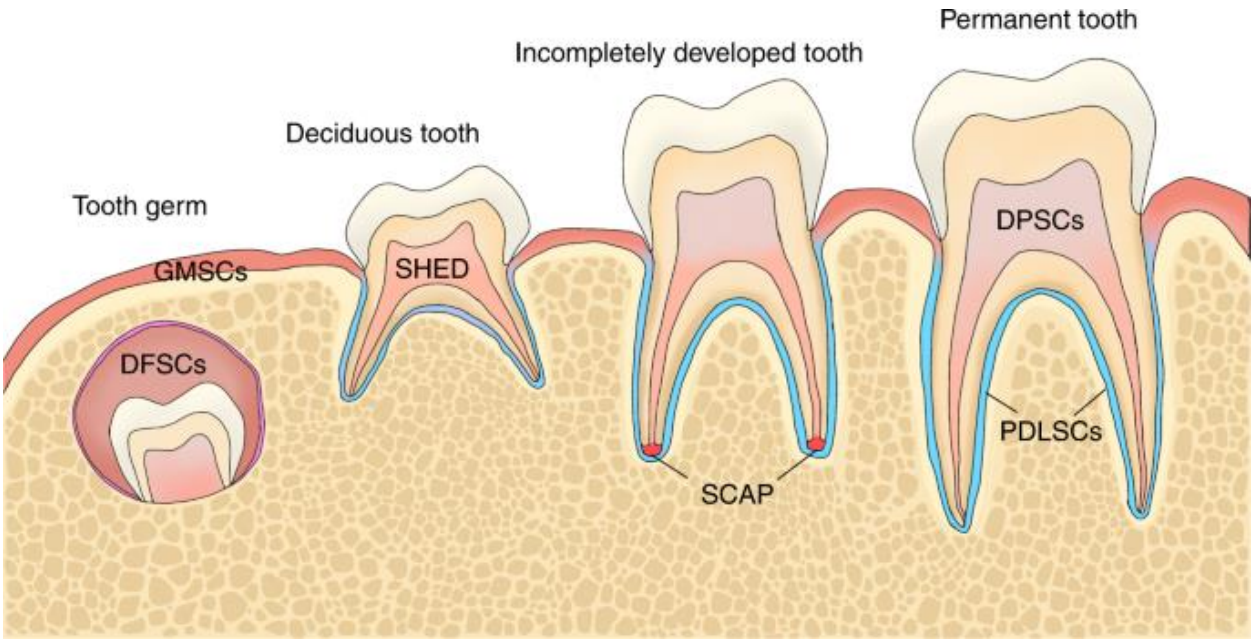

Figure 2: Illustration showing the locations of the different dental tissue–derived stem cells within the various types of teeth in which they are found. Dental follicle stem cells (DFSCs) are harvested from the developing tooth germ and isolated from the connective tissue around the tooth. Gingival mesenchymal stem cells (GMSCs) are derived from the gingiva around the tooth. Stem cells from human exfoliated deciduous teeth (SHEDs) come from the dental

pulp of exfoliated deciduous teeth. Stem cells from apical papilla (SCAPs) are harvested from the apical papilla of an incompletely developed tooth. Dental pulp stem cells (DPSCs) and periodontal ligament stem cells (PDLSCs) are present in permanent teeth and can be isolated from dental pulp and the periodontal ligament.[19]

Stem cell therapy uses the multidirectional differentiation characteristics of stem cells to repair diseased cells or restore the normal function of cells and tissues. It has become increasingly investigated for tissue and organ regeneration. The approach has the potential to significantly impact clinical practices as well as improve the overall well–being of individuals.[20]

Mesenchymal Stem Cells (MSCs)

MSCs are adult connective tissue cells that originate from the mesoderm. They have immunosuppressive and immunotolerant properties, high proliferation rates and the regenerative potential for tissue repair.[21] MSCs can create a more favorable environment for periodontal tissue repair and regeneration by suppressing the inflammatory response characterized by periodontitis. They secrete a diverse range of bioactive molecules, such as growth factors and cytokines, that have trophic and paracrine effects on neighboring cells and tissues, promoting tissue repair and regeneration. Another beneficial characteristic of MSCs is that they can differentiate into osteoblasts. Given that these cells are responsible for bone formation, this ability allows MSCs to aid in the regeneration of alveolar bone.[13]

The therapeutic potential of induced pluripotent stem cell–derived MSCs (iMSCs) has been explored in their capacity to treat periodontitis. It was found that, *in vivo*, iMSCs inhibit M1 macrophage polarization and the number of M1 macrophages by suppressing the NF–kB signaling pathway in periodontal tissues, supporting their anti–inflammatory and immunomodulatory effects. Additionally, they improved the inflammatory microenvironment by reducing the production of pro–inflammatory cytokines (IL–1B, IL–17) and reactive oxygen species, while enhancing the secretion of anti–inflammatory cytokines (IL–10) and growth factors. In this mouse study, under the inflammatory conditions of periodontitis, iMSCs preserved the osteogenic potential of periodontal ligament stem cells and alleviated alveolar bone loss.[22]

Bone Marrow–Derived MSCs (BMSCs)

There is a strong demand for applying BMCs in regenerative medicine because they are readily isolated from bone marrow. They provide an alternative source of mesenchymal stem cells for tissue engineering as they can undergo multilineage differentiation, including blood cells, cardiac cells, osteogenic cells, and other somatic and germ cells *in vitro* as well as *in vivo.* BMSCs can be expanded in culture to produce enough cells for craniofacial and dental tissue engineering purposes. A study showed progress in the regeneration and healing of alveolar bone defects upon linking recombinant human bone morphogenetic protein with silica–coated calcium hydroxyapatite rabbit bone marrow stem cells.[23] Another study in 2019 with dogs with class II periodontitis showed drastic increases in the formation of new bone, cementum, and the periodontal ligament in teeth treated with canine bone marrow mesenchymal stem cells.[24]

Adipose–Derived Stem Cells (ASCs)

The use of ASCs is considered advantageous compared to other sources of stem cells due to the large number of cells that can be easily and quickly isolated from adipose tissue. They secrete growth factors that promote the regeneration of periodontal tissue as well as encourage the neovascularization of damaged tissues, making them an excellent candidate for treating periodontitis.[25] Rat models with periodontitis were injected with ASCs in a clinical trial in 2022. The findings suggested that ASCs can alleviate ligature–induced periodontitis, as evidenced by reduced alveolar bone loss, a significant decrease in the ratio of iNOS+/CD206+ macrophages, and stimulation of M2 macrophage polarization via the indoleamine 2,3–dioxygenase–dependent kynurenine–aryl hydrocarbon receptor–nuclear factor (erythroid–derived 2)–like 2 pathways.[26] A separate study in 2025 tested local vs systemic administration of ASCs in rat models of periodontitis. The results showed that local ASC administration provided superior therapeutic benefits compared to systemic delivery. Locally administered ASCs significantly enhanced bone regeneration, reduced inflammation, improved periodontal tissue architecture, and mitigated cardiac dysfunction, whereas systemic injection was less effective at restoring periodontal integrity.[27] Lastly, an experiment with Wistar rats suggested that ASCs can promote periodontal tissue regeneration *in vivo*, as injection of ASCs into test rats with periodontitis resulted in a periodontal ligament–like structure and alveolar bone regeneration.[28]

Umbilical Cord MSCs (UCMSCs)

Human UCMSCs (hUCMSCs) have been evaluated as cell sources for periodontal regeneration as they can be harvested inexpensively and inexhaustibly. Since they are primitive to MSCs, hUCMSCs exhibit high plasticity and developmental flexibility. hUCMSCs possess osteogenic potential, minimal *in vivo* immunorejection, high extracellular matrix secretion, anti–inflammatory abilities, and the capacity to contribute to the regeneration of both soft and hard periodontal tissues under inflammatory periodontitis conditions.[29] In 2023, a clinical trial with female mice with periodontitis found that hUCMSCs and their extracellular vesicles have the potential to reduce the inflammatory response associated with the disease by downregulating pro–inflammatory cytokines and upregulating anti–inflammatory ones.[30] Similarly, results from a 2024 clinical trial showed that hUCMSCs can promote bone tissue regeneration upon injection of human umbilical cord mesenchymal stem cell–derived extracellular vesicles (HUC–MSCs–EVs) in rat models of periapical periodontitis. HUC–MSCs–EVs facilitated the expression of osteogenic genes and proteins, including runt–related transcription factor 2, alkaline phosphatase, and osteopontin. This allowed for fewer inflammatory cells, decreased osteoclast formation, increased number of blood vessels, and regeneration of periodontal tissues, and therefore, jawbone regeneration in periapical periodontitis.[31]

Dental Pulp Stem Cells (DPSCs)

DPSCs can be easily obtained from extracted teeth, and their harvesting process does not involve any invasive procedures. Their ability to proliferate rapidly and to resist lipopolysaccharide–induced oxidative stress in the periodontitis environment has made DPSCs effective for inducing periodontal regeneration. Moreover, DPSCs exhibit low immunogenicity, strong osteogenic differentiation potential, and immunoregulatory capacity. In China, a clinical study was conducted in 2025 that demonstrated that DPSC injections improved attachment loss, periodontal probing depth, and bone defect depth in patients with stage III periodontitis.[32] Dental pulp stem cell–derived exosomes (DPSC–EXO) were used to treat rats with experimental periodontitis, which showed that DPSCs play an important role in inhibiting periodontitis by promoting tissue regeneration. It was found that the DPSC–EXO treatment regulated inflammation by inhibiting the IL–6/JAK2/STAT3 signaling pathway during acute inflammatory stress, polarized macrophages from the M1 to the M2 phenotype, effectively reduced alveolar bone loss, and promoted periodontal epithelial healing.[33]

Periodontal Ligament Stem Cells (PDLSCs)

Isolated from periodontal ligament tissue, PDLSCs exhibit self–renewal and multipotent capacities. Their plasticity to differentiate into osteoblastic cells has made them a promising source of stem cells for treating periodontitis.[34] The exosomes secreted by PDLSCs have been investigated for their ability to mediate tissue regeneration. The results demonstrated that exosomes derived from healthy periodontal ligaments (h–PDLSCs) could rescue the osteogenesis capacity of endogenous stem cells under an inflammatory environment and promote regeneration of alveolar bone. Treatment of h–PDLSC exosomes led to an increase in the formation of mineralized nodules as well as the expression of osteogenic genes and proteins by mechanistically suppressing the overactivation of canonical Wnt signaling, thereby restoring the osteogenic differentiation capacity. Also, the rat models with periodontitis treated with h–PDLSCs–exosomes exhibited accelerated bone formation in the alveolar bone defect.[35]

Dental Follicle Stem Cells (DFSCs)

DFSCs are in the dental follicle tissue of the tooth germ and derived from the neural crest. They are direct precursor cells of periodontal tissues as they form the periodontal ligament, cementum, and alveolar bone proper in the late stages of tooth development. DFSCs are being used to treat inflammatory diseases in animal models because they can undergo osteogenic, adipogenic, chondrogenic, neural, and cardiomyocytic differentiation in a specific induced environment.[36] They can be isolated and grown under defined tissue culture conditions, increasing their potential for use in tissue engineering applications such as periodontal regeneration and bone regeneration.[37] The therapeutic effects of periodontitis treatment using lipopolysaccharide (LPS) pretreated DFSCs–derived exosomes (L–D–Exo) were tested in two separate studies. The first study found that LPS–preconditioned DFC–small extracellular vesicles promoted PDLSCs and macrophage proliferation, inhibited intracellular reactive oxygen species (ROS) levels, reduced the Nuclear factor Kappa–B Ligand receptor activator (RANKL)/osteogenic protective protein) OPG ratio of PDLSCs by inhibiting ROS/Jun amino–terminal kinases (JNK) signaling under inflammatory conditions, and promoted macrophages to polarize toward the M2 phenotype via ROS/extracellular signal–related kinases (ERK) signaling.[38] The other study concluded that L–D–Exos inhibit miR–184 to facilitate periodontal regeneration while targeting the Peroxisome proliferator–activated receptor alpha (PPARa)–protein kinase B (Akt)–JNK signaling pathway to suppress oxidative stress in periodontal tissues.[39]

Gingival Mesenchymal Stem Cells (GMSCs)

GMSCs are a distinctive homogenous subset of MSCs within the lamina propria of the gingival tissue.[40,41] They develop from neural ectomesenchyme along with contributions from the perifollicular mesenchyme and the dental follicle proper.[40] GMSCs are very easy to collect clinically as they can be isolated from attached and free gingiva, inflamed gingival tissues, and hyperplastic gingiva. They have unique immunomodulatory functions, display positive signals for pluripotency–associated markers, and self–renewal properties, making them an excellent stem cell source for regenerative dentistry.[41] A 2022 clinical trial with Wistar rats with periodontitis evaluated the osteogenic regenerative capacity of GMSCs when combined with melatonin (MEL). The antioxidant properties of MEL protected GMSCs from cellular damage related to oxidative stress, effectively promoting the production of osteogenic cells under oxidative stress.[42] Additionally, preconditioning GMSCs with tumor necrosis factor–alpha (TNF–a) is ideal for treating periodontitis. TNF–a stimulation increases exosome secretion from GMSCs and enhances exosomal CD73 expression, which induces anti–inflammatory M2 macrophage polarization, thereby regulating inflammation and osteoclastogenesis. This was demonstrated through local injections of GMSC–derived exosomes preconditioned with TNF–a in ligature–induced periodontitis model mice experiencing reduced periodontal bone resorption and the number of tartrate–resistant acid phosphate–positive osteoclasts.[43]

Stem Cells from Apical Papilla (SCAPs)

SCAPs have demonstrated to be crucial for angiogenesis/revascularization, neuronal growth, the regeneration of the pulp–dentin complex, apexogenesis, and may be applicable in treating systemic disease.[44] Human stem cells from the apical papilla (hSCAPs) have proven to play a crucial role in the restoration of bone lesions as a consequence of apical periodontitis. Treatment with hSCAPs with miR–199a–5p mimics enhanced cell proliferation and osteogenic differentiation of hSCAPs while silencing endogenous Interferon Induced Protein with Tetratricopeptide Repeats 2 expression to alleviate the inhibitory effect of miR–199a–5p on the osteogenic differentiation of hSCAPs. Subcutaneous ectopic bone formation *in vivo* was also observed, indicating bone lesion repair under periapical inflammatory conditions.[45] A separate study investigating the treatment of apical periodontitis in rats with berberine (BBR) and SCAPs concluded that BBR promoted SCAP osteogenesis, resulting in the formation of tissue, roots, root walls, and small apex diameters. The expression of B–catenin was also induced and enhanced upon entering the nucleus, upregulating more runt–related nuclear factor 2 downstream to increase root repair in immature teeth with apical periodontitis by activating the canonical Wnt/B–catenin pathway in SCAPs.[46]

Stem Cells from Human Exfoliated Deciduous Teeth (SHEDs)

SHEDs not only exhibit the basic characteristics of stem cells, but they also have great potential for inhibiting inflammation and promoting tissue regeneration. Thus, SHED therapy may provide a new direction for treating inflammation and corresponding tissue defects, like that observed in periodontitis.[47] They display increased migratory ability and neurogenic potential as well as express extracellular matrix, osteogenic, and odontogenic proteins. As a result, in vivo, SHEDs treated with dentin matrix have successfully regenerated periodontal tissues, including periodontal ligament fibers, blood vessels, and alveolar bone.[48] A study using rat models with periodontitis in 2018 found that multidose delivery of SHEDs can cause periodontal tissue regeneration. SHEDs altered the cytokine expression profile in gingival crevicular fluid, reduced gum bleeding, increased new attachment of periodontal ligament, decreased osteoclast differentiation, and promoted monocyte/macrophage conversion to CD206+ M2–like phenotype. This resulted in the SHED administration significantly increasing periodontal regeneration, alveolar bone volume, and decreasing the distance from the cementoenamel junction to the alveolar bone crest.[49]

CONCLUSION

Stem cells can revolutionize the treatment of periodontitis. Their capacity to regenerate structures of the periodontium, such as the alveolar bone, periodontal ligament, and root cementum, can give people the opportunity to recover from periodontitis rather than learning to live with it. Stem cells have this potential because they can stimulate M2 macrophage polarization, which effectively reduces inflammation associated with periodontitis while promoting revascularization and neuronal growth to support tissue regeneration. Another key characteristic of stem cells is their competence in promoting osteogenesis, allowing for osteoblast differentiation and limiting osteoclasts. The stem cells reviewed have shown promise in animal models, but continued research with human subjects is needed to further investigate their regenerative properties as well as their application in treating periodontitis. Although stem cell therapy remains experimental, mainly costly, technically demanding, and ethically challenging,

it is a cutting–edge approach that holds the future of true tissue regeneration, like what is needed to treat periodontitis.[50]

REFERENCES

1. Umapathy VR, Natarajan PM, Swamikannu B. Regenerative strategies in dentistry: harnessing stem cells, biomaterials and bioactive materials for tissue repair. *Biomolecules*. 2025;15(4):546.
2. Tomokiyo A, Wada N, Maeda H. Periodontal ligament stem cells: regenerative potency in periodontium. *Stem Cells Dev*. 2019;28(15):974–985.
3. Chan BP, Leong KW. Scaffolding in tissue engineering: general approaches and tissue–specific considerations. *Eur Spine J*. 2008;17(Suppl 4):467–479.
4. Geisinger ML. NexGen regen? Challenges and opportunities for growth factors and signaling agents in periodontal regeneration at intrabony defects. *Front Dent Med*. 2023;4:1239149.
5. Chen Y, Huang H, Li G, et al. Dental–derived mesenchymal stem cell sheets: a prospective tissue engineering for regenerative medicine. *Stem Cell Res Ther*. 2022;13(1):38.
6. Staples RJ, Ivanovski S, Vaquette C. Fiber guiding scaffolds for periodontal tissue engineering. *J Periodontal Res*. 2020;55(3):331–341.
7. Preshaw PM, Seymour RA, Heasman PA. Current concepts in periodontal pathogenesis. *Dent Update*. 2004;31(10):570–578.
8. Kinane DF. Aetiology and pathogenesis of periodontal disease. *Ann R Australas Coll Dent Surg*. 2000;15:42–50.
9. Komlós G, Csurgay K, Horváth F, Pelyhe L, Németh Z. Periodontitis as a risk for oral cancer: a case–control study. *BMC Oral Health*. 2021;21(1):640.
10. Eke PI, Wei L, Borgnakke WS, et al. Periodontitis prevalence in adults ≥65 years of age in the USA. *Periodontol 2000*. 2016;72(1):76–95.
11. Cleveland Clinic. *Periodontitis: symptoms, causes, & treatment*. Cleveland Clinic Health Library. 2024.
12. Graziani F, Karapetsa D, Alonso B, et al. Nonsurgical and surgical treatment of periodontitis: how many options for one disease? *Periodontol 2000*. 2017;75(1):152–188.
13. Bharuka T, Reche A. Advancements in periodontal regeneration: a comprehensive review of stem cell therapy. *Cureus*. 2024;16(2):e54115.
14. Quimby JM. Stem cell therapy. *Vet Clin North Am Small Anim Pract*. 2019;49(2):223–231.
15. National Institutes of Health. *Stem Cell Basics*. National Institutes of Health. 2016.
16. Mantesso A, Nör JE. Stem cells in clinical dentistry. *J Am Dent Assoc*. 2023;154(12):1048–1057.
17. Zhai Q, Dong Z, Wang W, et al. Dental stem cell and dental tissue regeneration. *Front Med*. 2019;13(2):152–159.
18. Li P, Ou Q, Shi S, et al. Immunomodulatory properties of mesenchymal stem cells/dental stem cells and their therapeutic applications. *Cell Mol Immunol*. 2023;20(6):558–569.
19. Li Y, Duan X, Chen Y, et al. Dental stem cell–derived extracellular vesicles as promising therapeutic agents in the treatment of diseases. *Int J Oral Sci*. 2022;14:2.
20. Zhai Q, Dong Z, Wang W, et al. Dental stem cell and dental tissue regeneration. *Front Med*. 2019;13(2):152–159.
21. Hernández–Monjaraz B, Santiago–Osorio E, Monroy–García A, et al. Mesenchymal stem cells of dental origin for inducing tissue regeneration in periodontitis: a mini–review. *Int J Mol Sci*. 2018;19(4):944.
22. Chen L, Liu Y, Yu C, et al. Induced pluripotent stem cell–derived mesenchymal stem cells (iMSCs) inhibit M1 macrophage polarization and reduce alveolar bone loss associated with periodontitis. *Stem Cell Res Ther*. 2025;16(1):223.
23. Khorasani HR, Sanchouli M, Mehrani J, et al. Potential of bone marrow–derived mesenchymal stem cells for maxillofacial and periodontal regeneration: a narrative review. *Int J Dent*. 2021;2021:4759492.
24. Rezaei M, Jamshidi S, Saffarpour A, et al. Transplantation of bone marrow–derived mesenchymal stem cells, platelet–rich plasma, and fibrin glue for periodontal regeneration. *Int J Periodontics Restorative Dent*. 2019;39(1):e32–e45.
25. Tobita M, Mizuno H. Adipose–derived stem cells and periodontal tissue engineering. *Int J Oral Maxillofac Implants*. 2013;28(6):e487–e493.
26. Li H, Yuan Y, Chen H, et al. Indoleamine 2,3–dioxygenase mediates the therapeutic effects of adipose–derived stromal/stem cells in experimental periodontitis by modulating macrophages through the kynurenine–AhR–NRF2 pathway. *Mol Metab*. 2022;66:101617.

27. Elhaieg A, Farag A, Koung Ngeun S, et al. Therapeutic potential of local and systemic adipose–derived mesenchymal stem cell injections in a rat model of experimental periodontitis: implications for cardiac function. *Int J Mol Sci*. 2025;26(9):3984.
28. Tobita M, Uysal AC, Ogawa R, et al. Periodontal tissue regeneration with adipose–derived stem cells. *Tissue Eng Part A*. 2008;14(6):945–953.
29. Shang F, Liu S, Ming L, et al. Human umbilical cord MSCs as new cell sources for promoting periodontal regeneration in inflammatory periodontal defect. *Theranostics*. 2017;7(18):4370–4382.
30. Wang X. Human umbilical cord mesenchymal stem cells and their extracellular vesicles modulate pro– and anti–inflammatory cytokines in ligature–induced periodontitis. *Iran J Immunol*. 2023;20(4):446–455.
31. Gao J, Zhu D, Fan Y, et al. Human umbilical cord mesenchymal stem cells–derived extracellular vesicles for rat jawbone regeneration in periapical periodontitis. *ACS Biomater Sci Eng*. 2024;10(9):5784–5795.
32. Liu Y, Liu Y, Hu J, et al. Impact of allogeneic dental pulp stem cell injection on tissue regeneration in periodontitis: a multicenter randomized clinical trial. *Signal Transduct Target Ther*. 2025;10(1):239.
33. Qiao X, Tang J, Dou L, et al. Dental pulp stem cell–derived exosomes regulate anti–inflammatory and osteogenesis in periodontal ligament stem cells and promote the repair of experimental periodontitis in rats. *Int J Nanomedicine*. 2023;18:4683–4703.
34. Maeda H, Tomokiyo A, Fujii S, et al. Promise of periodontal ligament stem cells in regeneration of periodontium. *Stem Cell Res Ther*. 2011;2(4):33.
35. Lei F, Li M, Lin T, et al. Treatment of inflammatory bone loss in periodontitis by stem cell–derived exosomes. *Acta Biomater*. 2022;141:333–343.
36. Zhang J, Ding H, Liu X, et al. Dental follicle stem cells: tissue engineering and immunomodulation. *Stem Cells Dev*. 2019;28(15):986–994.
37. Honda MJ, Imaizumi M, Tsuchiya S, et al. Dental follicle stem cells and tissue engineering. *J Oral Sci*. 2010;52(4):541–552.
38. Huang Y, Liu Q, Liu L, et al. Lipopolysaccharide–preconditioned dental follicle stem cell–derived small extracellular vesicles treating periodontitis via reactive oxygen species/mitogen–activated protein kinase signaling–mediated antioxidant effect. *Int J Nanomedicine*. 2022;17:799–819.
39. Chen L, Zhang J, Yu J, et al. LPS–pretreated dental follicle stem cell–derived exosomes promote periodontal tissue regeneration via miR–184 and PPARα–Akt–JNK signaling pathway. *Stem Cell Res Ther*. 2025;16(1):347.
40. Shetty SS, Sowmya S, Pradeep A, et al. Gingival mesenchymal stem cells: a periodontal regenerative substitute. *Tissue Eng Regen Med*. 2025;22(1):1–21.
41. Grawish ME. Gingival–derived mesenchymal stem cells: an endless resource for regenerative dentistry. *World J Stem Cells*. 2018;10(9):116–118.
42. Solá VM, Aguilar JJ, Farías A, et al. Melatonin protects gingival mesenchymal stem cells and promotes differentiation into osteoblasts. *Cell Biochem Funct*. 2022;40(6):636–646.
43. Nakao Y, Fukuda T, Zhang Q, et al. Exosomes from TNF–α–treated human gingiva–derived MSCs enhance M2 macrophage polarization and inhibit periodontal bone loss. *Acta Biomater*. 2020;122:306–324.
44. Wu PH, Wang YH, Lin YC, et al. Roles of basic fibroblast growth factor, stem cells from dental pulp and apical papilla in the repair and regeneration of dental pulp and other tissues/organs. *J Dent Sci*. 2025;20(4):2066–2075.
45. Hu J, Huang X, Zheng L, et al. MiR–199a–5P promotes osteogenic differentiation of human stem cells from apical papilla via targeting IFIT2 in apical periodontitis. *Front Immunol*. 2023;14:1149339.
46. Cui Y, Xie J, Fu Y, et al. Berberine mediates root remodeling in an immature tooth with apical periodontitis by regulating stem cells from apical papilla differentiation. *Int J Oral Sci*. 2020;12(1):18.
47. Su J, Ge X, Jiang N, et al. Efficacy of mesenchymal stem cells from human exfoliated deciduous teeth and their derivatives in inflammatory diseases therapy. *Curr Stem Cell Res Ther*. 2022;17(4):302–316.
48. Yang X, Ma Y, Guo W, et al. Stem cells from human exfoliated deciduous teeth as an alternative cell source in bio–root regeneration. *Theranostics*. 2019;9(9):2694–2711.
49. Gao X, Shen Z, Guan M, et al. Immunomodulatory role of stem cells from human exfoliated deciduous teeth on periodontal regeneration. *Tissue Eng Part A*. 2018;24(17–18):1341–1353.
50. Mohammad Mirzapour S, Jalali F. Stem cell therapy for regenerating periodontal bony defects: a narrative review. *J Adv Periodontol Implant Dent*. 2025;17(1):1–14.