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Oral stem cells in combination with hydrogels as biomimetic bioactive platforms for periodontal tissue engineering

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Oral stem cells possess the capability to repair themselves and multipotent differentiation capacities, indicating that they have significant prospects in regenerative medicine. Nonetheless, due to the circulatory system's rapid clearance capability, they can only work consistently in certain areas for tissue healing. Thanks to their loose, porous architecture and high biocompatibility, hydrogels can act as transporters for oral stem cells, thereby delaying their release and enhancing their retention in specific regions. Oral stem cell-loaded hydrogels can be a valuable solution when specific areas require oral stem cells for optimal functioning, considering various types of hydrogels and the variables that affect their ability to transport and release oral stem cells. This review discusses the mechanistic processes underlying periodontitis, mentions current therapeutic techniques and their limitations, and explores oral stem cells and their regenerative capacities and design criteria of oral stem cells-laden hydrogels. Along with an assessment of the shortcomings in present investigations on the fundamental processes and innovative uses of oral stem cells in periodontal reconstruction, with the goal of offering fresh perspectives for upcoming research, the ongoing difficulties and disputes associated with oral stem cell-laden hydrogel personalized treatment options are also covered.

KEYWORDS

bone regeneration, engineering, hydrogels, oral stem cells, periodontal

1 Introduction

Periodontitis is a chronic inflammatory condition of the tissues surrounding the teeth, resulting in breakdown of periodontal tissues and potentially leading to tooth extraction (1). Periodontitis' clinical signs include chronic gingival hemorrhage and tenderness, periodontal pocket formation, and bone loss (2). Over 11% of people worldwide suffer from periodontitis (3). Extensive periodontitis affects an estimated 800 million to 1.4 billion persons worldwide (4). Furthermore, periodontitis is intimately connected with the emergence of generalized inflammation, negative pregnancy results, and specific disorders (5–7). The negative change to the periodontal health impacts the quality of life of people (8).

Periodontal wound healing is a complicated process due to the periodontium's distinct morphology and makeup. By lowering the bacterial population in the periodontium and altering the surrounding milieu to minimize inflammatory processes, currently available traditional methods for periodontal therapy concentrate on halting the progression of periodontitis. To promote tissue reattachment, contemporary non-surgical procedures, like phase I therapy, and surgical treatments are employed to remove damaged tissue and thoroughly clean the root surface. By creating a lengthy junctional epithelial connection, these methods typically lead to a reconstruction process that heals the wound site. This non-physiological epithelial contact does not strongly connect the root surface and the surrounding gingiva (9, 10).

This technique cannot be regarded as real periodontium regeneration because it only partially repairs the injured cementum or alveolar bone. There are several restrictions on the treatment results, even if healing by repair may be useful in stopping further disease development and, consequently, any eventual extraction of teeth. First, the absence of tissue regeneration may restrict the therapeutic ability to improve the teeth's current movement. Furthermore, gingival recession is a common side effect associated with this therapy, which can make affected teeth more susceptible to root cavities, in addition to being aesthetically unappealing. Lastly, it is hypothesized that the region may be more vulnerable to future illness recurrence if the original morphology is not restored (11).

In recent decades, biotechnology advancements have created an opportunity to optimize periodontal regeneration (12). Oral stem cells possess self-renewal capacity while maintaining their "stemness" (13). Oral stem cells can differentiate in multiple directions, self-renew, and can regenerate into diverse tissues, organs, and cells (14).

There has been a great deal of clinical study on oral MSCs, and many important discoveries have been made (15–17). MSCs are extensively employed to repair several kinds of damaged tissues in addition to restoring hematological function and treating autoimmune illnesses (18). Based on distinct genomic profiling characteristics that influence clinical, pharmacological, and therapeutic options to the best possible disease treatment, personalized or targeted medicine is a rapidly developing area of healthcare (19–21). Scientists have discovered that combining oral stem cells with biomaterials can compensate for the shortcomings of oral stem cells in targeted reconstruction applications, thanks to advancements in biotechnology (22–24). Hydrogels are biomimetic platforms that have been widely employed in tissue restoration and repair (25). The application of hydrogels loaded with oral stem cells can enhance the survivability of these cells and facilitate their delivery to the defect site for prolonged *in situ* release, even though the hydrogels themselves are comparatively bioactive (26). Numerous investigations have demonstrated that hydrogels loaded with oral stem cells possess potentials in tissue regeneration and repair (27–31). In this article, we highlight the origins, capacities, extraction, and characterization techniques of oral stem cells, as well as a summary of their current-day utilization in periodontal regeneration. We then go over hydrogels and the parameters that influence the loading and release of oral stem cells. We present a summary of numerous methodologies for loading oral stem cells into hydrogels, as well as approaches to characterize hydrogels with oral stem cells. Moreover, we describe the implementation of oral stem cell-loaded hydrogels in regenerative periodontal applications.

2 Mechanisms of tissue destruction in periodontitis

Periodontitis is mostly caused by poor dental hygiene, as well as a variety of genetic and environmental factors. To avoid or treat periodontal defects, a thorough knowledge of these variables and the underlying molecular pathways is essential. Gingivitis is the first stage of periodontal inflammation, and the progression to periodontitis is influenced by a number of variables, notably the switch of aerobic bacteria in dental plaque to anaerobic ones, genetic changes, and host environment factors. Although microbes share in the etiology of periodontitis by directly compromising oral tissues, they can cause detrimental

Abbreviations

ALP, Alkaline phosphatase; BOP, Bleeding on probing; BSA, Bovine serum albumin; CAL, Clinical attachment level, CM; Cellular matrix; CS, Chitosan; DECM, Decellularized extracellular matrix; DFO, Deferoxamine; DFSCs, Dental follicle stem cells; DPSCs, Dental pulp stem cells; ECM, Extracellular matrix; EVs, Extracellular vesicles; FRESH, Freeform reversible embedding of suspended hydrogels; GelMA, Gelatin methacrylate; GMSCs, Gingival mesenchymal stem cells; GMSs, Gelatin-based microspheres; HGF, Hepatocyte growth factor; HMZ, Hyaluronic acid methacryloyl/ZnO; IDO, Indoleamine 2,3-dioxygenase; IL, Interleukin; JE, Junctional epithelium; MAPK, Mitogen-activated protein kinase; MSCs, Mesenchymal stem cells; NBG, Nanoinspired bioactive glass; NHPA, Nanohydroxyapatite; OCN, Osteocalcin; OSR, Osteoinductive reagents; PDGF, Platelet derived growth factor; PDL, Periodontal ligament; PDLSCs; Periodontal ligament stem cells; PEG, Poly(ethylene glycol); PEGDA, Poly(ethylene glycol) dimethacrylate; PLGA, Poly(lactic-co-glycolic acid); PLL, Poly-L-lysine; PRF, Platelet rich fibrin; rhBMP-2, Recombinant bone morphogenic protein-2; RUNX2, Runt-related transcription factor 2; SCAPs, Stem cells from apical papilla; SHEDs, Stem cells from shedding deciduous teeth; SPMs, Specialized pro-resolving mediators; TAZ, Transcriptional coactivator with PDZ-binding motif; TG-GELs, transglutaminase-cross-linked gelatins; TGF-β, Transforming growth factor beta; TGSCs, Tooth germ stem cells; TIMPs, Tissue inhibitors of metalloproteinases; WHMP, Whitlockite; YAP, Yes-associated protein; β-TCP, Beta tricalcium phosphate.

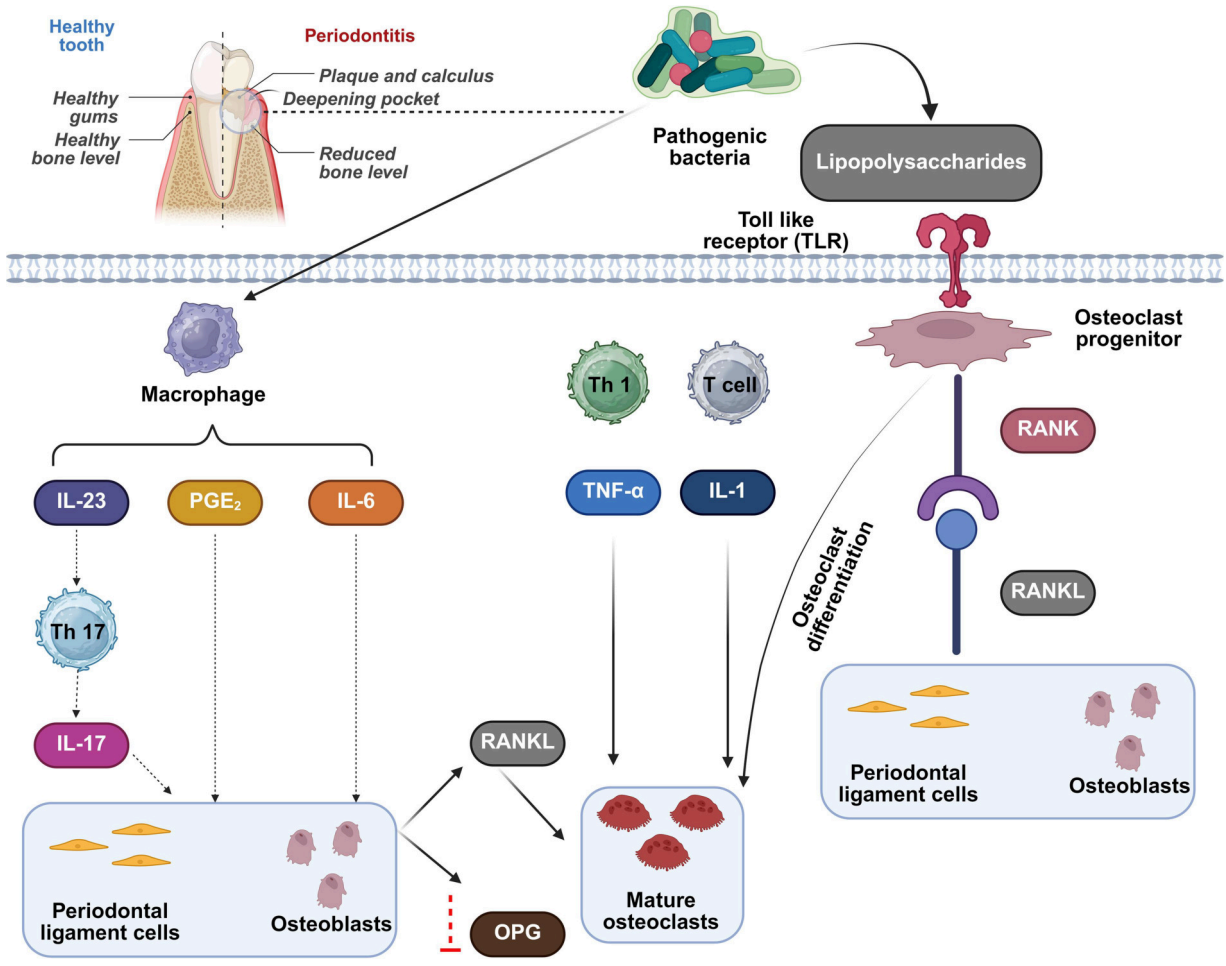


FIGURE 1
Mechanistic processes in periodontitis. This figure was created based on the tools provided by Biorender.com (accessed November 2, 2025).

inflammation in the vulnerable host by forming extremely sticky biofilms on tooth surfaces.

Contemporary microbiological and mechanistic investigations have increased our comprehension of the microbe-human dynamics in periodontitis (Figure 1) (32–34). Furthermore, such research in people and experimental animals has demonstrated that (i) the periodontal dysbiosis is significantly more varied and complicated than formerly assumed, and (ii) the microbes implicated cause illness via polymicrobial synergies and dysbiosis (25, 35, 36). In other words; periodontitis does not occur due to just one or a limited number of bacterial species. Inflammation is a vital element of the overall biological process where host cells strive to confront numerous dangers such as invading infections, injured cells, and irritants (37, 38). The primary roles of inflammatory responses are to eliminate the starting point of illness or cell injury, to remove apoptotic and dead cells and contaminants, and to initiate tissue repair via adaptation of the local blood vessels and the release of several molecules interacting with neutrophils, along with various cell types (39, 40). In reaction to tissue infection, damage, or inflammatory conditions, neutrophils are the earliest cells to be recruited from the circulatory system to the diseased area (41, 42).

The mechanism of neutrophil extravasation involves a complex sequence of minimal- and high-affinity adhesion contacts between neutrophils and the endothelium (43). While neutrophils were formerly associated with acute inflammation, they are increasingly recognized as important actors in chronic inflammatory diseases (44). In fact, neutrophils are functionally flexible and perform previously unexpected roles, such as modulating adaptive immune leukocytes (45). Neutrophils, for example, can attract Th17 cells by producing the chemokines CCL2 and CCL20. Th17 are CD4+ T helper cells that produce interleukin-17 at inflammatory sites (46). In periodontitis, Th17 represents an osteoclastogenic fraction that connects activated T cells to pathological destruction of bone (47).

In addition, neutrophils secrete the B lymphocyte stimulant and a proliferation-inducing ligand (APRIL), two important cytokines that enhance the viability, division, and development of B lymphocytes into plasma cells (48, 49). Periodontitis includes both innate and adaptive immune components. To regulate periodontally associated immunological and

inflammatory reactions, neutrophils, antigen-presenting cells, and T and B lymphocytes form an intricate series of collaborations with one another and with humoral pathways, such as complement (50). It is now well accepted that complement has activities beyond its conventional duty of marking and killing bacteria (51). Complement, for instance, can increase antigenic responses by engaging with Toll-like receptors on innate leukocytes, as well as modulate the activation and development of B cells and T-cell subtypes (52). In periodontitis, inflammation-driven bone loss is regulated by a trio of proteins, including RANKL, RANK, and osteoprotegerin. Stimulated T and B lymphocytes generate RANKL, and osteoblasts, in the inflammatory periodontium (53) The conjugation of cell-surface or soluble RANKL to RANK on osteoclast precursors causes osteoclast maturity and stimulation. However, the RANKL/RANK-mediated mechanism is inhibited by the decoy receptor osteoprotegerin (54). The optimal outcome of an inflammatory reaction is its prompt cessation, so that it does not develop into a chronic condition and have potentially negative consequences. In fact, ongoing inflammatory processes underlie numerous long-term conditions, particularly periodontitis (55).

3 Periodontal regeneration: challenges and opportunities

The continuous deterioration of dental anchoring structures, especially the PDL, is the hallmark of periodontitis, which can ultimately lead to tooth loss. Despite there are numerous therapeutic therapies available, most of them concentrate on symptomatic alleviation and do not provide strong evidence to back up the PDL's functional regeneration (56).

The cementum, PDL, and bundle bone make up the intricate organ known as the tooth attachment complex. From an embryological perspective, all of these structures have an ectodermal origin, which distinguishes them from bone tissues, which typically originate from the mesoderm (57, 58). The PDL fibers have been embedded into the cementum, a thin layer of mineralized tissue covering the dentin of the tooth root. The tooth cushioning mechanism is performed by the PDL. Sharpey's fibers, which are strings of collagen, make up its structure, in addition to veins and nerves that supply nutrition and sensation to the adjacent tissues (59, 60).

That portion of bone nearest the root surface is called the bundle bone. It differs from the alveolar bone due to the insertion of Sharpey's fibers. A bundle bone alone, without any alveolar bone, covers several teeth that are located outside of the alveolar bone housing. When attachment destruction happens, tissue enzymes break down the PDL and bundle bone, leaving the cementum on the tooth surface coated with calculus and bacterial plaque (61–63).

Oral stem cells have drawn a lot of interest as a possible pathway for PDL regeneration because of their affinity and MSCs characteristics. As a result, several therapeutic approaches have been created to boost the effectiveness of therapies centered around oral stem cells and achieve better clinical results. Because of their strong regeneration potential and immunity-modulating characteristics, oral stem cells have garnered considerable attention in bioengineering (64).

Oral stem cells are MSCs with higher multipotent differentiating potential, as was previously indicated. Relying on specific inductive circumstances, they can develop into odontoblasts, osteoblasts, etc. One approach that shows promise for correcting chronic dysbiosis is the use of homogenous MSCs *in situ*. With the potential for functional PDL repair, oral stem cell-based periodontal regenerative cell treatment has become a revolutionary method in periodontal reconstruction (65).

PDL is primarily made up of fibers, cells, and their neighboring extracellular matrix (ECM), with circulatory processes providing nutrients. About 50%–75% of the PDL fibers' volume is made up of collagen fibrils, mostly type I collagen, with lesser participation from types III, IV, V, VI, and XII collagen. The main fibers are the most important parts of the fiber bundles formed by these collagen fibers. By penetrating the alveolar bone on one aspect and the cementum on the other, these fibers serve as the tooth's anchorage. Furthermore, the major fibers incorporate elastic fibers (oxytalan), which control blood circulation and aid in the advancement of the neuronal and vascular system inside the PDL (66, 67).

The process of developing PDL is intricate and ever-changing. PDL fiber bundles are first formed when the tooth root grows, and then stem cells inside the dental follicle next to the root differentiate. These stem cells then develop into cementum and alveolar bone, where Sharpey's fibers and collagen fibers released by PDLCs mineralize to create a mature PDL. This system allows for continuous rebuilding and offers nutrition and mechanical support. Development between progenitors and PDLSCs may support tissue regeneration, maintenance, and repair at the cellular level. When subjected to mechanical stresses, osteocytes function as a crucial mechanosensory role (68).

Under mechanical stresses, osteoblasts and osteoclasts shape the alveolar bone by mediating bone production and breakdown. Certain mechanosensing non-coding RNAs, like microRNAs, may disrupt the synthesis of associated biomarkers. Additionally, factors that control bone and tissue metabolism activate several signal pathways. Under mechanical stresses, these elements aid in maintaining the normal state of the gingiva, PDL, and bone that make up periodontal health (69).

Biofilm and calculus are commonly removed mechanically utilizing ultrasonic equipment. Several evaluations have reported the advantages of local and systemic antimicrobial medications. Nevertheless, overconsumption of antimicrobial drugs may result in resistance to therapies and other adverse effects. The efficacy of periodontal treatment is determined by the clinician's knowledge and ability to eliminate periodontal pathogens. Phase I therapy is commonly utilized in conjunction with local or systemic antibacterial medicines. Inability to completely remove periodontal bacteria frequently results in a recurrence. Because existing therapies are ineffective and microbial resistance to available antimicrobial drugs has increased, there is a need to discover more efficient strategies and therapeutic approaches for treating periodontal bacteria (70).

Currently, numerous periodontal treatments can result in varying patterns and levels of periodontal reconstruction. Periodontal investigations have resulted in the development of some clinical procedures for high-level and more effective regeneration and restoration of periodontal defects, as well as enhanced implant site development (71, 72).

The application of biologics has ushered in a new era of tissue engineering. The progression of regeneration is thus greatly reliant upon the accessibility of suitable cell sources, stimulating and developmental components, and, in fact, the ECM released by these cells. While the precise events associated with periodontal healing are still unknown, suitable precursor cells have to move in the direction of the root surface and bond to it, where they can divide and differentiate into the components necessary for a functional attachment (73).

Furthermore, wound stability following surgical operations, defect filling with a 3D implantable device, and primary intention healing are essential issues that must be addressed to achieve true periodontal regeneration, according to existing research findings. Consequently, periodontal specialists will be able to efficiently control associated parameters to maximize clinical outcomes and enhance the reliability of periodontal regeneration treatments if they have a thorough understanding of the numerous elements that can impact clinical outcomes (74).

A novel way to enhance current periodontal disease treatment plans is through tissue engineering. The attraction of precursor cells capable of transforming into specialized regenerative cells, their division, and the formation of the unique components that comprise the periodontium are essential for the regenerative processes involved in periodontal wound repair. While utilizing the regenerative capacity of PDLSCs is an important tissue-engineering technique for periodontal regeneration, an additional strategy might include incorporating oral stem cells into a prefabricated 3D matrix that is subsequently placed into the defect following an appropriate *in vitro* culture. The origins of cells, improving engineering techniques, and Modifying biomaterials are all very difficult issues that call for novel approaches (75, 76).

The most fundamental dilemma regarding the comprehensive method to apply remains uncertain, notwithstanding opportunities for breakthroughs in biotechnology. to fundamentally alter how surgeons restore patients with periodontal abnormalities. For tissue-engineering treatments in periodontology, the available data are far from adequate, particularly for preclinical testing (77).

The majority of clinical assessments are restricted to treatments that demonstrate encouraging outcomes in these preliminary studies. There is little likelihood that tissue-engineering technologies will be widely adopted in clinical settings for periodontal regeneration in the near future (78).

It is evident that the adoption of regenerative approaches in periodontal treatment holds enormous promise for the future and can address a diverse set of patient requirements. To ensure that the advancement of innovative clinical therapies is backed by solid evidence and that such methods are effective, top-notch clinical trials of already accessible medications are always crucial.

There are several conventional therapies for periodontitis, each addressing a distinct part of the disease's origin and pathophysiology. Antibacterial medication therapy is often employed. Nevertheless, typical treatments become inefficient owing to medication resistance and the appearance of undesirable consequences.

Significant improvements concerning periodontal regeneration can be guided by a quick examination of results from current therapy modalities, underscoring the necessity of strong collaboration between fundamental research and clinical experts (79).

4 Overview of oral stem cells

Oral stem cells can adhere to plates and form colonies when grown in the right environments (Figure 2 and Table 1) (80). They are excellent options for tissue regeneration purposes because of their strong capacity to proliferate and propensity for multilineage transformation, encompassing osteogenic, chondrogenic, and adipogenic lines (81). Additionally, oral stem cells possess immune-modulating effects that enable them to regulate and preserve the periodontal microbiota's balance through the immune system's reaction (82). Additionally, injury signals can attract and deploy endogenous stem cells in particular niches to injured sites via a mechanism known as homing (83). They can transform into numerous kinds of cells at the site of damage, allowing for tissue regeneration (84).

4.1 Dental pulp stem cells (DPSCs)

DPSCs are MSCs collected from the pulpal tissue of permanent teeth, often impacted wisdom teeth or teeth taken for orthodontic procedures. They are thought to be readily obtainable sources of MSCs, but they are associated with the significant drawback of compromising the tooth`s vitality in order to collect the pulpal tissues. These cells exhibit the classic MSCs features, including multi-potency, rapid proliferation, and immune-modulating activities (85). Moreover, DPSCs can develop into endothelial cells, as well as their angiogenic potential (86). DPSCs demonstrated mineralization capacity and osteogenesis (87). Due to their limited ability to generate cementum, the therapeutic value of DPSCs for PDL reconstruction can be considered doubtful (88).

DPSCs can be effectively isolated from both periodontally healthy (hDPSCs) and periodontally compromised teeth (pDPSCs). Both of them have no morphological variations in early passage cells. Cryopreservation can alter the shape of pDSPCs. Early passage cells exhibited no substantial change in the favorable transcription of MSCs' biomarkers CD73, CD90, and CD105. Nevertheless, repeated passaging and cryopreservation influenced biomarker transcription in pDPSCs. Both cell types show modest transcription of the hematopoietic b, such as CD34, CD45, and the MHC class II antigen HLA-DR. PDPSCs express more HLA-DR than hDPSCs. pDPSCs exhibit much slower growth rates and wound healing characteristics than hDPSCs. The migration capacity of pDPSCs can be significantly boosted during late passage following cryopreservation. There is no discernible change in osteogenic capability between them. Yet, pDPSCs have

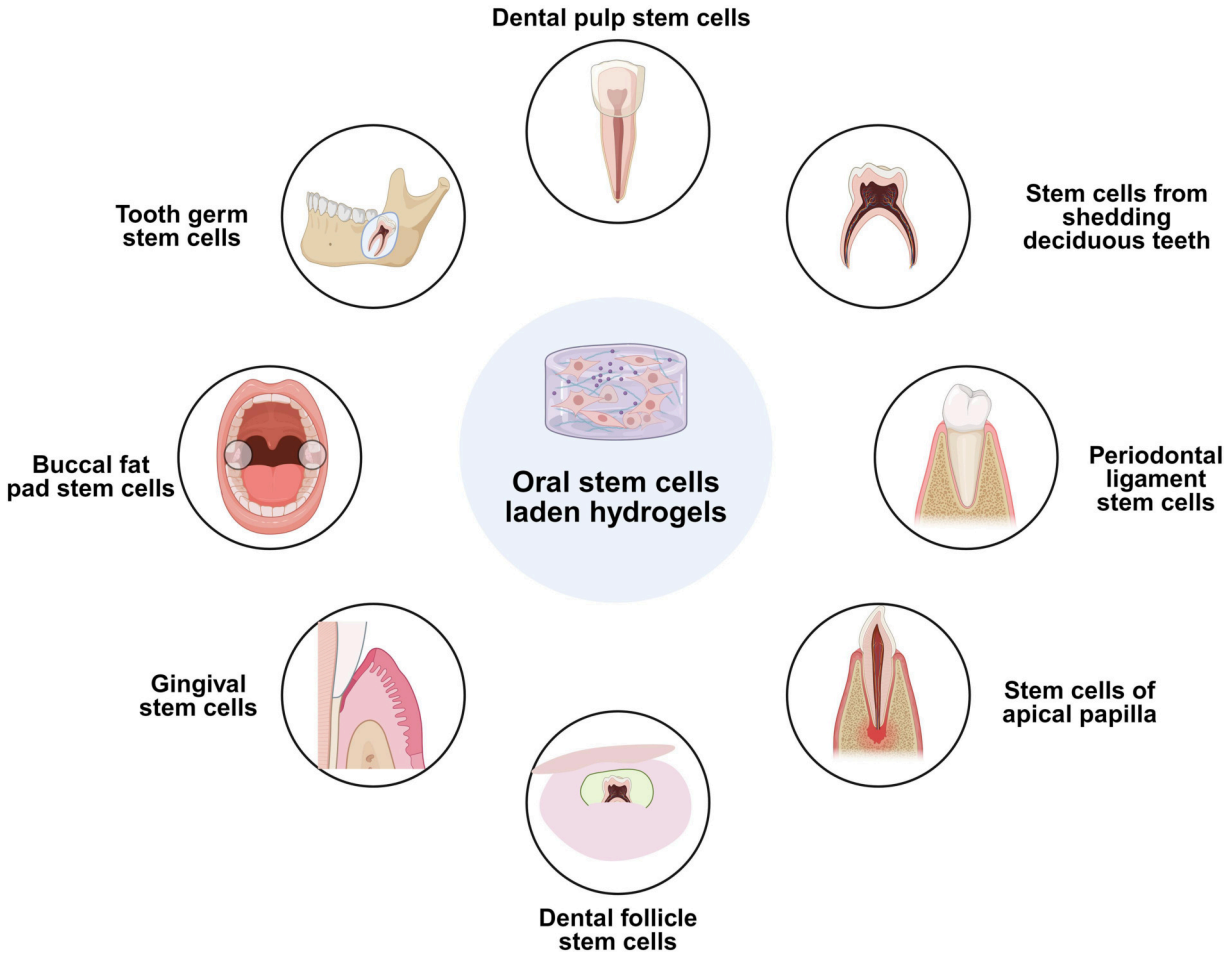


FIGURE 2
Different types of oral stem cells. This figure was created based on the tools provided by Biorender.com (accessed November 2, 2025).

much poorer chondrogenic capacity than hDPSCs. However, pDPSCs demonstrated increased osteogenesis and chondrogenesis at late passage and following cryopreservation (89).

4.2 Stem cells from shedding deciduous teeth (SHEDs)

SHEDs offer an exceptional, non-invasive source of MSCs. Because of their ease of separation, multipotential differentiating capability, and low antigenicity, they may be a viable choice for periodontal regeneration. SHEDs are conveniently accessible via noninvasive techniques since they are extracted from deciduous exfoliated teeth (90). SHEDs have an elevated level of multiplication and immune-modulating capabilities, comparable to BMMSCs, which are more challenging to get. SHEDs, like DPSCs, are derived from dental pulp (17, 91). Yet, SHEDs express greater quantities of stemness-related genes than DPSCs, preserving greater flexibility during *in vitro* passaging (92). SHEDS are robustly proliferating and can transform into several cellular types, notably osteoblasts and adipocytes (17). SHEDs can produce functional vessel-like constructs following transplantation (93).

SHEDs, when maintained in osteogenic settings, dramatically enhance the pro-angiogenic activity (94). Recently, Kato et al. (95), verified SHEDS's pro-angiogenic function, which secretes angiogenesis-promoting molecules for primary endothelium cells (95). SHEDs exosomes-shuttled miR-222 promote aggregation and angiogenesis of PDLSCs via upregulation of TGF-β/SMAD system (96).

Gao et al. (97), found that multiple dosing of SHEDs lowered gingival hemorrhage, promoted new PDL attachment, and suppressed osteoclast development. Micro-computed tomography research revealed that SHEDs delivery substantially enhanced periodontal regeneration and alveolar bone mass. Additionally, a spike in the levels of CD206+ M2 macrophages was detected after the application of SHEDs (97).

4.3 Periodontal ligament stem cells (PDLSCs)

PDL comprises a range of cell types, notably MSCs called PDLSCs, that share in periodontal healing and reconstruction. Several investigations have been conducted to identify PDLSCs

TABLE 1 Oral stem cells uniqueness across various tissues (113, 130, 133, 138–142).

Dental stem cells	Source	Benefits	Drawbacks	Isolation time	Reference
DPSCs	Dental Pulp	• Conveniently accessible and adequate source. • Be isolated first, with further investigations and clinical applications. • Strong ability to generate vessel-rich tissue. • Increased differentiation capability of cementoblasts and osteoblasts	• Inadequate supply of viable autologous cells.	2000	(138)
SHEDs	Exfoliated deciduous teeth	• More proliferative and potentially active than DPSCs. • Capable of generating neural tissue. • Maintains stemness following cryopreservation.	• Insufficient source. • Insufficient investigations and clinical uses.	2003	(133)
PDLSCs	Periodontal ligament	• Increased proliferation potential. • Stronger self-renewal capacity. • Strong ability to construct cementum/PDL-like structures with functional attachment. • Homogenous for functional regeneration. • Reduced immunological antigenicity	• Minimal access to healthy autologous cells. • Decreased osteogenic ability.	2004	(139)
DFSCs	Dental follicle	• Particular markers. • Stronger proliferative potential. • More flexibility and multipotential ability. • Robust capacity for producing connective tissue and PDL-like tissue. • Reduced immunogenicity	• Restricted autologous cell source. • Low cell count. • Poor hard tissue formation potential. • Insufficient research and clinical applications	2005	(143)
SCAPs	Apical papilla	• Specialized markers. • Increased proliferative potential. • Greater flexibility and multipotential capability (derived from growing tissue). • Better mineralization ability. • Low immunogenicity.	• Limited supply for autologous cells. • Low cellular abundance. • Lack of research and clinical applications	2006	(144)
GMSCs	Derived from healthy gingiva	• Straightforward and sustainably accessible. • Increased proliferative potential. • Quick wound healing without scarring. • Strong ability to create connective and bone-like tissues. • Immunomodulatory and anti-inflammatory properties	• Limited availability of healthy homologous cells. • Insufficient cell count	2009	(141)
BFPSCs	Buccal fat pad	• Ease of extraction. • Low donor site morbidity. • Multilineage capacities to develop into chondrocytes, osteoblasts, or adipocytes. • BFPSCs exhibited fibroblast like shape.	In ability to promote PDL regeneration		(130)
TGSCs	Tooth germ	• GSCs can develop into osteogenic, adipogenic, neurogenic, odontogenic, and chondrogenic lineages. • TGSCs express considerably more SOX2, MYC, and KLF4 mRNAs than human embryonic stem cells.	• Invasive approach. • Questionable cellular viability. • Demonstrate varied proliferating and developing characteristics.		

BFPSCs, Buccal Fat Pad Stem Cells; DPSCs, Dental pulp stem cells; SHEDs, Stem cells from human exfoliated deciduous teeth; PDLSCs, Periodontal ligament stem cells; DFSCs, Dental follicle stem cells; SCAPs, Stem cells from apical papilla; GMSCs, Gingival mesenchymal stem cells; PDL, Periodontal ligament; TGSCs, Tooth germ stem cells.

and examine their multipotency (98–101). PDLSCs are multipotent and can transform into osteogenic, neuronal, and adipogenic cell lines (102).

PDLSCs help maintain the physiologic homeostasis of periodontal tissues (103). PDLSCs have architectural and proliferative characteristics comparable to those of MSCs, as indicated by biomarkers (104). PDLSCs injections can improve periodontal regeneration, restore the decline in population diversity, and raise the number of colonies of *Bifidobacterium* and *Lactobacillus*. *In vitro*, PDLSCs prevent the development of periodontal pathogens, including *Staphylococcus aureus* and *Fusobacterium nucleatum*. The fundamental mechanism for activity is thought to entail the synthesis of LL-37 (105).

4.4 Stem cells from apical papilla (SCAPs)

SCAPs are a distinct population of MSCs found in the apical papilla of young permanent teeth. These cells have critical MSCs behaviors such as particular biomarker activity, self-renewal, division, mobility, multipotency, and immunosuppression features (106). Furthermore, significant evidence suggests that SCAPs can develop into several types of cells, like osteoblasts and odontoblasts, which may be a promising option for periodontal engineering (106, 107). Clinical evaluations, CT scans, and histopathological data revealed that SCAPs might dramatically increase periodontal regeneration 12 weeks following injection into a periodontitis animal model (108). This work validates the idea of employing SCAPs as an appropriate substitute stem cell resource for PDL regeneration in the future. Moreover, under inflammatory settings, the human apical papilla was shown to be mildly inflamed, retaining SCAPs viability and stemness while increasing its osteogenic and angiogenic capabilities (109).

4.5 Dental follicle stem cells (DFSCs)

DFPCs are a kind of dental MSCs that live in the dental follicle and is essential for tooth formation and function. DFPCs are neural crest-derived cells with multipotential transformation capabilities. More significantly, they offer advantages over other stem cells, such as ease of isolation and abundance, dynamic self-regenerating capacity, and absence of ethical concerns, which makes them an appealing choice in biotechnology. DFSCs are MSCs located in the tooth follicle and so share biological similarities with PDLSCs (24). In the inflammatory periodontal milieu, DFSCs have the potential to stimulate the division, osteogenic, and adipogenic transformation of both PDLSCs and inflammation-prone PDLSCs to various extents. Furthermore, when cultured together with DFSCs, the cell layering and ECM of PDLSCs/inflamed PDLSCs sheets expanded *in vitro*, whereas periodontal regeneration accelerated *in vivo* (110).

DFSCs, which are more undeveloped and demonstrate more DSPP than PDLSCs, can produce periodontal ligament (PDL) like constructions *in vitro* (111). A range of pluripotency biomarkers, notably octamer-binding transcription factor 4 (OCT-4), and NANOG, were demonstrated to be produced by DFPCs, confirming their multipotency and self-renewing capabilities (112). In contrast to other oral MSCs, DFSCs have a greater proliferation ability and osteogenic characteristics (113). Following *in vivo* implantation, DFSCs can replace the root by generating cementum and PDL (114). DFSCs had greater concentrations of osteogenic biomarkers, such as RUNX2 and ALP, than DPSCs and SHEDs (115).

4.6 Gingival mesenchymal stem cells (GMSCs)

GMSCs are a separate homogeneous group of MSCs that arise from neural ectomesenchymal tissues (116). GMSCs distinguish themselves from other oral MSCs due to their simplified accessibility and availability, as well as their exceptionally lengthy cultivation sustainability, lack of tumorigenicity, and persistent telomerase activity (117, 118).

Mitrano et al. (119), identified and analyzed GMSCs, which meet the basic specifications for MSCs, including multilineage differentiation, expression of MSCs markers, and increased adhesion (119). GMSCs demonstrated immune-modulating properties similar to those of other oral MSCs, inducing anti-inflammatory macrophage polarization and inhibiting osteoclasts, thereby lowering periodontal bone resorption *in vivo* (120). GMSCs' osteogenic ability has been established, and when transplanted into rats' gingival lesions, they restored healthy tissue (121). In rats, GMSCs-derived CM had a similar potential to stimulate PDL regeneration as PDLSCa-derived CM (122). *In vivo* transplantation of GMSCs can successfully regenerate bones (123).

4.7 Buccal fat bad stem cells (BFPSCs)

The mouth houses a unique fatty tissue known as the buccal pad of fat or Bichat's pads (124).

Several investigations have employed BFPs as an autogenous transplant to reconstruct small- to medium-sized maxillofacial lesions (125–127). Furthermore, they are currently being utilized to generate MSCs called BFPSCs, which share characteristics and behavior with the more well-known dermal MSCs (128). This innovative procedure for producing BFPSCs has significant advantages because BFP collection is simple, involves just a small incision with local anesthetic, and generates low donor-area complications (129).

Farre-Guasch and colleagues (130) were among the initial researchers to identify BFPSCs (130). Utilizing rhBMP-2, Hiraishi et al. (131), verified the osteogenic capacity of BFPSCs. Additionally, only in cells containing recombinant bone morphogenic protein-2 (rhBMP-2) and osteoinductive reagents (OSR) were adipogenic genes readily visible. Yet, transplanting BFPSCs grown in this setting resulted in the most significant *in vivo* bone production. Therefore, when subjected to rhBMP-2 to induce mature osteoblastic development, BFPSCs consistently produced manufactured bone (131).

In surgically produced defects in rabbits' jaws, BFPSCs and cellular matrix (CM) both promote bone regeneration, indicating that BFPSCs primarily enhance bone regeneration via releasing paracrine substances. Regenerative dentistry is significantly influenced by the findings of MSCs' paracrine action on bone regeneration, and utilizing their CM can help tackle several problems and issues associated with cell transplantation. Specifically, CM provides greater convenience for medical professionals during clinical applications and is portable and easy to store (132). It is predicted that buccal fat pad tissue could offer valuable transplant material because it is readily accessible and has a rich vascularized area; however, further research is necessary to confirm this.

4.8 Tooth germ stem cells (TGSCs)

TGSCs have grown in popularity as a cell origin with great promise for transformation into many lineages. MSCs with endothelium and epithelial cells are essential for tooth formation, rendering them an ideal cellular reservoir for dental regeneration. TGSCs were discovered by a pedodontist, Dr. Songtao Shi, while working on his six-year-old daughter's deciduous teeth in 2003 (133). The tooth germ is a cluster of primitive cells that participate in the formation of teeth and related structures (134). MSCs-like properties can be observed in cells generated from the third molar tooth germ. MSCs-specific surface antigens are expressed by human dental germ cells (135). TGSCs' multipotency enables them to develop into osteoblasts, odontoblasts, adipocytes, and brain cells. Human TGSCs exhibit immune-regulatory characteristics (136). Guzman et al. (137), demonstrated that the application of human TGSCs has immune-suppressing actions in mice (137).

5 Creating biohybrid platforms utilizing cell-laden hydrogels

Regenerative dentistry has an increasingly important role in therapeutic therapy. Under some conditions, oral stem cells can differentiate into several lineages. Scientists are particularly interested in utilizing them in bioengineering. To optimize the effectiveness of MSCs, material research can offer biomimetic platforms as well as reliable methodologies for understanding the numerous differentiation processes involved in MSCs development. Pharmaceutical applications are portrayed in biomaterials development via macromolecule-inspired hydrogels. Hydrogels possess numerous properties due to their unique composition (145). First, hydrogels possess an inherent softness that can be adjusted by modifying the level of cross-linkers, allowing the matrix to exhibit optimal elasticity and strength under various conditions (146). Secondly, hydrogels are safe to utilize with living things because they are biocompatible. Hydrogels should have minimal impacts on cell survival, according to *in vitro* testing on hydrogel cytotoxicity (147). Moreover, they should act as supportive scaffolds for cell attachment, division, and transformation, and promote mass transfer, which is another source of hydrogels' biocompatibility (148).

5.1 2D design VS 3D design

Extracellular matrix (ECM) components, including proteins and glycans, are secreted by living cells in tissues to form complex networks that regulate cell behavior and enable cells to fulfill specific roles, providing crucial cues and substances for cell migration and proliferation (149). Nevertheless, since 2D well plates are unable to facilitate biomacromolecule agglomeration or the spatial space necessary for cell adhesion, they are absent from conventional 2D cell culture techniques (150). Complex photophilic polymeric chains, protostructures, and elevated water levels make hydrogel matrices the ideal substrates for simulating *in vivo* cell culture conditions (151). As a result, hydrogels are frequently employed as synthetic substrates or frameworks in biohybrid networks, offering the benefits of long-term survivability, self-healing, and bottom-to-top construction (152).

Cells can be directly embedded in the hydrogel matrix, seeded on films or fibers, or seeded on a decellularized matrix to create common hydrogel-based biohybrid systems (153). The development of tissue engineering has led to notable breakthroughs in sophisticated manufacturing techniques, with 3D bioprinting being the most promising of these (154–157). Hierarchical designs can be formed from bottom to top thanks to this technological capacity to build cells at the microscale in customizable 3D areas (158). 3D printing is more reliable than traditional manufacturing techniques when it comes to creating various biological networks and systems, and accurately specifying the architecture of cells. These benefits over conventional manufacturing techniques have been demonstrated in domains such as clinical healthcare, biological science, and organ regeneration (159). Inkjet, extrusion, and photosensitive approaches are among the various types of 3D printing techniques that are primarily accomplished by sequential layering of sensitive inks (160, 161). These techniques are also well-suited for cell-laden, sensitive hydrogel engineering, which enables a variety of biohybrid functions. It is now simpler to load cells into scaffolds to assist cell functionalization, thanks to the 3D printing process that creates hydrogel scaffolds (162). There are several advantages to using hydrogels as platforms for cell seeding, particularly in regenerative applications, such as bone regeneration and repair. As cells are suspended directly in the hydrogel solution, cell-containing hydrogel bioinks enable the direct fabrication of 3D designs (163).

Because of its intricacy, reconstruction of the periodontium requires the synchronized repair of several structures. Numerous 3D printing processes, such as the freeform reversible embedding of suspended hydrogels (FRESH), employed by Lin et al. (164) are utilized to carry out this operation (164) with a bioink incorporating type I collagen, thereby building collagen microfibers. The findings demonstrated that the growth, attachment, and vitality of the cytoskeleton were satisfactory, and the PDLSCs were effectively implanted (164).

However, Tian et al. (165) utilized a hydrogel, hydroxyapatite nanoparticles, and PDLSCs to combine synthetic and natural materials, thereby generating a bioink (165). This bioscaffold enhanced the mechanical characteristics and swelling capacity while also effectively stimulating cellular viability, division, and differentiation. Zhu et al. (166),, also employed PDLSCs in GelMA hydrogel at various levels (3%, 5%, and 10%). The addition of PDLSCs helped create new cells, but the 10% GelMa demonstrated lower cell longevity (166). One benefit of hydrogels is that they may be administered directly via injection into the targeted region using less invasive techniques (Figure 3). Kandalam et al. (167) effectively enclosed GMSCs in

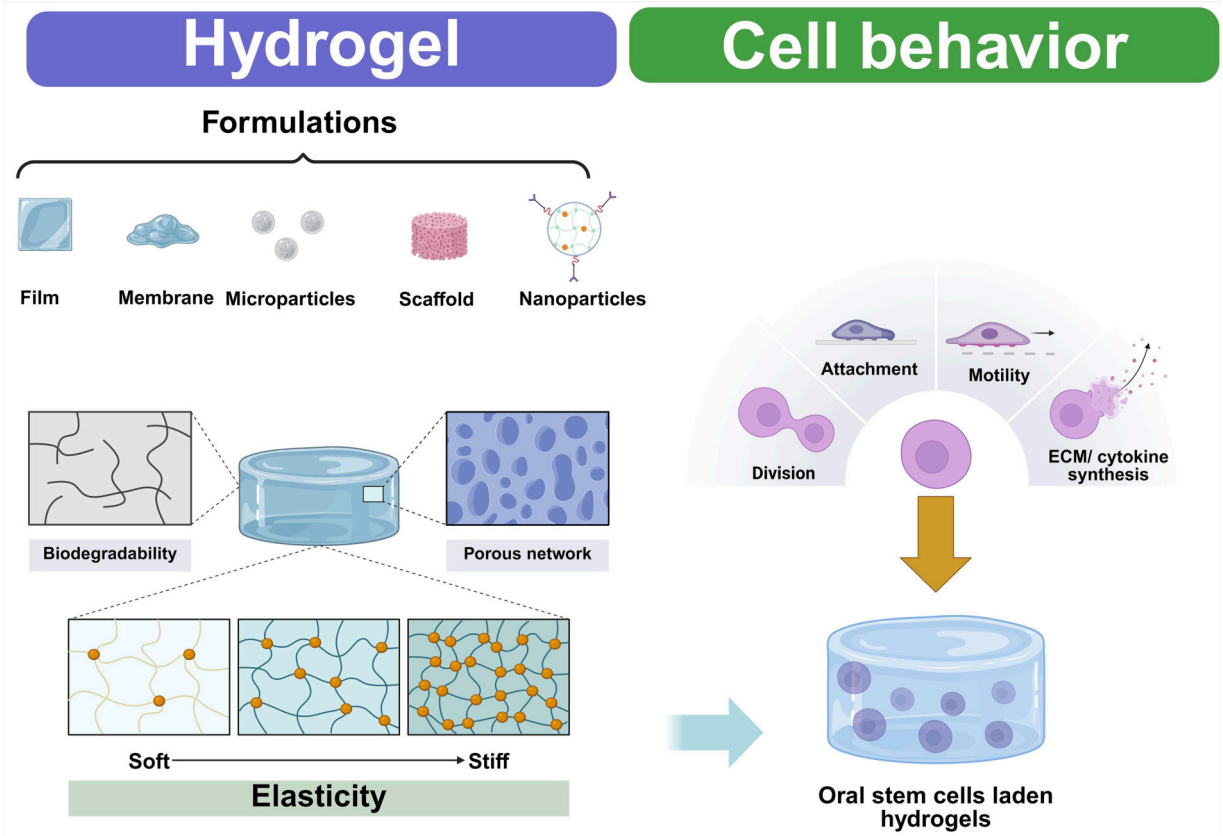


FIGURE 3
Design criteria of oral stem cells-laden hydrogels for regenerative purposes. This figure was created based on the tools provided by Biorender.com (accessed November 2, 2025).

PuraMatrix™, a self-assembling hydrogel. The GMSCs immobilized with 0.5% PuraMatrix showed exceptional attachment and multiplication ratios.

5.2 Cost-effectiveness and manufacturing of hydrogels

Hydrogels must be both economical and simple to manufacture, in addition to having a therapeutic impact, to be commercially successful and widely used. Enhancing the ability to attract native cells might encourage the therapeutic application of biomaterials by eliminating the challenges and costs related to the development, preservation and delivery of cellular materials, besides safety and ethical issues (168).

Hydrogels can be manufactured from a broad spectrum of materials, including both artificial and organic sources, and can be utilized in various formulations (169, 170). Natural hydrogels exhibit good biological compatibility and minimal immunological response (171, 172), yet this is often accompanied by inadequate scalability and limited control over mechanical properties (170, 173–175).

Manufactured hydrogels possess an identifiable framework, consistent material sources, and an extended shelf life, and can be constructed in several batches with reproducibility. The fundamental challenges are their low bioactivity, antigenic byproducts, and static makeup, which provides no biological data to cells. Thus, they may be employed in combination with bioactive molecules to mitigate these shortcomings (176–178).

Isaac et al. (179), used immersed electrosprayed polyethylene glycol (PEG) hydrogel microparticles, which were subsequently used to make tetrazine click chemistry to prepare microporous annealed particle-based hydrogels (TzMAP) by attaching norbornene-loaded PEG hydrogel microspheres. Incorporating PDLSCs during annealing resulted in cellular viability proportions of 87% ± 5% at 24 h. The inclusion of PDLSCs and platelet-derived growth factor (PDGF)-BB into TzMAP led to enhanced cellular division and movement, which are crucial for periodontal tissue regeneration (179).

Hydrogels can be carefully manufactured for optimized cell dispersion and tissue formation through self-assembling or 3D printing processes (180–182). For encapsulation of PDLSCs, a bioprinting technique used injectable composite hydrogels made of GelMA and PEG dimethacrylate (PEGDA). The use of PEG improved droplet control. *In vivo* tests demonstrated that PDLSCs-containing hydrogels stimulated bone formation in rat periodontal defects when compared to hydrogels lacking cells (183).

5.3 Mechanical properties

Natural polymeric hydrogels derived from microbes, plants, or animals have garnered considerable interest recently, owing to their exceptional biodegradability and biocompatibility (184). However, their practical uses are limited by their weak mechanical characteristics, unpredictable rates of breakdown, and the likelihood of immunological responses. To meet the potential needs for dental applications, both artificially produced and organic composite hydrogels have been proposed. The most often used injectable matrix for cellular transportation is composite hydrogels (185).

Tissue engineering is based on hydrogels, which provide a framework for cell adhesion, proliferation, and transformation. By modifying their functional components, cross-linking techniques, and synthetic materials, the physical-chemical characteristics of hydrogels can be tuned to satisfy the unique biomechanical requirements of various tissues. Because hydrogels can be customized for specific medical applications, they have been utilized in medication delivery, regenerative medicine, and other fields of medical research. Many novel hydrogels have been manufactured to enhance the interaction between targeted cells and hydrogels, thereby promoting tissue regeneration (186).

Rapidly cured microporous hydrogels based on gelatin and GelMA were shown in a prior work (187). Via photopolymerization and enzymatic cross-linking, these hydrogels set after 2.5 min of injection, enabling consistent cell dispersion and substantial cellular dissemination and division within a week. Furthermore, these hydrogels may carry hMSCs primed with interferon-gamma, increasing the production of anti-inflammatory substances, including interleukin-6 and prostaglandin E2. Therefore, these hydrogels offer a potential method of delivering cells. Another safe method for cell transplantation is the use of hydrogel particles. Hydrogel particles, which are formed of microscopic 3D network structures built of biopolymers, shield cells from shear pressures during transplanting, maintaining cell viability (187).

According to recent research, the physical characteristics of hydrogels (like the stiffness, durability, surface charge, and other physical factors of ECM can be altered to control cell expansion, division, and transformation; therefore, they impact the regenerative processes. The majority of research has produced hydrogels with varying stiffness by altering their composition or applying external stimuli. The investigation of variations in cell activity has also made extensive use of these hydrogels with varying stiffness. For instance, the stiffer the hydrogel, the more likely the oral stem cells can develop into bone, making it a potential option for regenerative dentistry (188, 189).

He et al. (190) developed and evaluated stiff transglutaminase-crosslinked gelatins (TG-GELs) with SDF-1α and/or IL-4 as a potential platform in periodontal therapy. According to their findings, IL-4 could encourage the transformation of Mφs to the M2 phenotype, which may promote BMSCs' osteogenesis *in vitro*. Furthermore, the inclusion of SDF-1α might continuously encourage the functionality of BMSCs. Periodontal regeneration was considerably enhanced after implantation of these bioactive gels into periodontal defects as opposed to TG-GELs carrying either IL-4 or SDF-1α alone. These findings suggest that improving the ability of high-stiffness hydrogels to modulate macrophages (Mφ) and attract cells is a feasible and successful method for performing targeted periodontal regeneration. Therefore, if the synchronized crosstalk between stem cells and Mφs is appropriately guided, very simple, designed biomaterials can give significant functional advantages and good regeneration results with the help of carefully chosen signaling molecules (190).

5.4 Biodegradability

Biodegradability is a key design factor that influences the pharmacokinetics and pharmacodynamics of hydrogels. Hydrolysis of ester, carbonate, or anhydride chains; metabolic breakdown of peptide, polysaccharide, or proteolysis by enzymes like matrix metalloproteinases; or redox- and pH-triggered disintegration of dynamic covalent bonds. To optimize decomposition dynamics, polymer molecular weight, crosslinking capacity, hydrophilic properties, and the introduction of labile functional chains must all be balanced out. Customized breakdown allows synchronicity with tissue healing timeframes, ranging from fast disintegration for bursting delivery to delayed degradability for extended reinforcement. Furthermore, breakdown metabolites must be non-toxic, immune-compatible, and quickly eliminated to avoid long-term inflammation (191).

5.5 Biocompatibility

Biological compatibility is determined by the hydrogels' capacity to keep encapsulated or invading cells viable and functioning. Polymeric purity, minimal endotoxin concentration, the absence of harmful crosslinking by-products, and the preservation of homeostasis during gelation are all important variables. Moderate gel formation settings are required, whether by light triggering and enzymatic processes. Mechanical qualities also impact cellular activity; hydrogels with insufficient durability can impede cell dissemination, relocation, lineage determination, and ECM deposition. To avoid hypoxic or apoptotic areas inside cell-laden structures, nutrition, oxygen, and waste byproducts flow must be optimal (192).

Biocompatibility refers to the capacity of hydrogels to interact with host tissues without causing unfavorable immunologic or inflammatory responses. After administration, hydrogels interact with immune cell populations, notably macrophages. Biomaterial chemical composition, charge concentration, crosslinking methods, architectural characteristics, and decomposition products all impact the behavior of macrophages toward pro-inflammatory or pro-regenerative phenotypes (190).

5.6 Sensitivity to environmental factors

Stimuli-sensitive hydrogels provide dynamic features that allow for sensing and responding to surrounding signals. They

can be activated by heat, light, pH, and chemicals, thereby imparting them with environment-sensitive properties (193–195). Along with these qualities, hydrogels also exhibit other common traits, such as softness, swelling capacity, and water retention capacity. Additionally, the polymer chains in hydrogels can be purposefully altered or tailored to enhance particular qualities (196). For instance, hydrogels can acquire stimuli-sensing capabilities by linking polymers to biological molecules, which adds living things, such as proteins, to polymer chains (197). Temperature-sensitive platforms encounter sol-gel transformations around physiological temperatures when the hydrophobic-hydrophilic balance shifts within the polymeric matrix. pH-sensitive hydrogels with ionized motifs exhibit swelling or deswelling activity depending on protonation status. Enzyme-sensitive hydrogels include peptide chains or degradable components that can be preferentially degraded by illness or tissue-related enzymes. Glucose and redox-reactive hydrogels use reactive boronate ester bonds or oxidative breakdown of highly reactive links to provide tailored medication release under metabolic or inflammatory conditions. Light-sensitive hydrogels contain photosensitive molecules, allowing for precise time- and space-based manipulation of gelation and breakdown. These behavioral modifications improve accuracy, decrease undesirable outcomes, and increase therapeutic variety (198).

5.7 Immune-modulating properties

Hydrogels intended for periodontal regeneration should reduce acute inflammation, prevent persistent fibrotic encapsulation, and optimally establish an immunological microenvironment favorable to tissue regeneration. The inclusion of immune-modulation elements, bioactive substances, or anti-inflammatory drugs might help modulate immunological reactions at the location of administration. Additionally, by influencing redox reactions, hydrogels can be utilized for tissue restoration (199). Elevated ROS synthesis can control the associated biological reactions during tissue regeneration and raise the amount of MSCs-related protein secretome (200). Additionally, some composite hydrogels can alter the behavior of macrophages by making the hydrogel more rigid, changing them to an anti-inflammatory M2 type, and encouraging tissue reconstruction by controlling associated immunological and inflammatory responses (201). By altering the associated biophysical characteristics of hydrogels and influencing the presentation of relevant factors, it can generally impact the phenotypic or proliferative maturation of cells.

Despite the use of modern treatments, chronic oral inflammatory illnesses such as pulpitis, periodontitis, and peri-implantitis present serious clinical problems and frequently cause irreparable tissue loss. By actively encouraging the suppression of inflammation and tissue regeneration while maintaining host defense, specialized pro-resolving mediators (SPMs) provide a revolutionary treatment paradigm. Nevertheless, SPMs' low affinity to inflammatory tissues, limited bioavailability, and quick disintegration impede their practical application. Promising platforms to overcome these obstacles include smart biomaterial-based delivery systems, particularly stimuli-responsive hydrogels. These devices enhance the stability and therapeutic efficacy of SPMs by enabling their regulated, localized, and environmentally induced release (202).

Hydrogel-mediated SPM administration not only reduces inflammation but also maintains tissue integrity and encourages regeneration, according to preclinical research in oral inflammation models. To facilitate clinical acceptance, future strategies will focus on enhancing dosage procedures, ensuring long-term bioactivity, and addressing manufacturing and regulatory challenges. Biomaterial-based approaches have an opportunity for transforming the medical management of oral inflammatory illnesses and promoting regenerative dental treatments by improving the delivery and prolonged bioactivity of SPMs (203).

Numerous inflammatory conditions, such as periodontitis, are characterized by excessive ECM degradation by MMP-1. Under optimal circumstances, MMP activity is carefully regulated—for example, by tissue inhibitors of metalloproteinases (TIMPs)—to maintain homeostasis. MMPs hydrolyze peptide bonds with a high degree of amino acid affinity. Nevertheless, MMP activity persists under pathophysiological conditions, leading to unfavorable alterations in tissue structure and function, and accelerating the course of the disease. Over the past 25 years, numerous investigations have been conducted on the construction and creation of molecules that block MMP activity in an effort to alleviate this (204–206).

Huang et al. (207) constructed an injectable dual-crosslinked protein hydrogel by integrating gelatin and bovine serum albumin (BSA) using a rapid, straightforward, and cross-linker-free manufacturing technique. Its cross-linked, interconnected design offered extra support to optimize thermal stability and mechanical characteristics. CD/BSA/GEL hydrogel was produced by adding the potent oxidant ClO_2. To administer targeted high-concentration medication effectively, this hydrogel is easily injectable into periodontal pockets. It reacted with and alleviated elevated protease components in the periodontal inflammatory milieu, allowing for the prolonged release of ClO_2 and bioactive cargo. This system downregulates the expression of inflammatory genes and maintains cell motility, expansion, division, and osteogenic potential while exhibiting substantial antimicrobial characteristics. The CD/BSA/GEL hydrogel successfully minimized inflammatory reactions and encouraged periodontal bone regeneration (207).

The prevalence and progression of periodontitis are clearly positively correlated with H2S, a common metabolite of periodontal bacteria. H2S can control numerous biological processes at physiological quantities. Nonetheless, excessive H2S in the periodontal pocket can exacerbate the progression of periodontitis by inducing oxidative stress, releasing proinflammatory cytokines, causing mitochondrial damage, and promoting apoptosis in human gingival fibroblasts. Even worse, by preserving bacterial redox balance and boosting antibiotic resistance, H2S promotes bacterial survival and growth. However, eliminating H2S is often overlooked when treating periodontitis. To improve the management of periodontitis, Xie et al. (208)

developed a type of hyaluronic acid methacryloyl/ZnO (HMZ) hydrogel with the ability to scavenge H2S. By reacting with ZnO, the HMZ hydrogel was able to eliminate H2S and had high injectability and cytocompatibility. Consequently, the HMZ hydrogel restored mitochondrial homeostasis, reduced inflammation mediated by the cGAS-STING signaling pathway, and increased cell survival from 13% to 120% for human gingival fibroblasts and from 22% to 94% for human periodontal ligament fibroblasts after 48 h. Additionally, the HMZ hydrogel demonstrated effective plaque biofilm removal and adequate antibacterial properties *in vitro* and *in vivo*. In summary, a potential approach based on H2S elimination was created to increase the efficacy of periodontitis treatment (208).

5.8 Organization of cellular activities

Since hydrogel stiffness affects stem cell activity, including development, attachment, and relocation, it is an essential component of stem cell administration (209). To influence the destinies of stem cells, investigators can modify the stiffness of hydrogels. For instance, stiffer hydrogels could stimulate osteogenic development, whereas softer hydrogels may support adipogenic transformation or preserve stem cell properties. Due to this adaptability, specific niches may be created that can enhance the effectiveness of stem cell treatments (210, 211).

Osteogenic differentiation results from a greater nuclear-cytoplasmic ratio of Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ) on the surface of the stiffer hydrogel. The nuclear-cytoplasmic proportion of YAP/TAZ is lower on the scaffold's less rigid surface, causing the cells to develop into adipocytes (212, 213).

Since they may be utilized to carry medications and cells and replicate the chemical makeup of the extracellular matrix, hydrogels are regarded as promising biomaterials. Properly controlled synthetic procedures can produce artificial polymeric hydrogels with well-specified, well-defined chemical compositions, precise molecular weights, enhanced stiffness, and customizable microstructures. Nevertheless, synthetic polymer hydrogels are often either biodegradable or biocompatible, which makes them inappropriate for cell reinforcement (21).

Although hydrogels have demonstrated potential as transporters for stem cell transplants, there are still obstacles (19). Cell mortality after delivery, limited cell attachment after transplantation, challenges to extended cell longevity, and insufficient reinforcement are all significant factors influencing the effectiveness of periodontal regenerative therapies (204, 214). Currently, there is no ideal hydrogel cellular vehicle to address these challenges (215, 216).

6 Integration of oral stem cells and hydrogels in periodontal regeneration

The inclusion of oral MSCs into hydrogels creates an integrated foundation for tissue healing through the integration of gels' architectural and protective qualities with their ability to regenerate stem cells (Figure 4) (217, 218). This blend enhances cellular activity, optimizes immunological modulation, and ensures long-lasting biological efficacy, all of which are crucial for treating periodontitis (219). Researchers have discovered that oral MSCs in hydrogels significantly improve collagen accumulation and tissue epithelialization when compared to standard therapies, resulting in faster wound healing (220–222). Hydrogels are effective MSC carriers due to their unique features, including the capacity to transfer physiologically active substances. Hydrogels incorporating MSCs or their exosomes significantly enhance cellular recruitment and division, thereby accelerating re-epithelialization and wound healing. Additionally, the hydrogel-exosome complex activates key regeneration pathways, such as the PI3K/Akt pathway (197).

6.1 DFSCs laden hydrogels

DFSCs sheets exhibit high extracellular secretion capacity and efficiency in periodontal regeneration. DFSCs sheets produced from passage 4 cells outperformed DFSCs suspensions in terms of vitality and osteogenic transformation potential. Following 10 days of culturing, DFSCs sheets showed upregulation of osteogenic biomarkers. In comparison to the cell suspension, the cell sheet exhibited superior regenerative and paracrine capabilities *in vivo*. The modified DFSCs sheets revealed considerably greater concentrations of VEGF and angiopoietin-1 in comparison with DFSCs suspensions, as well as improved osteogenic initiation effects (223).

Tri-layered hydrogel formed of chitin-poly(lactic-co-glycolic acid) (PLGA) composite hydrogel. The first layer contained nanoinspired bioactive glass (nBG). The second layer contained fibroblast growth factor 2, and the third layer was loaded with nBG/platelet-rich plasma. It was biocompatible and promoted cementogenesis, fibrogenesis, and osteogenesis of human DFSCs both *in vitro* and *in vivo* (224). A 3D bioprinted biomimetic cell-laden bioink containing gelatin methacrylate/decellularized extracellular matrix (GelMA/dECM). The dECM exhibited strong immune-modulating properties while minimizing local inflammation *in vivo*. This hydrogel substantially promoted harmonious PDL fiber regeneration and enhanced bone mineralization *in vivo* (225).

6.2 DPSCs-laden hydrogels

Although deferoxamine (DFO) promotes angiogenesis during bone regeneration and wound healing, its effect on DPSCs driven angiogenesis remains uncertain. Here, DFO was loaded into gelatin-based microspheres (GMSs), and thermally responsive injectable hydrogels containing chitosan and collagen were created to allow for regulated DFO release. Due to its advantageous physical characteristics and biocompatibility, the DFO-GMS-laden hydrogel composite enabled prolonged DFO administration for up to 15 days. *In vitro*, DFO successfully

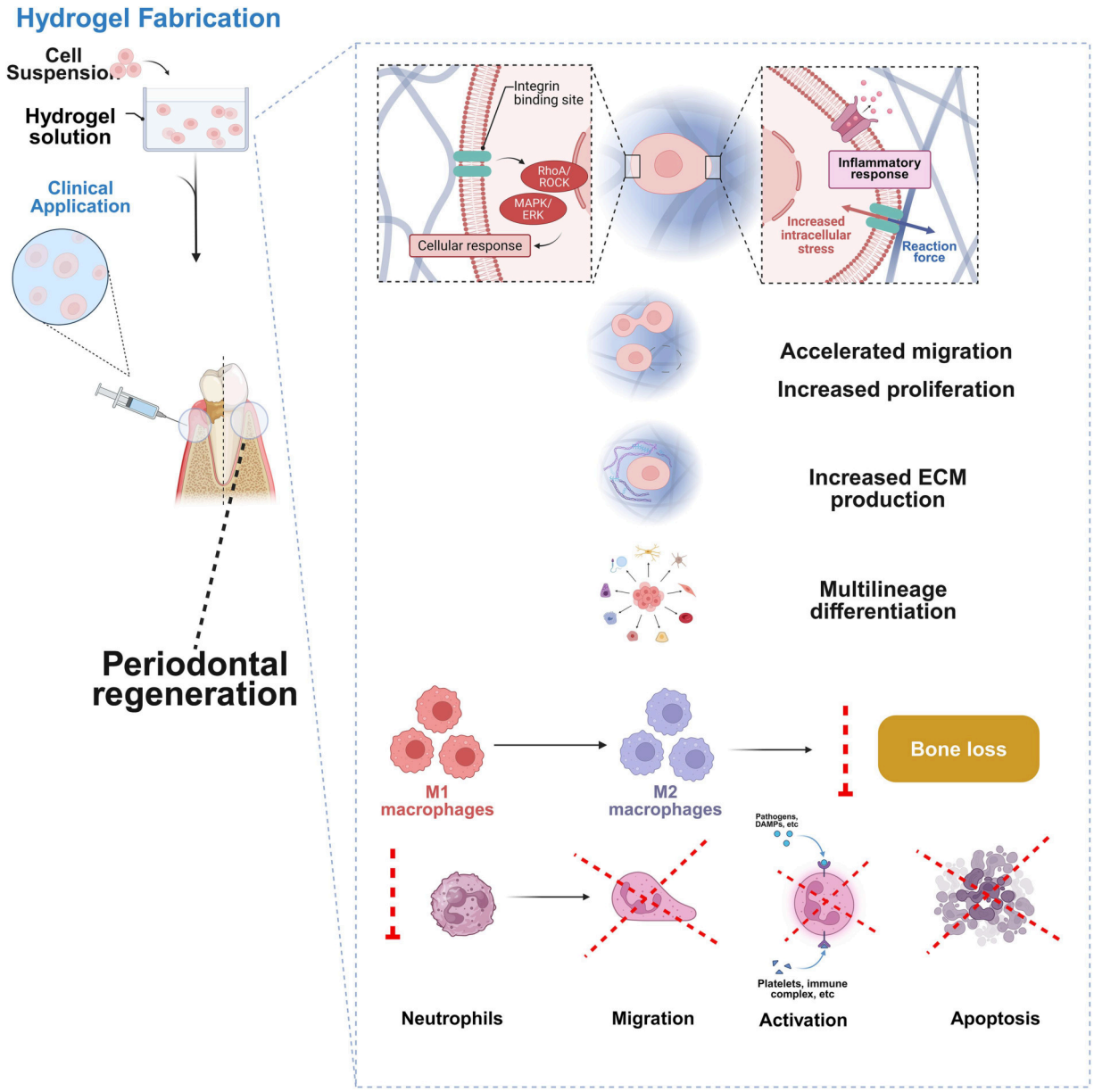


FIGURE 4
Implementation of oral stem cells-laden hydrogels in periodontal regeneration. This figure was created based on the tools provided by Biorender.com (accessed November 2, 2025).

induced tube formation, increased the release of molecules linked to angiogenesis, and encouraged DPSCs' movement (226).

In addition, Divband et al. (227), created new injectable hydrogels *in situ* using chitosan biguanidine and carboxymethylcellulose that were loaded with rhBMP-2 and VEGF. They investigated the impact of the fabricated hydrogels on the osteoblastic development of DPSCs. These hydrogels considerably boosted the growth of DPSCs and were non-toxic. Additionally, they displayed noticeably increased ALP, COL1α1, and OCN genetic and protein transcriptions (227).

Wang et al. (228), investigated hyaluronic acid (HA) and polyethylene glycol loaded with DPSCs' extracellular vesicles (EVs), which successfully relieved inflammation, expedited revascularization, and encouraged tissue mineralization *in vivo* (228).

GelMA-based biomaterials are frequently employed as scaffolds due to their biological compatibility, adjustable characteristics, and functional capacities. Nevertheless, the biological effects of its photo-crosslinking mechanism on MSCs, as well as stress-reduction methods, have yet to be fully investigated. Integrating DPSCs-CM into the GelMA hydrogel demonstrated increased cellular survival, growth, movement, and osteogenic transformation (229).

An injectable thermally responsive Cs/β-glycerophosphate/ hydroxyapatite hydrogel can preserve typical adherent DPSCs

cell shape, encourage fast multiplication, promote high cell viability, and enhance osteogenic activity (230).

6.3 GMSCs-laden hydrogels

It is found that alginate is a potential non-toxic platform for GMSCs encapsulation (231). Moreover, alginate hydrogel could promote osseointegration of GMSCs *in vitro* (231). Fawzy El-Sayed et al. (232) explored the regenerative capacity of GMSCs to reconstruct periodontal tissue when combined with HA-sECM that releases IL-1ra. GMSCs exhibited stem and MSCs properties. Interleukin (IL)-1ra-loaded and unloaded GMSCs/HA-sECM demonstrated increased clinical attachment level (CAL), decreased junctional epithelium (JE), and enhanced bleeding on probing (BOP) compared to negative controls (232). Wang et al. (76) developed a CS/ oxidized chondroitin sulfate (OCS) hydrogel by freeze-casting process to carry PDLSCs and GMSCs with the goal of inducing periodontal tissue regeneration. The PDLSCs and GMSCs loaded hydrogels demonstrated outstanding biocompatibility, more significant bone tissue healing, and generated more organized PDLs *in vivo* (76).

Furthermore, Ansari et al. (233) created an alginate/GelMA hydrogel formulation that encapsulates GMSCs. The GMSC-hydrogel could speed up wound healing by increasing collagen production, encouraging angiogenesis, and blocking local proinflammatory cytokines (233). Balaban et al. (120) verified that the local treatment of GMSCs in fibroin/chitosan oligosaccharide lactate hydrogel (F/COS) resulted in significant new bone growth and less lengthy junctional epithelium creation with well-organized PDLs and connective tissues (120).

Moshaverinia et al. (234) demonstrated that microencapsulation of PDLSCs and GMSCs in RGD-alginate hydrogel improved MSCs survival and osteogenic transformation *in vitro*. Moreover, PDLSCs loaded hydrogels could restore the damaged bone by stimulating the creation of mineralized tissue, while GMSCs had much inferior osteogenic differentiation competence (234). Pouraghaei Sevari et al. (235) developed alginate-whitlockite (WHMP) hydrogels, which showed enhanced elasticity without impacting the viability of GMSCs. Additionally, alginate-WHMP hydrogels stimulate the mitogen-activated protein kinase (MAPK) system, which regulates various osteogenic biomarkers in encapsulated GMSCs, particularly RUNX2 and osteocalcin (OCN). They could inhibit osteoclastic activity, likely thanks to the liberation of WHMP Mg^{2+} ions and GMSCs osteoprotegerin. GMSCs encapsulated in an osteogenic niche may improve bone repair *in vivo* (235). Kandalam et al. (167) employed a self-assembled hydrogel scaffold, PuraMatrix™ (PM), and/or BMP2 and loaded them with GMSCs. GMSCs-laden hydrogels could enhance bone regeneration upon *in vivo* application (167).

6.4 SCAPs-laden hydrogels

The good physical characteristics and biodegradability of a temperature-sensitive hydrogel have been demonstrated, making it an effective scaffold. Thermosensitive hydrogel in conjunction with lentiviral PDGF-BB loaded with SCAPS dramatically increased new bone growth and mineralization (236). Dutta et al. (237) demonstrated that 3D bioprinted temperature-sensitive poloxamer-407 (P407) hydrogels are non-toxic for encapsulating SCAPs, leading to high cellular survival and increased cell migratory potential. After 14 days of *in vitro* growth, the 3D hydrogels containing PAI-1 showed significantly higher levels of osteogenic biomarkers (237).

6.5 SHEDs laden-hydrogels

Chen et al. (238), created an injectable antimicrobial peptide-/(GelMA-AMP) hydrogel that contains hypoxia-inducible factor (HIF-1α), which promoted osteogenic transformation in SHEDs (238). Qu et al. develop SHEDs laden with metformin (MF)-loaded mesoporous silica nanospheres (MSNs)-/ (GelMA) photo-cured hydrogels. This bioactive hydrogel did not affect cell survival and showed significant activation of osteogenic-related genes (excluding OCN) (238).

6.6 PDSCs-laden hydrogels

Ivanov et al. (239), demonstrated that PDLSCs grown in a 3D collagen I hydrogel with dECM for 14 days exhibited phenotypic traits comparable to those of osteoblast-like cells. The discharge of bone-forming biomarkers (OC, OPN, and ALP) demonstrates this capacity. In 3D culture, the inclusion of fibronectin to the dECM promotes the most efficient conversion of PDLSCs into osteoblasts (240). PDLSC-laden GelMA and PEG dimethacrylate hydrogel can promote PDLSC survival and spreading (239). HydroMatrix™ (HydM) is a synthesized self-assembly peptide that can produce hydrogels with thermal or ion concentration variations. Nagy et al. (183) discovered that PDLSCs can attach, live, relocate, and multiply on HydM, and the gel promotes osteogenic transformation, encourages the viability of PDLSCs and their osteogenic transformation *in vitro*, as well as hastens osteogenesis *in vivo* (183).

6.7 BFPSCs

Saputra et al. (241) constructed a nanohydroxyapatite-chitosan (nHPA-CS) hydrogel injectable scaffold loaded with PRF and BFPSCs. The NHPA-CS scaffold develops a native microenvironment that stimulates BFPSCs' driven regenerative capacity, whereas PRF promotes osteogenic differentiation and multiplication of BFPSCs. The integration of nHPA-CS, platelet-rich fibrin (PRF), and BFPSCs exhibits osteoinductive capacity in patients with aggressive periodontitis (241). Bastami et al. (242) developed a 3D β-tricalcium phosphate (β-TCP)/gelatin/BMP2/chitosan (CS)/collagen composite and explored its impact on hBFPSCs. This hydrogel might serve not only as a structurally and physiologically suitable scaffolding, but also as an

osteoinductive graft, supplying rhBMP2 during a therapeutic window for hBFPSC development into the osteoblast lineage (242).

7 Challenges of translating research from the laboratory to clinical practice

Oral stem cells loaded hydrogels encounter concerns such as cell viability and breakdown, inadequate mechanical characteristics, decomposition issues, and biocompatibility and antigenicity (243–245). These issues stem from the difficulty of tailoring the hydrogel's biomechanical features to the biological context of the stem cells while maintaining the cells' stability and functionality as the hydrogel breaks down and tissue grows (226, 228, 246).

The homogeneous distribution of molecules across the hydrogel network is crucial for preserving controlled characteristics and enhancing the functionality of the hydrogel (247). Effective dispersion methods and surface modifications are necessary to improve biocompatibility with the hydrogel matrix, thereby addressing this issue. Hydrogels must maintain their long-term stability to be used effectively (27, 248). The cytotoxicity and adaptability of hydrogels are crucial concerns, as some may have deleterious effects on stem cells or other cells (249, 250). Scalability and cost are essential factors to consider when evaluating the use of hydrogels in therapeutic applications (219). Large-scale production necessitates streamlining manufacturing processes while guaranteeing material quality and homogeneity (197). Cost-effective synthesis processes and raw material availability must be examined to ensure the feasibility and accessibility of these materials for broad use (251).

7.1 Scaling up

Limitations with employing stem cells include decreased survival of fewer cells, restricted division, and the stem cells' capability to differentiate. Although oral stem cells have demonstrated enhanced periodontal regeneration, there is still a lack of pre-clinical and clinical evidence, and more carefully thought-out studies with a bigger sample size are necessary to determine whether employing stem cells to boost periodontal healing is feasible (252). The effectiveness of stem cells in promoting periodontal regeneration is reduced when their sustainability is reduced as a result of late glycosylation byproducts in a hyperglycemic condition (253). DPSCs have shown the ability to mineralize. Indeed, it has been established that human DPSCs encourage osteogenesis both *in vitro* and *in vivo*. DPSCs' low ability to generate cementum raises doubts about their efficacy for periodontal regeneration. Despite these experiments showing oral stem cells' capacity for regeneration, the majority of them lack comprehensive quantitative methods to assess the cells' capacity for self-renewal, proliferation, and differentiation, particularly *in vivo* (87, 254, 255).

Furthermore, preceding their clinical use, the laboratory tests must address the subsequent concerns: 1) Significant apoptosis in cells at the transplantation site, thus the longevity and functionality of oral stem cells *in vivo* must be enhanced. 2) The relationship between implanted cells and the native cells must be investigated; 3) *In vivo* cell lineage mapping of implanted oral stem cells is essential to comprehend their destiny and activities. 4) Because some oral stem cells are frequently engaged in carcinoma, the biochemical pathways that enable oral stem cells to select between self-renewal, malignancy, and transformation should be thoroughly investigated (22, 256).

In addition, while these experiments are extremely helpful in discovering the characteristics of oral stem cells, they do not completely mirror the biological and pathological state of the injured tissues in the human body. Double-blind, randomized controlled studies are required to prove their genuine regeneration ability. Because clinical studies require a high quantity of clinical-grade cells within a short period, preservation and handling of oral stem cells are viable options for clinical use (256). After Hiroshima University established an institutional tooth bank in Japan in 2004, numerous biotechnology companies specializing in teeth banking have begun operations. With improved preservation technologies, regenerative dentistry could potentially act as a portal to an extensive spectrum of rejuvenating therapies by successfully tapping these beneficial stem cell reserves (257).

7.2 Regulatory hurdles

While the technical details of the banking procedure should worry an interested person, there is typically little information accessible from the public side of dental banks that enables people to distinguish between solutions. Their selection will most certainly be heavily affected by both regional accessibility and industry-specific, or more specifically, financial variations across banking centers (258). Additionally, prolonged stem cell preservation is not currently covered by medical insurance policies in the United States and is not a regular service in the majority of nations. A straight cost analysis may be useless because charges are liable to fluctuation, and there are many other types of plans available. However, as a rule of thumb, the initial processing may cost between $500 and $2,000 (US dollars), and the yearly maintenance can cost between $99 and $264. For a 20-year contract with no annual maintenance fees, several businesses offer a fixed fee of between $2,000 and $3,000 (259). In fact, this is Oothy's sole product, with the notion of preserving stem cells from deciduous teeth as a sustainable therapeutic investment. Therefore, choosing a service based solely on expense is undoubtedly a challenging and intimidating task, and it still fails to account for the specific services provided by each tooth bank. In this regard, NDPL, Oothy, and Stem-Save can collect a large number of teeth simultaneously. Still, BioEden and Tooth Bank do not charge for handling teeth until a satisfactory stem cell extraction is achieved. Some businesses provide full reimbursement if the entire procedure fails, while others offer credits for future teeth. Licensing and reliability are two additional unpredictable criteria. While every center

guarantees security for cryopreservation operations, liquid nitrogen storage, and patient privacy, it is challenging for individual customers to compare centers based on these features. Eventually, it is realistic to expect dentists or other healthcare professionals to attract potential patients to the notion of oral stem cell banking and to suggest personalized banking services, which will have the most significant impact on any subsequent preference (260).

7.3 Ethical considerations

Despite the promising potentials of stem cells, numerous investigations are necessary to establish the safety and efficacy of these cells in periodontal applications. However, the standardized design and improvement of oral stem cell cryopreservation techniques must overcome significant hurdles, such as culture-driven variances, patient-associated variations, and the effects of culture medium additions. Only in this manner can we enhance and strengthen oral stem cells as potential therapeutic options for patients who have few or no other treatment options (261). These stem cells are becoming increasingly essential not just in dental care, where they play a crucial role in tissue regeneration and preservation, but also in other medical sectors, where they are gaining popularity. In summary, further examinations are required to confirm the seemingly regenerative ability of these stem cells. Still, it appears extremely promising to examine their regeneration capacities in a wide range of disorders, given that they are easily accessible, exist throughout life, and possess remarkable multipotency (262).

8 Future perspectives

Oral stem cells offer potential for numerous purposes, such as pharmaceutical testing and regenerative applications (233, 263). These applications need the production of exceptional stem cells in huge quantities (264).

The immunity-regulating properties of stem cells render them a promising treatment for periodontitis (265, 266). However, there is limited evidence of stem cell-based modulation of the immune system. Because periodontal defects are packed with calculus, bacterial biofilms, and plaque, it is exceedingly difficult to replicate highly contaminated environments in animal models (267). Additionally, oral stem cell-dependent immunomodulation pathways exhibit several differences. Several factors, including the origin of stem cells and the experimental methodology, can influence the quantity and quality of stem cells. The results of immunomodulation and regeneration might be affected by the subjects and methods used for stem cell extraction and transplantation (254, 266).

With structural difficulties, especially in furcation areas and small periodontal pockets, periodontal disease raises the probability of extraction of teeth and systemic health issues, necessitating sophisticated medication delivery methods. By infiltrating epithelial cells and evading intracellular inflammatory reactions, the bacterium *Porphyromonas gingivalis* accelerates the progression of the illness. Contemporary hydrogel delivery technologies do not sufficiently promote medication delivery and the removal of bacteria. Making use of chaotropic anions' ability to permeable membranes (268, 269).

Wang et al. (19) developed an iodide-functionalized gelatin/poly-L-lysine (PLL) hydrogel. This method displayed improved injectability, resulting in adequate pocket penetration and strong mucosal adherence. Significant amounts of iodide (5–10 mM) discharged at mucosal interfaces could enhance PLL trans-epithelial transport by membrane fluidization, boosting intracellular *P. gingivalis* clearance. Iodide levels (0.5–1.0 mM) inhibited inflammation while promoting osteogenesis *in vitro* and *in vivo*. This versatile device utilizes chaotropic ion interactions to substantially promote intracellular transport of antimicrobial peptides, enabling collaborative elimination of bacteria while simultaneously achieving immune modulation, osteogenesis, and MSCs survival, thereby contributing to targeted hydrogels for periodontal therapy (19).

Notwithstanding hurdles, as cell-laden hydrogel-based technology has evolved, substantial advancement has been achieved in stem cell multiplication and guided differentiation (233, 263). Many hydrogel features, such as biodegradable properties, durability, and porosity, perform critical roles in stem cell multiplication and differentiation (270, 271). Hydrogels' biochemical and physical features can be precisely tuned to mimic the natural environment in which diverse stem cells reside *in vivo* (272). As a result, various properties of hydrogels, including biodegradability, stiffness, shape, and metabolites, play important roles in determining their destiny and can impact stem cell differentiation and proliferation (170). These are important concerns to consider when dealing with hydrogels and stem cells (273). Hydrogels are an appealing option for regenerative applications; however, when conducting experiments with hydrogels, a variety of elements, characteristics, and metrics must be considered to achieve the desired outcomes (274). When employing hydrogels, the base material, whether natural or synthetic, should be chosen, and the overlaps and disparities should be evaluated. Additionally, the use of hybrid hydrogels and their accompanying properties must be investigated (249). The porosity of hydrogels should also be examined, and correlations between morphology and adhesion should be developed (221).

One should consider the likelihood of insufficient mechanical aspects and system consistency; while restricted, possible solutions to these issues may involve the introduction of peptides (275). A thorough examination of hydrogels would also include a study of the host's reaction to the treatment, particularly when employing hydrogels implanted with stem cells (276). Returning to the selection of hydrogels, the cellular response is a good indicator of which hydrogel to utilize. An ideal hydrogel is one that completely disintegrates while also allowing cells to grow in a manner that matches the native tissue perfectly, which is where the problem lies (277). As a result, tackling the issues related to cell-laden oral stem cells hydrogels necessitates a collaborative effort spanning various

disciplines, including material science, biology, and engineering (278). By addressing these problems and highlighting future-oriented viewpoints, the integration of hydrogels and stem cells presents an opportunity to transform the field of regenerative healthcare (181, 279, 280). This can accelerate the advancement of novel treatment options for tissue repair and regeneration, leading to substantial advances in customized and personalized medicine (281–284).

9 Conclusion

Considering the increasing incidence of periodontitis and the potential risk it poses to retaining the entire dentition, the emphasis has shifted to microscopic PDL rebuilding to improve therapeutic outcomes for an increasing number of periodontal diseases. This paper focuses on oral stem cells, which have been recognized for their outstanding multipotency and immune-modulating properties. It provides a physiological summary as well as an explanation of how they are used in periodontal therapeutic applications. The primary mechanisms driving periodontal regeneration include restoring defective collagen metabolism, limiting tissue degradation, boosting regeneration of other damaged tissues, and promoting ordered PDL regeneration. Furthermore, this study gives a detailed overview of the application forms and recent developments in oral stem cells, highlighting their importance in the reconstruction of periodontal tissues in individuals with periodontitis. It describes potential investigation prospects in periodontal regeneration and offers a platform for exploratory investigations in PDL regeneration. Despite the significant improvement so far, numerous barriers still require consideration and improvement. A thorough comprehension of the processes regulating oral stem cells and their regeneration is still in its early stages of development. Moreover, the best option of oral stem cells for periodontal regeneration remains a topic of debate, prompting further exploration into diverse oral stem cell types, donor selection guidelines, and established techniques for cell collection and storage. In addition, disparities between experimental and clinical regenerative findings underscore the need for in-depth investigation of the basic processes, advancement of oral stem cell techniques, and the utilization of novel approaches such as bioactive factor combinations, innovative methods of administration, and specialized functional adjustments. Furthermore, it is crucial to investigate application strategies tailored to periodontal patients, enabling better alignment with therapeutic needs. To summarize, oral stem cells have tremendous promise for PDL regeneration because of their exceptional effectiveness, regeneration capability, and immune-modulating characteristics.

Periodontitis causes the alveolar bone to resorb and lose its connection gradually. Complete regeneration of periodontal tissue in both form and function is clinically challenging for individuals with severe periodontitis, making the condition particularly catastrophic for these patients. In the medical management of periodontitis, oral stem cell-loaded hydrogels can considerably accelerate periodontal reconstruction since they have the capacity to promote periodontal regeneration. Additionally, the hydrogels prevented the formation of periodontitis while hastening the recovery of healthy periodontium.

This review emphasizes the importance of functioning periodontium for patients with periodontitis, suggests additional investigation goals in periodontal regeneration, and offers an overview of fundamental periodontal regeneration investigations. It provides a concise yet informative summary, as well as a helpful reference for prospective studies in the associated fields.

Author contributions

NT: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MeA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MoA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MH: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. ME: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. GA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. HS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. OG: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. DR: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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