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Stem cell-based tissue engineering for the regeneration of periodontal structures: A systemic review of current progress and barriers

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Abstract

Periodontal disease (PD) is characterized by gum inflammation, ranging from reversible gingivitis to irreversible periodontitis. Periodontitis compromises the foundation of oral health by degrading periodontal tissues that support teeth, namely the periodontal ligament (PDL), underlying alveolar bone (AB), cementum (CM), and the gingiva. Disruption of the structural integrity of teeth leads to a multitude of oral issues and eventual tooth loss. The focus of this review is to explore treatment modalities that use stem cell therapies and tissue engineering to aid in tissue regeneration while also overcoming the intracellular molecular pathways that lead to tissue degradation. Research from PubMed and Google Scholars, from 2000 to 2025 was conducted, applying predefined inclusion and exclusion criteria. The combined findings show that orally-derived and non-oral stem cells have promising regenerative potential, specifically: periodontal ligament stem cells (PDLSCs), dental pulp stem cells (DPSCs), stem cells from the apical papilla (SCAPs), bone marrow-derived stem cells (BMSCs), adipose tissue stem cells (ADSCs), and human umbilical cord mesenchymal stem cells (UCMSCs). Among the different stem cell types reviewed, PDLSCs revealed the highest regenerative potential of periodontal tissue in vivo, particularly when combined with bioengineered scaffolds. However, challenges such as limited clinical translation, minimal autologous availability, and adverse immune responses remain significant barriers. Furthermore, optimizing scaffold design and refining immunomodulatory strategies are the next steps in making stem cell-based tissue engineering clinically viable for periodontal regeneration.

Keywords: Periodontal diseases, mesenchymal stem cells, periodontitis, stem cells, regeneration, tissue scaffolds

Introduction

Introduction to Periodontal Disease: Current Insights and Therapeutic Goals

Periodontal disease (PD) is a common condition that causes inflammation to the gums and can potentially result in the degradation of the periodontium—the supporting foundation of teeth. It is ranked as the 11th most prevalent disease nationally and therefore should be regarded as a public health concern [1]. While many factors contribute to the development and severity of PD, poor oral hygiene is a major contributor to the onset of the disease, as inadequate brushing and flossing provide an optimal environment for bacteria to accumulate [2]. PD is categorized into two main types: gingivitis and periodontitis, respectively. Gingivitis is seen in up to 90% of individuals globally [3] but is manageable upon early detection, improved oral hygiene practices, and clinical assessments—including probing periodontal pocket depth, radiograph bone loss evaluation, and bleeding upon minimal probing—before escalating to periodontitis, the more severe stage responsible for extensive tissue destruction. Periodontitis is seen in more than half of the adult population globally and is characterized by the degradation of the periodontium, consisting of the periodontal ligament (PDL), cementum (CM), gingiva, and underlying alveolar bone (AB) [4]. It should be noted that the destructive progression of this disease is driven by immune dysfunction rather than the pathogens themselves, and therefore, patients' susceptibility varies based on many etiologic factors [5]. This hyperactive inflammatory nature of the immune system links periodontitis to several systemic conditions, including heart

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disease, diabetes, respiratory diseases, pregnancy complications, Alzheimer's disease, and more [6]. In addition to systemic implications, the progression of periodontitis can result in pain during mastication, impacting nutritional intake, tooth mobility, and, eventually, tooth loss. Early detection of PD is vital to prevent its progression, but it is often left undiagnosed due to its lack of persistent symptoms during the reversible stage. It isn't until periodontitis causes irreversible damage that clear signs of PD make diagnosis possible. Given the detrimental effects of periodontitis, oral health restoration and preservation have been the focus of PD research. Stem cell-based TE has shown promising potential in regenerating the once-thought-to-be irreversible damage caused by periodontitis.

To truly reverse the damage caused by periodontitis, researchers have shifted focus from symptom management to tissue restoration. Current non-surgical approaches, like the mechanical removal of plaque, are for halting disease progression. In severe cases, surgical interventions to control bacterial infections and reduce pocket depths are performed to preserve natural dentition [7]. Implantology is commonly used as a solution to address tooth loss, however, they are not without issues. Decreased bone density at the defected site creates challenges for proper implant placement and the risk of peri-implantitis, inflammation of gums around the implant, limit their long-term success [8]. Guided bone regeneration (GBR) and guided tissue regeneration (GTR) are also common surgical methods aimed at regenerating lost bone and tissue. These approaches, however, regenerate structures by isolating the defected site from cellular invasion to allow for self-renewal of the damaged tissue, which is beneficial in repairing specific structures, but fail to restore the intricate architecture of the periodontium [9]. In addition, factors such as gingival thickness and structural complexity at the defected site can hinder the success of these methods [10]. Ultimately, current treatment options are constrained by their incapacity to repair lost or damaged periodontal tissues and are associated with variable outcomes and potential post-operative complications [11]. Given these limitations, researchers are turning to regenerative approaches, specifically tissue engineering (TE) using stem cells (SCs) and bioengineered scaffolds offer a promising alternative for periodontal restoration. Stem cell-based TE approaches utilize various mesenchymal stem cells (MSCs), including periodontal ligament stem cells (PDLSCs), dental pulp stem cells (DPSCs), stem cells from the apical papilla (SCAPs), bone marrow-derived stem cells (BMSCs), adipose-derived stem cells (ADSCs), and human umbilical cord mesenchymal stem cells (UCMSCs). Each of these stem cell types offers vast regenerative potential, influencing tissue repair and integration in their own ways. Most notably, PDLSCs have demonstrated diverse lineage differentiation, including cementoblasts, osteoblasts, adipocytes, and chondrocytes in vitro, PDL-like regeneration in vivo, angiogenic properties, immunomodulatory activity, and can release extracellular vesicles and important cytokines [12]. When coupled with the right scaffold and bioactive agents, these cells have a bright future in regenerative dentistry. However, the quantity of dental-derived MSCs has limits, and therefore, non-oral MSCs are being studied and are just as promising. TE using stem cell-based approaches for periodontal tissue regeneration holds a transformative potential that is soon to be unlocked with refined clinical practices to optimize their functions.

This systemic review, following PRISMA-P guidelines, aims to assess the possibility of TE and stem cell therapies in achieving true periodontal tissue regeneration. The proposed hypothesis is that integrating bioengineered scaffolds with dental and non-dental MSCs can enable complete periodontium regeneration by directing stem cell differentiation into osteoblasts, for AB, cementoblasts, for CM, and fibroblasts, for the PDL. However, despite promising preclinical findings, significant barriers remain. Issues such as limited stem cell viability, immune rejection, and the need for precise spatial and temporal delivery of bioactive agents hinder clinical translation. Additionally, the structural complexity of the periodontium requires scaffold designs that can support the simultaneous regeneration of multiple tissue types while maintaining functional integration. This review breaks down findings from preclinical studies to analyze the efficacy of these TE strategies and identify key challenges that are preventing widespread clinical adoption. By addressing these barriers, future research can refine stem cell-based regenerative approaches, optimizing their safety, efficacy, and long-term stability. Ultimately, transforming laboratory research to clinical application will determine whether TE can shift periodontal treatment from chronic symptom management to curative intervention.

Historical Background of Stem Cell Research in Regenerative Medicine

Stem cell investigation in dentistry initiated a paradigm shift in PD management by offering new therapeutic alternatives outside of mechanized procedures. The isolation of MSCs in the 1950s established the foundation for regenerative medicine. These multipotent cells, found in adult human bone marrow, were considered strong candidates for regenerative medicine as they possess the ability to directly and indirectly aid in tissue restoration [13]. Along with their multi-lineage differentiation capacities, MSCs are also able to migrate towards the site of injury, secrete molecules that that activate tissue repair mechanisms, regulate/suppress inflammatory responses, promote vascularization and cell multiplication through the release of bioactive agents [11]. As research progressed, scientists discovered that dental-derived MSCs, like PDLSCs and DPSCs, exhibited stronger potential for oral-specific tissue regeneration. By analyzing past discoveries, we can better understand how stem cell-based therapies advanced and what challenges have refrained the clinical application of these therapies.

The first dental-derived discovery in this line of research was the identification of DPSCs in the early 2000s [14]. These cells

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were of great significance because they are easily accessible, can be preserved for later use, have anti-inflammatory properties, low extraction cost, and produce dentin and pulp-like components better than other MSCs [15]. Early animal studies confirmed their ability to develop into odontoblast-like cells, forming calcified nodules, along with heightened proliferative and colony-forming abilities [16]. However, further studies raised concerns about their therapeutic application in PD treatment due to inconsistent clinical data and high rates of cell death upon extraction. It was noted that the time between extraction and transplantation influenced cell viability, with prolonged culture periods leading to increased telomere shortening and reduced regenerative potential [17]. These challenges prompted researchers to explore other dental-derived MSCs. The discovery of DPSCs was quickly followed by the identification of PDLSCs in 2004, a milestone in regenerative dentistry. Unlike DPSCs, which primarily contribute to dentin regeneration, PDLSCs are programmed to differentiate into the three main cells, osteoblasts, fibroblasts, and cementoblasts, required for AB, PDL, and CM generation, respectively, making them ideal candidates for periodontal TE [18]. Early studies, such as those by Dangaria et al. [19], demonstrated PDLSCs could regenerate functional periodontal tissue growth in vivo, by culturing them directly on tooth root surfaces on a rat model, along with producing extracellular vesicles rich in cytokines and exhibiting strong immunomodulatory properties. These findings positioned PDLSCs as one of the most promising cell types for restoring periodontal structures damaged by periodontitis. These initial discoveries laid the groundwork for scientists to unlock the potential of TE using various stem cells with similar regenerative properties as well as gaining more insight into the restorative potential of DPSCs and PDLCs.

Positive results from early studies on stem cells have established the stage for current investigations on periodontium tissue regeneration. While dental-acquired stem cells like DPSCs and PDLSCs are valuable, limited autologous amounts are attainable, and therefore researchers have also investigated adaptable, non-dental stem cells that have high regenerative capabilities for periodontal TE. In particular, BMSCs, ADSCs, and human UCMSCs have been used in TE and may be helpful in periodontal tissue restoration. Technologies and procedural methods for clinical applications of these cells have also seen great advancements, contributing towards making periodontal tissue regeneration a possibility [20]. Scholars employing stem cells and innovative materials have developed excellent regenerative treatments that improve on conventional approaches. Even with the progress of translating cellular therapy into clinical practice, more research on stem cells is still key to redefining patients' oral health and function. The following sections will examine the mechanisms underlying periodontal disease progress, the role of bioengineered scaffolds in stem cell-based therapies, recent advancements, and continued challenges in transitioning from laboratory settings to clinical practice.

Clinical and Research Consequences

Periodontal Disease: Cause and Effect

The host immune system in response to a microbial dysbiosis drives the progression of PD. Pathogen accumulation in the oral cavity initiates the onset of PD, but it is the host immune response that ultimately determines the severity of the disease. A dysregulated immune system is the catalyst for uncontrolled inflammation that ultimately leads to tissue destruction [21]. Understanding the mechanisms underlying PD progression is imperative for developing targeted therapies that not only eliminate pathogenic bacteria but also modulate immune responses to promote tissue regeneration and abate excessive inflammation. PD begins with the formation of bacterial biofilm on the tooth surfaces and gingival margins [2]. At this point, PD is in the early stage of gingivitis and the bacterial invaders within the biofilm are primarily gram-positive, facultative anaerobic bacteria (e.g., Streptococcus spp., Actinomyces) [22]. While localized acute inflammation of the gums and connective tissue is present, the innate immune response and mechanical removal of plaque can reverse the effects and restore tissue health [12]. If the biofilm is not removed promptly, the initial invaders mix with salivary proteins and overtime, oxygen levels within the biofilm decrease, creating an environment that favors the colonization of anaerobic gram-negative bacteria (e.g., P. gingivalis, F. nucleatum) [23]. As a result, the microbial-host homeostasis is disrupted, shifting the oral microbiome—also known as microbial dysbiosis. To put it simply, microbial dysbiosis is a term that refers to a depletion of the "good" symbiotic bacteria and a spike in "bad" pathogens, altering the immune system and fueling prolonged inflammation [7]. Inflammation can then spread laterally and apically, leading to collagen fiber degradation and the loss of PDL attachment, marking the shift from gingivitis to periodontitis [24]. It should be noted that a dysregulated host immune response can be attributed to different genetic and environmental factors, and therefore individual susceptibility varies. A breakdown of the intracellular pathways will be discussed next as the mechanisms underlying PD progression is essential for developing targeted therapies, such as bioengineered scaffolds, that not only eliminate pathogenic bacteria but also modulate immune responses to promote tissue regeneration.

Activation of the innate immunity is the first responder to the dental biofilm. The gram-negative bacteria release key virulence factors, lipopolysaccharides (LPS), that activate immune cells [25]. These cells release pro-inflammatory proteins, like interlukin-1beta (IL-1beta), tumor necrosis factor-alpha (TNF-alpha), IL-17, and IL-6, which in turn promote neutrophil recruitment to the injured site [2]. As neutrophils are the primary cells for infection control, TNF-alpha plays a crucial role in inducing endothelial cell adhesion molecule expression, allowing neutrophils to adhere to the vessel walls and migrate toward gingival connective tissue [26]. Neutrophils work to eliminate bacteria from the affected

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tissues by releasing reactive oxygen species (ROS), proteolytic enzymes (e.g. elastase, MMPs), and neutrophil extracellular traps (NETs) to eliminate pathogens from the affected tissues [7]. However, extensive neutrophilic activation and recruitment leads to the overexpression of their secretions, exacerbating tissue destruction. High levels of ROS trigger bone resorption and impair fibroblast production, damaging surrounding tissue [27]. On the other hand, NETs are important for identifying and trapping bacteria to limit their infectious spread, but the over-production of NETs contributes to ECM degradation [28]. Proteolytic enzymes, such as elastase, break down bacterial membranes, but in doing so, they also destroy elastin and collagen within the periodontium [29]. In essence, hyperactivation of neutrophils is seen with prolonged recruitment periods and delayed apoptosis, exacerbating tissue destruction [26]. Additionally, the two types of macrophages, M1 and M2, involved in the innate immune response are pro-inflammatory and anti-inflammatory, respectively. In PD, the balance between M1 and M2 is disrupted, shifting to more M1 macrophages and thus continuing the release of pro-inflammatory cytokines. However, these cells are important as they bridge the gap to the adaptive immune system by presenting antigens for T-cell recognition. If the infection is not resolved, further release of pro-inflammatory mediators is sustained, triggering the adaptive immune reaction.

When innate immunity fails to resolve the infection, adaptive immunity is activated. Dendritic cells and macrophages present bacterial antigens to T-helper (Th) cells which have been found to drive disease progression [26]. In PD, an overactive Th1 and Th17 response enhances inflammation and drives disease progression [28]. Th1 cells protect against intracellular pathogens by producing interferon-gamma (IFN-gamma) that activate macrophages for phagocytosis, intensifying inflammatory response, while Th17 produces interleukin-17 (IL-17) which enhances neutrophil recruitment while also degrading the ECM and bone density [30]. The predominate T-cell and macrophage presence is indicative of early stages of periodontitis [7]. As PD transitions to a chronic phase, B-cells and plasma cells become the dominant immune infiltrates [22]. These cells are responsible for the production of receptor activators of nuclear factor kappa-B ligand (RANKL), a chief molecule in osteoclast activation, and elevated levels of RANKL are associated with decreased bone density, as the activation of osteoclasts drives bone resorption [20]. Upregulation of RANKL is involved in IL-1beta, TNF-alpha, and IL-6 cytokine secretion, which subsequently activates osteoclastogenesis, and metalloproteinases (MMP-8, MMP-9) activation, which destroy ECM collagen, and therefore irreversible bone reabsorption occurs [23]. The immune-driven destruction of periodontal structures highlights the need for therapies that go beyond simple plaque removal. Regenerative approaches are the future for restoring lost tissue while modulating immune responses. Nonetheless, the severity of PD is influenced by various risk factors that contribute to PD susceptibility and progression, which will be explored in the following section. Given the fact that PD is not just an infection, but rather a host-mediated response to heightened inflammation, scaffold-based therapies must account for immune system hyperactivity without disrupting tissue regeneration.

Associated Risk Factors for PD Exacerbation and Progression

Many risk factors contribute to the manifestation and progression of PD. Non-modifiable risks are those that cannot be altered, such as age-related oral health decline and genetic predispositions to inflammatory diseases. Certain risks, on the other hand, can be considered modifiable as they are associated with lifestyle modifications that can prevent the progression of PD. These risks include factors such as oral hygiene practices, smoking, alcohol consumption, stress, certain medications that heighten inflammation, poor diet, and various dental issues. Periodontitis has also been associated with the increased risk of emerging and/or aggravating other systemic diseases prone to inflammation. Such diseases include rheumatoid arthritis, diabetes mellitus, birthing complications, respiratory and heart diseases, Alzheimer's disease, and more [4]. This interplay between PD and systemic diseases can lead to worsening health outcomes, emphasizing the importance of managing oral health. While TE offers a promising approach for restoring natural periodontal structures, its success is highly individual-dependent, with systemic conditions and environmental factors playing a significant role in treatment outcomes.

The most common modifiable risk factor is improvements in oral hygiene practices. At the initial sight of plaque formation, dentists should educate patients on proper oral care to prevent PD progression. Dental issues, like improper dental bridges, teeth grinding, gaps between teeth, and loose cavity flings, allow for bacterial buildup and should be addressed promptly [31]. Certain medications have also been linked to PD, emphasizing the importance of disclosing current drugs being taken at each dental visit. Immunosuppressants have been shown to be related to gingival enlargement, ultimately impacting oral hygiene and promoting plaque build-up [10]. Corticosteroids and certain cancer therapy drugs work by suppressing the immune system, impairing tissue healing, and risking PD onset [32]. Individuals especially vulnerable to PD should opt for alternative medication if possible. Smoking is a significant and crucial modifiable risk factors for PD, increasing the risk of the disease by nearly threefold, and suffering from significant loss of AB density and painful abscesses forming around teeth [33]. Nicotine and other compounds in tobacco are said to impair neutrophil function, fibroblast proliferation, and vascularization, all of which contribute to affected healing processes, as well as increasing ROS and pro-inflammatory cytokines [2]. The effectiveness of treatments also declines in smokers [3]. Understanding the negative effects that these risks pose on patients susceptible to PD is beneficial in preventing disease progression.

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Some of the earliest research linking oral and overall health dates back to the 1980s when a correlation between PD and diabetes was identified. Compared to non-diabetics, patients with diabetes have higher susceptibility to PD as their immune systems are weaker and therefore have impaired wound healing potential [3]. The persistent inflammatory mechanisms in response to periodontitis can lead to uncontrolled blood sugar levels, increasing the need for insulin, while persistent periodontal infection worsens insulin resistance, making control of diabetes more difficult [34]. PD also shares many risk factors with cardiovascular disease (CVD). Studies have found that pathogens associated with PD may contribute to atherogenesis, the buildup of plaque in arteries, which promotes inflammation within blood vessels—the leading cause of all CVDs [35]. According to an article by Muhammad Ashraf Nazir [33], there is a 19% increased rate of heart disease associated with PD. Additionally, the link between preterm low-birth-weight (PLBW) birth and PD has been a research hotspot. Hormonal changes in pregnant woman can trigger inflammation, increasing their risk of developing PD, which in turn can lead to circulating pro-inflammatory molecules (e.g., cytokines) as the immune system works to fight the inflammation [25]. Of these pro-inflammatory molecules, prostaglandin E2 (PGE2) has been shown to induce contractions, ultimately leading to PLBW labor [36]. PD also has direct effects on respiratory diseases as pathogens within the mouth can enter the lungs and cause inflammation, leading to possible infections [6]. The inhaled pathogens can participate in apoptosis of epithelial cells lining the airways, thereby replacing them with more pathogens that ultimately increase mucus production, and thus, disrupting the immune response [37]. Interestingly, PD can also be considered a risk factor for Alzheimer's disease. Researchers, Villar et al [3], studied the relationship between the two and found that periodontal pathogens and inflammatory molecules released in response to PD can reach the brain, aiding in the onset of Alzheimer's disease. Practicing proper oral hygiene may be the key to preventing the risk and progression of Alzheimer's disease. A study found that PD treatment reduced Alzheimer's disease-associated comorbidities, underscoring the importance of periodontal health [38]. Recognizing the correlation between systemic conditions and PD is essential for early intervention strategies. Patients with underlying systemic disease may require more frequent dental visits and personalized treatment plants that prevent PD by incorporating anti-inflammatory therapies and regenerative techniques.

Dental-Acquired Mesenchymal Stem Cells in Periodontics: PDLSCs, DPSCs, and SCAP

Among all stem cell populations, PDLSCs are considered the most valuable cells for periodontal TE. These multipotent cells are extracted from the PDL and are capable of complete regeneration of this tissue. Regeneration of the PDL is crucial as it is the tissue connecting the CM to the AB, and thus integral to the functionality of the periodontium [39]. Extensive clinical trials on their role in AB regeneration has been done, showcasing their ability to promote bone formation in vitro. Specifically, when combined with the ideal scaffold, such as hydroxyapatite, PDLSCs express osteoprotegerin (OPG) which resists osteoclast activity, therefore allowing for bone-building cells, osteoblasts to do their work [40]. Additionally, A study done in rat models with periodontal-like defects found that PDLCs not only regenerated the complete PDL, but also exhibited remarkable ECM secretion and anti-inflammatory effects [41]. Furthermore, these cells have also been shown to suppress the activity of macrophages and T-cells, whose overactivity contribute to tissue deterioration pathogen proliferation, which could enhance TE approaches [28]. Lastly, PDLSCs can develop into the three most crucial cell types needed for regeneration of the entire periodontium: Osteoblasts, cementoblasts, and fibroblasts. Combining all of their characteristics and properties, PDLSCs are promising cells for periodontal regeneration and have high success rates in lab settings.

DPSCs were among the first orally-derived stem cells to be extracted from the pulp tissue of adult 3rd molars. These cells are of considerable interest due to their high differentiation and proliferative potential [4]. Researchers have proposed that DPSCs from third molars may have higher growth potential, possibly due to their late eruption, making them favorable candidates for TE [42]. However, differences in proliferative capacity have been observed between third molar and premolar DPSCs, a potential result of different telomere lengths [43]. The limited number of autologous third molar DPSCs available from an individual may present challenges for clinical applications requiring large cell populations. Recent studies have revealed that these cells are a heterogeneous group of cells with subpopulations exhibiting distinct regenerative properties. For instance, CD34+ subsets have been linked to bone tissue formation, while other subsets demonstrate potential for dentin and pulp regeneration [44]. Additionally, some subpopulations have high numbers of genes related to angiogenesis thus possessing vasculogenic properties, contributing to the formation of blood vessels which is crucial in periodontal healing [20]. Further research is needed to characterize these subpopulations to optimize their application in dental TE done to understand these differences and optimize their application in dental TE. Post-extraction cell viability is another factor that needs to be fully understood as cell viability significantly declines.

SCAPs cells are postnatal stem cells derived from the apical papilla in the apex root of primary teeth, another cell type that hold value for TE. Comparing these cells to DPSCs and PDLSCs, SCAPs have a greater differentiation ability. The apical papilla tissue, at the root tip of incoming teeth, allows for these cells to not only be extracted from under-developed wisdom teeth, but they contain cells with greater differentiation potential [45]. In this regard, they benefit teeth that are not fully developed and have only rudimentary forming root structures, posing a limitation to the widespread use of these cells, specifically in

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adult patients [46]. In addition, they show high self-renewal and proliferation abilities, low immunogenicity properties, and the ability to various growth factors (GFs) [29]. SCAPs are particularly valuable in shaping and regenerating root structures as they can develop into odontoblast-like cells, cells essential for dentin formation—the structural base of teeth [47]. Studies have found that SCAPs have the potential to regenerate dentin and pulp-like structures in vivo [48]. Therefore, based on the features of tissue regeneration, SCAPs may be applied in treatments aimed at restoring tooth function and reducing the root of the same tooth. Consequently, SCAPs may provide future trends in regenerative therapies for endodontics and the periodontal field to enhance the outcomes of diverse clinical treatments.

Extraoral Non-dental MSCs in PD Regeneration: BMSCs, ADSCs and human UCMSCs

Aside from dental-derived stem cells, non-dental sources for stem cells are also being explored. One of the most notable non-dental cells with high regenerative capacities are BMSCs, multipotent progenitor cells found within adult bone marrow. Large amounts of these cells are typically extracted from the hip bone, specifically the iliac crest, but they can also be directly isolated from the jaw bones during dental procedures, like wisdom teeth extractions and implant placements, though in less quantities [49]. Identification of these cells is much easier than, for example, PDLSCs because BMSCs present with specific surface markers, such as CD44 and CD71, making isolation and extraction of these cells easy and thus, favorable [4]. These cells also present with anti-inflammatory and immunosuppressive functions. By inhibiting pro-inflammatory markers like IL-1 and TNF-a, they can reduce tissue damage caused by inflammation. They also mediate T-cell proliferation, as overactive T-cells can further exacerbate tissue damage [29]. Seeded BMSCs on scaffolds not only differentiate into bone-forming cells, but they can also release GFs that stimulate surrounding cells in bone regeneration [16]. The cellular activities of BMSCs make these cells advantageous for tissue engineering and may be an alternative source for stem cell cultivation, given their accessibility.

ADSCs are another type of MSCs that has shown regenerative potential. Due to the widespread use of cosmetic treatments like liposuction, the donor-site morbidity in response to extraction of these cells is negligible, making isolation in large quantities feasible [49]. Compared to BMSCs, they are similar in that they present with surface markers, making identification and extraction easier. However, isolation of these cells yields larger quantities and is done through a less invasive procedure; therefore, fewer complications are present at the donor site [29]. A study done on rat models where these cells were transplanted onto the affected periodontal tissue showed successful regeneration of AB, cementum, dental pulp, and PDL fibers [50]. Most notably, these cells secrete high levels of cytokines and (GFs), making them a superior choice of stem cells as (GFs) stimulate cell multiplication and differentiation, and cytokines enhance the repair process by recruiting/activating other cells [51]. These cells are superior due to their vast cellular functions and large quantity access when compared to dental-derived stem cells.

Researchers have been studying non-oral stem cells for periodontal tissue regeneration for many reasons, namely: (1) stem cell function declines as individuals age and (2) there are limited amounts of dental-derived autologous stem cells that can be collected from an individual. Human UCMSCs are typically collected from the blood of a newborn's umbilical cord and are minimally invasive and safe offer a large quantity of stem cells and can be stored for later use [52]. Compared to cells extracted from the adult periodontium, these cells are younger and have higher plasticity and developmental flexibility [4]. In other words, they can alter their differentiation pathways in response to the demands. In a study comparing PDLSCs and human UCMSCs, both had very similar regenerative capabilities of soft and hard tissues accompanied by inflammation, with UCMSCs showing better anti-inflammatory properties than PDLSCs [53]. These cells, while still in their early stage of research due to limited long-term clinical studies, are very promising and could be a possible source of stem cells as TE research progresses.

The Role of Bioengineered Scaffolds for Periodontal Regeneration

For PD-damaged tissue regeneration, scaffolds have been the focus of extensive research and are the primary tools used in TE. Biomaterial-based scaffolds are intricately engineered to provide tridimensional structural support and mimic the cells' natural ECM matrix, creating an environment that allows for key topographic activities, including cell adhesion, division, and differentiation. Bioactive agents and regenerative elements are also incorporated within scaffolds to facilitate proper cellular activity in regeneration and healing. Successful periodontium regeneration is a constituent of three structurally different and complex tissues, PDL, AB, and CM, requiring scaffolding material to be tailored to each tissue type [54]. In addition, regeneration must be simultaneous with PDL fibers properly positioned between the AB and CM in a longitudinal manner [55], for functional and anatomically correct tissue regeneration. Biocompatibility and biodegradability are also very crucial in bioengineered scaffolds. Upon transplantation of the scaffold, biocompatible scaffolds do not induce further immune and inflammatory responses, while biodegradable scaffolds break down at a rate that is compatible with the regenerating tissues [56]. Advancements in scaffolds and newfound studies on bioactive molecules and regenerative elements are bringing the clinical application of TE closer than ever.

Biomaterial scaffolds can be made from natural (e.g., collagen) and synthetic (e.g., hydroxyapatite) polymers. Natural polymer scaffolds are advantageous because they offer strong elasticity, biocompatibility, biodegradability, hydrophilicity and enhanced cell-to-cell interaction with surrounding tissues [57]. They are

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also less toxic and so do not trigger inflammatory responses upon transplantation. However, these natural polymer scaffolds are restricted in inducing hard tissue formation due to their lack of strong mechanical strength, making these scaffolds good candidates for PDL regeneration, but not for AB or CM. Synthetic polymers, on the other hand, are used in hard tissue formation as their molecular shape can be altered to increase their density to replicate bone mineral densities. Thus, to regenerate multiple structures simultaneously, composite scaffolds, a combination of natural and synthetic polymers, are typically used in conjugation, offering the advantages of both biopolymers and the versatility needed for the complexity of periodontal tissues. The gelatin-hydroxyapatite scaffold is an example of a composite scaffold that is used and has shown excellent capability for stem cell attachment and differentiation in simultaneous hard and soft tissue regeneration [54]. Arguably, the most important aspect of bioengineered scaffolds is the bioactive molecules and regenerating elements that are loaded along with the stem cells. Bioactive molecules like (GFs) and cytokines, significantly advance cell migration and regeneration activity by providing sustained stimuli through controlled, gradual release mechanisms [47]. For example, a scaffold containing PDGF, a growth factor that promotes MSCs and fibroblast proliferation, and IL-10, a cytokine that acts as an anti-inflammatory, can work together to create a favorable environment for regeneration [55]. Additionally, incorporating bioactive molecules like VEGF, angiogenesis inducer, FGF, triggers cellular division and tissue remolding, and TGF-beta, aids in healing and immune homeostasis, can improve cellular activity upon transplantation [11]. The basis of regeneration is for cells to proliferate and differentiate within the scaffold after placement, which can be achieved with the proper bioactive molecules and biomaterial scaffolds as the scaffolds themselves are not able to induce tissue restoration.

Scaffold technology is continuously being modified and improved to enhance cellular activity for regeneration. Multilayered scaffolds have emerged and support the simultaneous regeneration of multiple types of tissues within the periodontium. For instance, inorganic materials like calcium phosphate promote hard tissue formation [54], while organic materials are better for soft tissue like PDL. With multilayered scaffolds, each layer is designed to accommodate the specific tissue and mimic the natural transition zones [57]. Hydrogels, 3-dimensional hydrophilic polymers, are widely used in TE. Hydrogels have porous structures that allow for nutrient transport, contributing to creating a cell-friendly environment. Moreover, their stability after swelling in water makes them ideal for soft tissue applications [58]. 3D printing is a new way to design scaffolds as it allows for creating precise microstructures with region-specific properties, suitable for guiding soft and hard tissue formation [55]. In essence, 3D-printed scaffolds allow for the customization of scaffolds with enhanced detail and accuracy for guiding regeneration [9]. Electro-spun nanofibrous scaffolds, artificially made ECM, are especially good for cell migration and differentiation because of their high porosity and small pore sizes, which provide a large surface area for cell attachment, interconnectivity, and absorption of ECM proteins [39]. All of these advancements will contribute to the translation of cellular therapy from laboratory findings to clinical procedures.

Challenges in Periodontal Cellular Therapy

While the future of cellular therapy for PD looks promising, there is still much to be overcome before these therapies become effective and safe for use. Limited survival and retention of stem cells at the location of damaged tissue is a major issue. Often these cells don't stick to the damaged site, increasing cell death and migration rates [59]. Additionally, various stressors like hypoxia and inflammation further compromise the function and viability of the cells within the tissue. More research needs to be done on how to integrate the cells into the tissue architecture and optimize their survival for successful tissue regeneration. Another challenge is obtaining large quantities of autologous stem cells (i.e., an individual's cells), as it is often not possible to get enough from a single person [45]. Using non-autologous stem cells (i.e., donor cells) is an option; however, immunogenicity and immune rejection from the host can be triggered. This immune response to the non-autologous cells plus the bacteria in the defective tissue not only slows down the regenerative process but also risks further tissue destruction [60]. Strategies like preconditioning cells and adding immunosuppressive agents are being explored to overcome these barriers and make cellular therapy more clinically applicable. One example is the dual-drug delivery method, where antibacterial drugs are administered with the stem cells to control the infection after transplantation [49]. Refining these systems to promote stem cell survival and controlled host response will help in making cellular therapy more widespread in PD treatment.

The periodontium has structural complexity and multilayered compartments that require precise and timely bioactive molecular signaling to direct cells in regenerating tissues in a hierarchical manner. However, spatial and temporal delivery methods are the concerns that require further research and optimization. Spatial delivery ensures molecules reach the exact location of the periodontal defect, and temporal delivery releases these molecules at the right time. Currently, several gene therapies that allow for prolonged creation and release of multiple GFs by genetically altering the cells have been engineered for PD treatment [39]. The viability of these bioactive molecules is another problem, as many (GFs) have short half-lives and slim therapeutic windows, resulting in the need for controlled delivery systems to sustain long-term effects and minimize side effects [54]. Scaffolds can act as carriers to deliver the bioactive molecules and influence their release kinetics, which is why designing the right scaffold/carrier is crucial for cellular function within defective tissue. For instance, the scaffold/carrier for (GFs) should be able to denature proteins to a minimal extent upon transplantation, maintain a controlled and steady of these molecules, and should be absorbable to work over an extended period [58]. Moreover,

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the structure and composition of the scaffolds should be tissue-specific to accommodate the different microenvironments of the periodontium. For example, the porosity, which allows for tissue integration with surrounding tissue, infiltration of cells, and nutrient/waste exchange, will be different for each tissue. Finally, extended culture periods increase the risk of genetic and epigenetic alterations, as well as infections and pathogens being present in the cultures. These intricacies are imperative in the regenerative process of PD tissue, and further studies should be done to perfect the cellular activities after stem cell transplantation.

While overcoming biological challenges is the first step toward success, clinical trials, standardized treatment protocols, and long-term outcome data are needed before the transition to clinical practice. Current studies use small sample sizes with in vitro or in vivo in animal models, such as rats, that do not replicate the complexity of human anatomy and physiology, leaving a gap in long-term human data [4]. Along with differing anatomy, immune responses and progression of the disease also poses a limitation on the findings, making it difficult to transition from preclinical to clinical trials [11]. Ultimately, human clinical trials with larger sample sizes are needed to confirm recent findings, monitor long-term effects, and develop standardized guidelines for stem cell-based therapies. This is imperative as setting formal guidelines for using these therapies in routine practices will take time. Post-treatment outcomes must be monitored for years to follow up on the regenerative process. Additionally, variability in patients' response to the treatment must be noted as every individual's stem cells and characteristics—such as age, healthiness, and genetic factors—influence the healing and response outcomes. Future research should provide enough information for the treatment predictability and effectiveness in human cases, providing a sound basis for integrating cellular therapy into standardized PD treatment.

Future Directions in Dental Stem Cell Research

Future research in stem cell-based TE should focus on refining the delivery method of stem cells and integrating them into the periodontal defected tissues to enhance therapeutic performance. One of those ideas that seems especially worthy of examination is using tools like CRISPR gene activation (CRISPRa). CRISPRa could allow for improved adaptability of stem cells in the dynamic nature of the periodontium by allowing the expression of certain genes without altering the genome. Recent studies indicate that combining CRISPRa agents with biomaterial scaffolds can be delivered in vivo to the periodontal tissue, potentially reprogramming nearby cells into PDLSCs and creating a localized regenerative environment for periodontal tissue repair [55]. In that case, stem cell characteristics can be manipulated through genetic engineering techniques to enhance the potential of these therapies in treatment procedures. Moreover, conducting more research on the additional cocktail of bioactive agents, namely (GFs) and immunomodulators, could significantly elevate the efficiency of the stem cell application. These chemicals promote stem cell survival, differentiation, and multiplication through many signaling pathways. Thus, researchers can enhance stem cells' capacity to repair and restore tissues by identifying suitable bioactive components in treatment regimens.

Future studies on scaffolds will follow improvements, focusing on biocompatibility and efficacy. Advancements in biomaterials chemistry and fabrication should also be emphasized, specifically for constructing structural and functional cell-supportive templates capable of modulating cellular responses without affecting health. This may include using bioactive agents in scaffolds or using new materials that are better at mimicking the natural ECM. Sheet/pellet technology could be a more effective method for cell transplantation than scaffolds. Compared to injecting cells in fluid form, this method of culture and growth produces cells that are easier to handle, distribute, and transplant, minimizing cell death. In contrast to scaffolds, which try to mimic the ECM, sheet/pellet technology allows these cells to create their own ECM while growing in the lab, making them more adaptable and functional when transplanted into a patient's body [17]. Organ printing, a 3D bioprinting technique, is another innovation that could eliminate scaffolds. This technique utilizes self-assembling tissue spheroids, tiny clumps of cells, as elementary units to create larger tissue structures one layer at a time [8]. Nanoparticles may improve pharmaceutical efficacy and shield cells from pathologic tissue conditions. Also, periodontal ligament ECM analogs are designed to integrate stem cell therapies better. Such chemicals may slow stem cell growth and assist regenerated tissues fuse with healthy ones. Given the continuous advancement in technology, the future of complete tissue regeneration is very promising.

Oral stem cell research remains challenging despite promising preclinical and early clinical findings. The most significant issue is the need for more human-phase studies to test the safety and success of TE. Dangaria et al. [19] noted that stem cell therapies must be proven effective in the general patient population due to the lack of controlled, long-term, multiple-center research. Another critical topic is extending and integrating stem cell viability into host tissue. Immunogenicity and immune rejection must be overcome before stem cell treatment can be used in clinics. Finding a new source of cells should also be investigated, as PDLCs and DPSCs are not always attainable in large amounts from patients [45]. Sourcing stem cells from adult third molars (wisdom teeth) is an option that can be done in dental practices as the root of these teeth fully develop much later in life for most people, providing an excellent source of young stem cells, including PDLSCs, DPSCs and SCAPCs. Considering these future research directions, dental cellular therapy hopes to neutralize existing limitations and create an optimal environment for stem cells to fully serve in periodontal tissue regeneration. Modern development can shift the therapeutic perception of gum diseases and enhance the patients' prognosis for their treatment by using cell differentiation and tissue formation.

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Conclusion

Concluding Thoughts and Future Research Needs

Stem cell-based TE provides a novel alternative to conventional gum disease treatments by preventing disease progression, restoring damaged tissue, and providing long-term disease remission. There are still many hurdles to overcome, such as long-term viability, function, and integration of transplanted stem cells in the periodontal niche. More knowledge of stem cell behavior, better transplantation techniques, and refined regenerative materials are needed to address these challenges. Current research is focused on enhancing stem cell efficacy by using specific bioactive molecules, gene editing methodologies, and innovations in scaffolding material to optimize cellular activity. As tissue engineering advances, collaboration between researchers and clinicians will be key for transitioning these new therapies into clinical practice, ensuring they deliver effective care for patients with gum disease. Comprehensive clinical trials are needed to prove their efficacy and safety, standardize the techniques, and get them into dental practices. New technologies may provide more personalized treatments for each patient, adding to oral health management and improved quality of life. Overcoming these challenges could be the breakthrough for stem cell therapies in periodontal treatment, restoring oral health like never before.

While tissue engineering is a groundbreaking treatment alternative in dentistry, it is still important to note that preventative care and early diagnosis of PD are key to good oral health. Daily oral hygiene habits, like brushing and flossing twice a day, can help mitigate the risk of PD. Regular dental visits are also important, as dentists can do thorough examinations to look for signs of PD. Signs such as inflamed gums, bleeding upon probing, receding gums, and the presence of periodontal pockets can all be assessed during routine dental cleanings. Patients should also disclose their medical history and current medications to their dentist so they can get personalized care and address factors that may contribute to PD. Increasing public awareness of the connection between oral health and overall wellness is key to reducing the prevalence and effects of gum disease. In summary, proper oral care and advancements in regenerative therapies give patients preventative measures and lasting remedies for periodontal health.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

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