Van Diş Hekimliği Dergisi
Van Dentistry Journal
Cilt 5 (2024) ~ Sayı 1 Sayfa:12-23
ISSN(Online): 2757-6868 e-ISSN: 2757-6868

Derleme/Review

Evaluation of Stem Cell Applications in Periodontal Regenerative Therapy: A Current Perspective Between 2003-2022

Periodontal Rejeneratif Tedavide Kök Hücre Uygulamalarının Değerlendirilmesi: 2003-2022 Yılları Arasında Güncel Bir Perspektif

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ABSTRACT: The periodontium comprises the fundamental tissues of the tooth, namely the gingiva, periodontal ligament, cementum, and alveolar bone. Prolonged accumulation of microbial dental plaque on the tooth and gingival margin leads to pathological changes in the periodontal tissues. However, the mechanical and regenerative techniques employed to address the breakdown of periodontal tissue have been unsuccessful in fully restoring the periodontium to its original, disease-free condition. The growing understanding and recognition of the potential uses of stem cell therapy have led to the emergence of new perspectives on periodontal regeneration approaches. This review investigates mesenchymal stem cells and their use in periodontal regeneration treatment.

Keywords: Cell transplantation**,** mesenchymal stem cells, periodontal treatment, tissue engineering

ÖZET: Periodonsiyum dişin başlıca temel dokularını, diş eti, periodontal ligament, sement ve alveol kemiğini içerir. Diş ve diş eti kenarlarında mikrobiyal diş plağının uzun süreli birikmesi periodontal dokularda patolojik değişikliklere yol açar. Ancak periodontal dokunun uğradığı bu hasarı gidermek için kullanılan mekanik ve rejeneratif teknikler periodonsiyumu orijinal, hastalıksız durumuna tamamen döndürmede başarısız olmuştur. Kök hücre tedavisinin potansiyel kullanımlarının giderek daha iyi anlaşılması ve tanınması, periodontal rejenerasyon yaklaşımlarına ilişkin yeni bakış açılarının ortaya çıkmasına yol açmıştır. Bu derlemede mezenkimal kök hücreler ve bunların periodontal rejenerasyon tedavisindeki kullanımı araştırılmaktadır.

Anahtar Kelimler: Doku mühendisliği, hücre transplantasyonu, mezenkimal kök hücreler, periodontal tedavi

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INTRODUCTION

The periodontium is a complex structure that experiences age-related changes, as well as morphological changes associated with functional alterations and changes in the oral environment (1). Its main role is to connect the tooth to the jawbone and preserve the integrity of the surface of the oral cavity's masticatory mucosa. The structure comprises four distinct tissues: the gingiva, the periodontal ligament (PDL), the root cementum, and the alveolar bone.

The long-term accumulation of microbial dental plaque around the tooth-gingiva interface leads to a gradual breakdown of the soft and hard tissues of the periodontal complex (2). This process is influenced by the interaction between imbalanced bacterial populations and immune responses within the gingival and periodontal tissues. As the local oral microbiota becomes imbalanced and inflammatory responses occur, potential periodontal pathogens become more prevalent. This creates a continuous cycle where tissue degradation, inflammation, and enrichment of periodontal pathogens reinforce each other (3).

Periodontal regeneration involves the restoration of the injured periodontium following disturbances to its natural structure and function (4, 5). This process tries to regenerate the alveolar bone and cementum, as well as stimulate the production of new periodontal ligaments (6).

Various techniques have been employed to guarantee the restoration of periodontal tissue. Predisposing conditions are eradicated by the implementation of phase1 therapeutic procedures, such as root surface planning. Additional techniques involve the use of chemical agents to disinfect the root surface, the application of different types of graft materials (such as autogenous, allogeneic, and synthetic), the creation of a physical barrier using membranes, and the use of polypeptide growth factors and attachment factors (7). One specific method is guided tissue regeneration, which combines the use of grafts and membranes. This treatment aims to optimize root surface regeneration by focusing on the specific cell populations responsible for inducing periodontal regeneration. While there have been some clinical successes recorded, the outcomes of this surgery are regarded to be unpredictable (8). Tissue infection may arise during the healing process when the graft material and barrier membrane are applied, leading to a detrimental impact on regeneration. Despite the purpose of the membrane barrier being to impede epithelial migration, numerous histologic studies demonstrate the development of epithelial tissue between the membrane and the tooth surface (9).

Contrary to their intended purpose of periodontal regeneration, the aforementioned treatment modalities are incapable of completely restoring the compromised periodontium to its ideal condition prior to the disease.

The growing understanding and familiarity with the use of stem cell treatments in recent years has resulted in the emergence of new perspectives on periodontal regeneration therapies. Mesenchymal stem cells are distinguished from stromal cells in terms of their ability to undergo self-renewal and division over

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extended periods, their lack of specialization, and their capacity to detect signals of damage and differentiate into specific cell types (10,11). This review covers both preclinical and clinical investigations in the realm of tissue engineering, focusing on the utilization of mesenchymal stem cells (MSCs) derived from teeth and periodontal tissues.

1. What is a Stem Cell

A stem cell is characterized as a cell capable of unlimited growth in a controlled environment and has the capacity to differentiate into certain types of adult cells (12). These cells have a significant function in maintaining tissue stability and facilitating continuous regeneration throughout an individual's lifespan. Stem cell plasticity, which refers to their capacity to transform into various tissue types, is a key factor contributing to the growing favor of stem cells in regenerative medicine (10).

Differentiation refers to the process by which an undifferentiated stem cell transforms into a specialized cell with a specific function. These cells undergo mitosis without undergoing functional differentiation and divide in an asymmetric manner. One of the cells resulting from mitosis possesses identical traits to the stem cell, whereas the other cell exhibits the traits of the specific tissue it will eventually specialize into (13).

Stem cells are commonly categorized into three distinct types: embryonic stem cells, adult somatic or postnatal stem cells, and, more recently, induced pluripotent stem cells. Embryonic stem cells are multipotent cells obtained from the early mammalian embryo that have the ability to proliferate and differentiate into cells representing all three embryonic germ layers, namely mesoderm, endoderm, and ectoderm. These cells have the potential to differentiate into almost any form of cell, but they are unable to contribute to further embryonic tissues and hence cannot grow into a fetus or adult animal (14).

New efforts are being made to genetically reprogram somatic cells back to a pluripotent state in response to the significant ethical concerns raised by the use of embryos to derive human embryonic stem cell lines, despite their developmental potential. These endeavors have led to the creation of induced pluripotent stem cells, which exhibit comparable characteristics to embryonic stem cells. These cells are indistinguishable from embryonic stem cells in terms of their morphology, gene expression patterns, proliferation, and differentiation (15).

MSCs originate from the mesoderm layer in the early stages of embryonic development and possess the ability to transform into many mesenchymal tissues, including muscle, cartilage, bone, and fat. These cells are categorized as somatic stem cells and can be obtained from both human and animal sources. MSCs are often regarded as appropriate cells for the field of regenerative medicine. Under proper in vitro circumstances, they have the ability to differentiate into osteogenic, adipogenic, chondrogenic, and myogenic cells. In 1976, Friedenstein et al. successfully extracted MSCs from the bone marrow of mice (16). The cells were found to have a spindle-shaped morphology and the ability to attach to plastic surfaces. Recent advancements in technology and research on tissue

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engineering suggest that MSCs, which are present in various tissues such as fat, bone marrow, dental pulp, and PDL, have the capacity to differentiate into multiple cell types such as osteoblasts, chondrocytes, hepatocytes, and neurons. This differentiation is triggered by various stimulating factors (17-19).

The International Society for Stem Cell Research (ISSCR) categorizes cell populations as MSCs if, under laboratory conditions, they:

1. Exhibit fibroblast-like shape in cell culture conditions and adhere to plastic.

2. Express endothelium antigen (CD31), HLA-DR, and CD105 (SH2), but not hematopoietic-specific markers (CD45, CD34, CD11b, CD14, or CD79a).

3. Undergo in vitro differentiation into mesodermal cells, namely osteoblasts, adipocytes, and chondrocytes (20).

Furthermore, MSCs possess immunomodulatory characteristics. MSCs possess chemokine receptors on their surface, enabling them to travel to sites of inflammation or tissue injury in the body (21). Once there, they can restrict the activities of T lymphocytes, B lymphocytes, and natural killer cells, as well as prevent the development of dendritic cells (22). In addition, they possess immunomodulatory and anti-inflammatory characteristics through the production of cytokines. These cells can be utilized for the treatment of both acute and chronic disorders without causing suppression of the immune system, since they are immunologically autonomous (23).

Human-derived MSCs have the ability to develop into several cell types, including neurons (ectodermal), hepatocytes (endodermal), osteoblasts, adipocytes, and chondrocytes (mesodermal). Currently, MSCs may be derived from several tissues, such as:

• Bone Marrow Derived Mesenchymal Stem Cells (BM-MSCs)

• Adipose Tissue Derived Mesenchymal Stem Cells (AT-MSC)

• Dental Tissue Derived Mesenchymal Stem Cells (DT-MSCs):

• Apical Papilla Stem Cells (SCAPs)

• Stem Cells Derived from Human Exfoliated Deciduous Teeth (SHEDs)

• Dental Follicle Progenitor Cells (DFPCs)

• Dental Pulp Stem Cells (DPSCs)

• Periodontal Ligament Stem Cells (PDLSCs)

• Gingival Tissue Derived Mesenchymal Stem Cells (G-MSCs)

Recent research has demonstrated that MSCs play a significant role in regenerative cell renewal, tissue repair, and wound healing. Furthermore, they have been proven to be a safe and valuable resource for medical treatment and research (24-26).

2. Stem Cell Research on Regenerative Periodontology

A potential approach for regenerating periodontal tissue in the context of periodontal therapy involves incorporating progenitor cells into a pre-made three-dimensional structure, which is then inserted into the damaged area. This technology overcomes some limitations of conventional regeneration therapies by

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enabling the prompt administration of growth factors and progenitor cells directly into the damaged area. As a result, the typical delay in recruiting progenitor cells to the wound site is eliminated. For successful periodontal tissue engineering, the following crucial components are necessary:

1. A sufficient quantity of suitable precursor cells with the ability to develop into the necessary fully developed tissue types, such as osteoblasts, cementoblasts, and fibroblasts.

2. Appropriate signals to control tissue neogenesis and cellular differentiation.

3. A conductive three-dimensional extracellular matrix scaffold designed to promote and enhance cellular differentiation and the formation of new tissue.

This review examines several research that have tested different types of stem cells described above, as well as different types of scaffolds (15).

2.1. Embryonic Stem Cells

Kang et al. (27) demonstrated the successful differentiation of mouse embryonic stem cells (ESCs) into osteogenic lineages in a laboratory setting. They also showed that when mouse ESCs were combined with hydroxyapatite/tricalcium phosphate (HA/TCP) or ESC-derived embryoid bodies (EBs), they were able to form an osteoid structure within a tooth socket.

Inanc et al. (28) examined the impact of dental root surfaces on the adherence of cells and the initial growth of human embryonic stem cells (hESCs) when combined with the coculture of periodontal ligament fibroblast cells. The connection between periodontal progenitor-like cells produced from hESC and tooth root surfaces (RSs) is crucial for the potential utilization of these cells in investigating periodontal development and regeneration mechanisms, as well as in applications involving the engineering of periodontal tissues using cells.

Ohazama et al. (29) discovered that when combined with embryonic day 10 oral epithelium, ESCs exhibited the activation of certain odontogenic mesenchymal cell genes, such as Lhx7, Msx1, and Pax9. This indicates that ESCs have the potential to react to signals from the embryonic dental epithelium.

2.2. Induced Pluripotent Stem Cells

Tang et al. (30) utilized MSCs derived from induced pluripotent cells, which were obtained from bone marrow cells expressing the CD34-positive surface marker, to investigate osteogenic differentiation. In a separate animal study, the same method was employed to examine periodontal tissue regeneration, yielding positive outcomes (31). In a preliminary mouse study, induced pluripotent MSCs were administered intravenously through systemic and topical routes to experimental animals specifically designed to simulate periodontal disease. The study revealed a decrease in inflammation and the prevention of damage to the alveoli (32).

2.3. Bone Marrow Derived Mesenchymal Stem Cells

Houshmand et al. (33) examined the impact of enamel matrix derivative (EMD) and recombinant human transforming

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growth factor-beta (rhTGF-beta) on the differentiation of osteoblasts derived from human bone marrow mesenchymal stem cells (BMSCs) and human periodontal ligament stem cells (PDLSCs). The goal was to gain a deeper understanding of how biomaterials and growth factors can be used to improve stem cell-based methods for bone regeneration. No bone-related messenger RNAs were detected in any of the experimental groups after 5, 10, or 15 days of EMD treatment. On the 21st day, the alizarin red staining showed a negative result in the bone marrow-derived mesenchymal stem cells and periodontal ligament-derived stem cells treated with EMD. Osteonectin mRNA expression was detected in the BMSC culture supplemented with rhTGF-β on day 15, and this level of expression was found to be statistically similar to that of the positive control group. However, mineralization of the extracellular matrix was inhibited in both groups of stem cells.

Liu et al. (24) examined the impact of exosomes produced from bone marrow mesenchymal stem cells on the process of periodontal regeneration. The treatment with BMSC-sEV resulted in a substantial increase in the migration and proliferation of PDLCs ($p < 0.05$). Following 7 days of stimulation, the application of BMSC-sEV resulted in enhanced mineralization capacity of PDLCs, as indicated by alizarin red staining. Additionally, the mRNA levels of osteopontin, osteocalcin, collagen type I and fibronectin were considerably elevated in the BMSC-sEV group.

2.4. Adipose Tissue Derived Mesenchymal Stem Cells

The effectiveness of AT-MSCs inserted onto tissue scaffolds was assessed in a study conducted at the intersection of periodontal regenerative therapy and stem cell and tissue engineering. The study was conducted where a scaffold comprising β-TCP and AT-MSCs was inserted into the rectus abdominis muscle of a patient who had previously undergone hemimaxillectomy. The histological analysis of the sample, conducted 6 months post-procedure, revealed the existence of osteocytes and mineralized trabecular structures that exhibited appropriate bone shape. Following the placement of the harvested bone graft in the deficient region of the patient's maxilla, implant therapy was administered to the corresponding area. The researchers documented that the implant was successfully fixed with primary stability (34).

Tobita et al. (35) conducted an animal investigation in 2013 where they artificially produced class III furcation deficits in dogs. During the trial, one of the experimental groups was administered platelet-rich plasma (PRP), while the other group got both PRP and AT-MSCs. The participants in these groups were monitored for a duration of 2 months. Based on their findings, the researchers determined that the group treated with both AT-MSCs and PRP showed the formation of PDL fibers, as well as a significant presence of alveolar bone and cement-like structures after two months. In contrast, the group treated with PRP alone did not exhibit the formation of PDL fibers.

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To assess the periodontal regenerative capability of AT-MSCs, surgically induced fenestration defects were utilized in a rodent model. The experimental groups were designed as polyglycolide-polylactide scaffolds combined with AT-MSCs and cell-free. After a duration of five weeks, a greater amount of PDL, cementum, and bone formation was observed in the group that received a combination of AT-MSC compared to the group that did not get any cells (36).

2.5. Dental Tissue Derived Mesenchymal Stem Cells

As previously stated, mesenchymal stem cells can also be found in mammalian teeth. These dental MSCs share several in vitro traits with MSCs derived from bone marrow, including clonogenicity, expression of specific markers, and the ability to differentiate into cells resembling osteoblasts, chondrocytes, and adipocytes. This differentiation process aids in tooth growth and repair. The versatility and availability of MSCs have prompted a novel approach in dental regeneration research, as they may give rise to several types of cells (37).

Rats were subjected to a cranial defect in a study by Asutay et al. (38) that compared the osteogenic differentiation capabilities of DP-MSCs and scaffolds comprising HA and TCP. The study was designed to span a duration of 8 weeks, with the experimental groups being as follows:

- DP-MSC, HA, TCP
- HA combined with TCP
- Defect only

The study findings indicated that the experimental group, which included DP-MSC, exhibited notably elevated bone mineral density and calcification rate in comparison to the other groups.

A histological evaluation of the effectiveness of PDL-MSCs in periodontal regeneration was conducted by Mrozik et al. (39) To accomplish this, the researchers developed periodontal defect models derived from sheep models. The study involved the application of scaffolds containing alginate and gelatin to the control groups, and scaffolds containing PDL-MSCs, alginate, and gelatin to the experimental groups. Histological examinations conducted in the respective sites four weeks post-application revealed that the experimental group exhibited a larger surface area of freshly generated alveolar bone compared to the control group, along with a higher amount of cement formation.

A research was conducted to assess the effectiveness of PDL-MSCs and scaffolds containing calcium phosphate in regenerating periodontal tissue. Periodontal defect models were produced in dogs, and the results were examined at 4, 8, and 12 weeks using computed tomography, immunofluorescence analysis, and light microscopy. The results showed that vimentin and STRO-1 proteins were positive in PDL-MSCs, cytokeratin proteins were negative, and scaffolds containing calcium phosphate promoted osteogenic differentiation (40).

In a study by Yoo et. al (25) researchers assessed the impact of PDL-MSCs and scaffolds containing collagen on the healing of periodontal tissues. Dehiscence defects

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were surgically induced in the maxillary premolars and first molars of dogs. After 8 weeks, the healing of periodontal tissues was examined using histological analysis. The researchers documented that PDL-MSCs exhibited a positive effect on periodontal regeneration, namely in the development of cementum and new bone.

According to research by Duan et al. (41) where researchers utilized enamel matrix proteins and their derivatives, the study showed PDL-MSCs may differentiate into alveolar bone, periodontal ligament, and cementum.

In a different study examining how PDL-MSCs can differentiate, researchers found that these cells can become osteogenic, which means they can help the cement-periosteum complex grow again (42).

Li et al. (43) induced gingival defects in rats and examined the effectiveness of G-MSCs. After two weeks of applying G-MSCs to the defect region in the study group, the local gingival tissue and morphology exhibited similarity to that of normal healthy gingival tissue. In contrast, the defect areas in the control group had a greyish tint.

In a clinical trial examining the impact of DP-MSCs on osteogenic differentiation, collagen scaffolds incorporating DP-MSCs were implanted into molar extraction cavities with the purpose of generating compact bone. Following a three-year period of observation, examination of biopsy samples from the corresponding locations demonstrated the presence of osteocytes, newly formed bone structure, and Haversian canal structure enclosed by concentric layers of lamellae (44).

To determine the effect of DP-MSCs on osteogenic differentiation, DP-MSCs were implanted into the extraction sites of an experimental group using a collagen-containing scaffold in a 2017 clinical trial. The control group utilized a collagen scaffold that was devoid of cells. After a period of sixty days following the treatment, a histological examination of the relevant locations revealed that the experimental group, which received DP-MSCs, displayed differentiated bone structures containing the Haversian system. In contrast, the control group showed only minimal levels of these tissues (45).

Multiple clinical trials have assessed the effectiveness of DP-MSCs in promoting the regrowth of periodontal tissues. Periodontitis patients with intraosseous defects underwent surgical intervention to fill the defects with micro-sized collagenous scaffolds that contained DP-MSCs. The patients were then monitored for a duration of one year. The researchers observed a notable decrease in the depth of periodontal pockets and an increase in the amount of clinical attachment gain (46).

A clinical experiment was conducted to examine the use of PDL-MSCs in guided periodontal tissue regeneration (GDR). PDL-MSCs were employed in conjunction with the xenogeneic graft material Bio-Oss®. In the study, PDL-MSCs/Bio-Oss®/GDR and Bio-Oss®/GDR were utilized as the comparative groups (47). While both experimental groups exhibited a statistically significant elevation in alveolar bone height when compared to the initial measurements, the researchers determined that there were no statistically significant distinctions between the two groups.

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Altıkat et al. (48) examined the impact of 2D and 3D culture environments on the osteogenic differentiation of AT-MSCs, DP-MSCs, and PDL-MSCs. They found that the cells in the 3D study group, which were created using scaffolds containing HA, exhibited notable osteogenic differentiation compared to the other groups.

CONCLUSION

Mesenchymal stem cells possess the capacity to offer an alternative treatment paradigm in investigations of tissue engineering for periodontal regeneration therapy. While the complete understanding of the possible advantages and disadvantages of cell-based therapy studies is lacking, research conducted on animals and case series studies indicate that these therapies have promise in the field of periodontal regeneration therapy.

Conflict of Interest: The authors declare no conflicts of interest.

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Dr. Öğr. Üyesi Kadriye Merve ALTIKAT "Evaluation of Stem Cell Applications in Periodontal Regenerative Therapy: A Current Perspective Between 2003-2022" Van Diş Hekimliği Dergisi 2024;5(1);12-23

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Gönderim Tarihi: 12 Mart 2024; Kabul Tarihi: 27 Haziran 2024