Review Article

Stem Cell-Based Periodontal Regeneration: Role of Periodontal Ligament Stem Cells

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Abstract Periodontal disease leads to the irreversible damage of the structures that support teeth, such as the alveolar bone, periodontal ligament, and cementum. Traditional periodontal treatments are successful in managing infection and inflammation; however, achieving true regeneration of the lost tissues continues to pose a significant clinical challenge. Recent advancements in regenerative medicine have underscored the potential involvement of stem cells in the restoration of periodontal structures. Among the different populations of dental stem cells, periodontal ligament stem cells (PDLSCs) have garnered considerable attention due to their availability, ability to self-renew, potential for multi lineage differentiation, and essential role in maintaining periodontal health. This review article intends to provide an overview of the biological properties of PDLSCs, their regenerative capabilities, sources, mechanisms of action, and the current experimental and clinical evidence that supports their application in periodontal regeneration.

Keywords: Bone graft; CD 105, Cytokines; Mesenchymal Stem cells; Periodontal ligament

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INTRODUCTION

Periodontitis is a long-lasting inflammatory condition marked by the gradual destruction of the tissues that support the teeth, which can result in attachment loss and ultimately tooth loss if not treated. Conventional periodontal treatments, including scaling and root planning, surgical debridement, bone grafting, and guided tissue regeneration, primarily focus on halting the progression of the disease rather than fully regenerating the periodontium. Genuine periodontal regeneration necessitates the synchronized development of new alveolar bone, cementum, and functionally aligned periodontal ligament fibers.[1] With the progress in tissue engineering and regenerative medicine, therapies based on stem cells have surfaced as promising methods for periodontal regeneration. Dental tissues contain populations of mesenchymal stem cells, such as dental pulp stem cells, stem cells from shed deciduous teeth, progenitor cells from the dental follicle, and periodontal ligament stem cells. Among these, PDLSCs are regarded as particularly well-suited for periodontal regeneration due to their natural origin and essential role in preserving the integrity of periodontal tissues.[2]

The Regenerative Potential of Periodontal Ligament Stem Cells

Stem cells are undifferentiated cells capable of self-renewal and differentiation into specialized cell types.

Mesenchymal stem cells (MSCs) are multipotent stromal cells that can differentiate into osteoblasts, chondrocytes, adipocytes, and fibroblast-like cells. MSCs also possess immunomodulatory and anti- inflammatory properties, which are beneficial in the inflammatory microenvironment of periodontitis.[3] In periodontal regeneration, stem cells contribute through multiple mechanisms, including direct differentiation into periodontal tissues, paracrine secretion of growth factors and cytokines, modulation of immune responses, and enhancement of angiogenesis. These properties make MSCs attractive candidates for cell based periodontal therapies.[4]

Periodontal Ligament Stem Cells

PDLSCs were first identified as a distinct population of MSC-like cells within the periodontal ligament. They exhibit clonogenicity, high proliferative capacity, and the ability to differentiate into osteogenic, cementogenic, adipogenic, and chondrogenic lineages. Phenotypically, PDLSCs express typical MSC markers such as STRO-1, CD73, CD90, and CD105, while lacking hematopoietic markers.[5] Functionally, PDLSCs play a crucial role in periodontal tissue remodeling and repair under physiological and pathological conditions. Experimental studies have demonstrated that PDLSCs can generate cementum like structures and periodontal ligament like fibers when transplanted in vivo, highlighting their regenerative potential.[6]

Sources and Isolation of PDLSCs

PDLSCs are commonly isolated from the periodontal ligament of extracted teeth, particularly impacted third molars or teeth extracted for orthodontic reasons. The accessibility of these tissues makes PDLSCs an ethically acceptable and clinically feasible stem cell source. Isolation methods include enzymatic digestion and explant culture techniques, followed by in vitro expansion under controlled conditions.[7] The biological properties of PDLSCs can be influenced by donor age, systemic health, inflammatory status of the periodontal tissue, and culture conditions. PDLSCs derived from healthy periodontium generally demonstrate superior regenerative capacity compared to those obtained from periodontitis affected tissues.[8]

Mechanisms of Periodontal Regeneration by PDLSCs

The regenerative effects of PDLSCs are mediated through both direct and indirect mechanisms. Direct differentiation into osteoblast-like and cementoblast-like cells contributes to hard tissue formation. Indirectly, PDLSCs secrete a wide array of bioactive molecules, including vascular endothelial growth factor, transforming growth factor-β, and bone orphogenetic proteins, which promote angiogenesis, recruit endogenous progenitor cells, and enhance tissue repair.[9] Additionally, PDLSCs exhibit immunomodulatory effects by suppressing pro-inflammatory cytokines and regulating immune cell activity. This property is particularly relevant in periodontitis, where chronic inflammation impairs regenerative outcomes.[10]

Preclinical and Clinical Evidence

Numerous in vitro and animal studies have demonstrated the ability of PDLSCs to regenerate periodontal tissues when combined with suitable scaffolds and growth factors. In vivo studies have shown the formation of new bone, cementum, and periodontal ligament-like structures in periodontal defect models.[11] Limited clinical studies have explored the application of autologous PDLSCs in periodontal defects, reporting favourable outcomes in terms of attachment gain and defect fill. However, large-scale randomized controlled trials are still lacking, and standardized protocols for cell sourcing, expansion, and delivery remain to be established.[12]

Challenges and Limitation

Despite promising results, several challenges hinder the routine clinical application of PDLSC based therapies. These include variability in stem cell quality, risks associated with cell manipulation, high cost, regulatory issues, and uncertainty regarding long-term safety and efficacy. Furthermore, the hostile inflammatory microenvironment in periodontitis may compromise stem cell survival and function.[13]

Future Perspectives

Future studies ought to concentrate on improving stem cell delivery mechanisms, integrating PDLSCs with cutting-edge biomaterials and bioactive compounds, as well as creating cell-free methods like stem cell-derived exosomes. Progress in gene editing and three-dimensional bio printing could further improve the accuracy and reliability of periodontal regeneration techniques.[14,15]

CONCLUSION

Stem cell-based periodontal regeneration signifies a transformative approach in the treatment of periodontal disease. PDLSCs, owing to their distinctive biological characteristics and inherent connection to periodontal tissues, offer considerable potential for realizing authentic periodontal regeneration. While existing evidence is promising, additional rigorously designed clinical trials are crucial to convert these experimental results into standard clinical practice.

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