Misr Dental Science and Research Journal

Online ISSN: 297-315X

Stem Cell-Based Regeneration of Immature Permanent Teeth: A Comprehensive Review

Oral Pathology

Vol. 2, July, 2025

DOI: - **10.21608/mdsrj.2025.443673**

Abstract

The regeneration of immature permanent teeth with necrotic pulps presents a major challenge in endodontic practice due to incomplete root development, open apices, and fragile dentinal walls. Traditional treatments, such as apexification with calcium hydroxide or mineral trioxide aggregate (MTA), provide apical closure but fail to promote continued root maturation. In recent years, regenerative endodontic procedures (REPs) have emerged as a biologically based alternative, aiming not only to disinfect the canal but also to restore the pulp-dentin complex by stimulating tissue regeneration. Central to this approach is the use of stem cells, which provide the cellular basis for regeneration.

This review explores the pivotal role of stem cells in the regeneration of immature permanent teeth. We examine the biological principles underlying REPs, including the regenerative triad of stem cells, signaling molecules, and scaffolds. Particular emphasis is placed on stem cells from the apical papilla (SCAP), dental pulp stem cells (DPSCs), and periodontal ligament stem cells (PDLSCs), which have demonstrated the potential to differentiate into odontoblast-like cells and contribute to tissue regeneration. Current clinical protocols, including disinfection strategies, induction of bleeding, and scaffold placement, are discussed alongside the clinical outcomes reported in the literature.

Despite promising results, challenges remain, including variability in outcomes, limited long-term data, and ethical concerns related to stem cell use. Advances in stem cell engineering, bioactive scaffolds, and cell-free approaches such as exosome therapy are poised to refine and expand the scope of regenerative endodontics.

This review highlights the current state of stem cell-based regeneration, evaluates its clinical potential, and outlines future directions aimed at achieving predictable, functional regeneration of immature permanent teeth.

Introduction

Immature permanent teeth, often affected by trauma or caries during the early stages of root development, present unique anatomical and clinical challenges. These teeth are characterized by incomplete root formation, open apices, thin dentinal walls, and a wide root canal system. Such features compromise the structural integrity of the tooth and make it particularly susceptible to fracture. Moreover, the open apex complicates the achievement of an effective apical seal during endodontic treatment, increasing the risk of treatment failure.[1]

Traditionally, the management of necrotic immature permanent teeth has relied on apexification techniques, primarily using calcium hydroxide or mineral trioxide aggregate (MTA). While these methods aim to induce apical closure and allow for subsequent obturation, they do not promote continued root development or strengthen the root walls. Long-term calcium hydroxide use has also been associated with an increased risk of root fracture. Thus, although apexification achieves infection control and apical barrier formation, it fails to restore the full functional and structural integrity of the tooth.[2]

In response to these limitations, regenerative endodontic procedures (REPs) have emerged as a biologically based alternative. Rooted in the principles of tissue engineering, REPs aim not only to disinfect the root canal system but also to stimulate the regeneration of the pulp-dentin complex, promoting continued root development. Central to this regenerative approach is the use of stem cells, which possess the capacity to differentiate, self-renew, and contribute to the formation of new tissue within the root canal space.[3.4]

This paradigm shift from synthetic repair to biological regeneration represents a significant advancement in endodontic therapy. Stem cell-based strategies offer the potential to regenerate vital pulp-like tissue, restore root development, and reinforce tooth structure—ultimately improving both prognosis and functionality in immature permanent teeth.[5]

1. Biological Basis of Regeneration

Regenerative endodontics aims to restore the structure and function of the pulp-dentin complex by utilizing principles of tissue engineering. At the core of this approach lies a triad of essential components: stem cells, signaling molecules (growth factors), and scaffolds. Together, these elements orchestrate a microenvironment conducive to tissue regeneration. Understanding the biological basis of this process is crucial to optimizing clinical outcomes in regenerative endodontic procedures (REPs), especially for immature permanent teeth.[6]

1.1. The Regenerative Triad

1.2. Stem Cells

Stem cells are undifferentiated cells capable of self-renewal and differentiation into multiple specialized cell types. In the context of regenerative endodontics, stem cells from the apical papilla (SCAP) are particularly significant due to their proximity to immature teeth and their proven potential to differentiate into odontoblast-like cells. Other relevant sources include dental pulp stem cells (DPSCs), periodontal ligament stem cells (PDLSCs), and stem cells from exfoliated deciduous teeth (SHED). These cells contribute to the regeneration of pulp tissue and the continued development of root structures by producing dentin-like mineralized tissue and promoting angiogenesis and neurogenesis.[7]

Signaling Molecules / Growth Factors

Growth factors are crucial for regulating stem cell behavior. They influence cell proliferation, migration, and differentiation, and include molecules such as bone morphogenetic proteins (BMPs), vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-β), and fibroblast growth factor (FGF). These signaling molecules can be released from dentin during irrigation or introduced exogenously via scaffold materials. They play a pivotal role in recreating the cellular environment needed for successful pulp regeneration.[8,9]

Scaffolds

Scaffolds serve as a three-dimensional framework that supports cell attachment, migration, and differentiation. In REPs, scaffolds can be natural, such as the blood clot formed during induced bleeding, or synthetic, including materials like collagen, platelet-rich plasma (PRP), or platelet-rich fibrin (PRF). Ideal scaffolds are biocompatible, biodegradable, and capable of delivering cells and growth factors while mimicking the extracellular matrix of native pulp tissue.[10]

1.3. Tissue Engineering Principles

1.4. Role of the Microenvironment and Vascularization

Successful regeneration depends not only on the presence of stem cells and scaffolds but also on creating a conducive microenvironment that supports cell survival and differentiation. Vascularization is critical in this context, as it ensures the delivery of oxygen and nutrients necessary for tissue development. In immature teeth, the wide-open apex facilitates vascular ingrowth, which is beneficial for pulp revascularization and long-term tissue viability.[11]

Cellular Interactions Necessary for Pulp-Dentin Regeneration

Regeneration of the pulp-dentin complex requires coordinated interactions between stem cells, signaling molecules, and their microenvironment. These interactions influence the differentiation of stem cells into odontoblast-like cells, capable of producing tubular dentin and restoring functional pulp tissue. Additionally, the presence of immune cells, endothelial cells, and nerve fibers plays an important role in recreating the natural architecture and function of the dental pulp. This biological framework forms the foundation upon which regenerative endodontic procedures are built. The next section will explore how these principles are translated into clinical protocols and therapeutic strategies.[12-14]

2. Stem Cells in Dental Regeneration

2.1. Types of Dental-Derived Stem Cells

Stem Cells from the Apical Papilla (SCAP)

SCAP are located at the root apex of immature permanent teeth and are considered the most critical stem cell source in regenerative endodontics. These cells exhibit high proliferative capacity and the ability to differentiate into odontoblast-like cells, playing a central role in root development. SCAP are also capable of surviving infection and inflammation, making them ideal for clinical use in regenerative endodontic procedures (REPs).[15]

Dental Pulp Stem Cells (DPSCs)

DPSCs are mesenchymal stem cells residing within the dental pulp. They have demonstrated potential to differentiate into odontoblasts, osteoblasts, and even neural cells under specific conditions. Although more applicable in mature teeth, their regenerative capacity makes them a promising tool for bioengineering pulp-like tissue.[16]

Periodontal Ligament Stem Cells (PDLSCs)

PDLSCs, derived from the periodontal ligament, have been shown to regenerate cementum and alveolar bone, but they also contribute to dentin regeneration when placed in the pulp space. They offer supportive functions when used in conjunction with other stem cells.[17]

Induced Pluripotent Stem Cells (iPSCs)

iPSCs are reprogrammed somatic cells that possess pluripotency similar to embryonic stem cells. While their use in endodontics remains experimental, they hold enormous potential for generating patient-specific, immune-compatible cells. Ethical and safety considerations still limit their clinical application.[18]

Stem Cell Properties [19-22]

Multipotency

All dental-derived stem cells are multipotent, meaning they can differentiate into multiple cell lineages, including odontogenic, osteogenic, and neurogenic cells.

Self-Renewal

These cells can undergo numerous cycles of cell division while maintaining their undifferentiated state, ensuring long-term regenerative potential.

Immunomodulatory Capabilities

Dental stem cells can modulate immune responses, creating an environment conducive to tissue repair and reducing inflammation.

Mechanism of Action

Stem cells contribute to regeneration through several key mechanisms:

- **Differentiation into Odontoblast-like Cells**: These cells are responsible for forming dentin, which contributes to root maturation and thickening of dentinal walls.
- **Secretion of Bioactive Molecules**: Stem cells release cytokines and growth factors that promote angiogenesis, neurogenesis, and tissue remodeling.

- **Interaction with Host Environment and Scaffolds**: Stem cells respond to the chemical and mechanical signals from the scaffold and surrounding microenvironment to orchestrate tissue regeneration.

3.Clinical Application of Stem Cells in Regenerative Endodontics

3.1 Scaffold-Based Regenerative Endodontic Protocols

- Induction of Blood Clot: A widely used in vivo scaffold, the blood clot provides a natural matrix rich in platelets and growth factors to support stem cell migration and attachment.
- Platelet-Rich Plasma (PRP) and Platelet-Rich Fibrin (PRF)**:** These are autologous preparations that enhance the regenerative environment by delivering high concentrations of growth factors.
- Collagen and Synthetic Scaffolds: Provide structure and stability, and can be modified to release bioactive molecules over time.[23]

3.2 Disinfection Strategies Prior to Stem Cell Recruitment

Effective disinfection is essential to create a biocompatible environment without eliminating resident stem cells.

- Triple Antibiotic Paste (TAP)**:** A mix of ciprofloxacin, metronidazole, and minocycline. While effective, minocycline may cause tooth discoloration.
- Calcium Hydroxide: Less toxic to stem cells but may be less effective in eliminating bacteria in complex canal systems.
- Irrigation Protocols: Use of sodium hypochlorite (NaOCl) followed by ethylenediaminetetraacetic acid (EDTA) helps remove biofilms while preserving growth factors in dentin.[24]

Outcomes in Clinical Cases

Clinical studies and case reports have demonstrated:

- Root Lengthening**:** Continued development of root structures post-treatment**.**
- Thickening of Dentinal Walls**:** Strengthening the tooth against fracture**.**
- Apical Closure**:** Formation of an apical barrier facilitating obturation**.**
- Return of Pulp Vitality**:** Rare but has been documented in some cases using pulp sensibility tests and imaging.[25]

4 Current Evidence and Limitations [26]

While clinical outcomes are promising, the current body of evidence includes variability in protocol, patient selection, and assessment methods. Limitations include:

- **Variability in Treatment Response**: Outcomes can differ based on age, etiology, and technique.
- **Limited Histological Evidence**: True pulp-dentin complex regeneration is rarely confirmed due to the difficulty of histological sampling.
- **Regulatory and Ethical Challenges**: Use of stem cells, especially iPSCs and allogenic cells, is regulated and ethically complex, limiting broader application.

Conclusion

Stem cell-based regenerative endodontics represents a biologically sound and transformative approach for treating necrotic immature permanent teeth. Unlike conventional methods, it offers the potential for true tissue regeneration—promoting continued root development, reinforcing structural integrity, and potentially restoring pulp vitality. While significant challenges remain in terms of standardization, long-term efficacy, and regulatory acceptance, ongoing advances in stem cell biology, scaffold engineering, and clinical techniques continue to drive the field forward. With further research and refinement, stem cell therapy may soon become the standard of care in managing immature permanent teeth.

References

1. Shuai Y, Ma Y, Guo T, et al. Dental stem cells and tooth regeneration. Adv Med Biol 2018;1107:41-52. 5.
2. Zhai Q, Dong Z, Wang W, Li B, Jin Y. Dental stem cell and dental tissue regeneration. Front Med 2019;13(2): 152-9. 6.
3. Cerneckis, Jonas, Hongxia Cai, and Yanhong Shi. "Induced pluripotent stem cells (iPSCs): molecular mechanisms of induction and applications." Signal Transduction and Targeted Therapy 9.1 (2024): 112.
4. Kyaw MS, Kamano Y, Yahata Y, Tanaka T, Sato N, Toyama F, Noguchi T, Saito M, Nakano M, Harada F, Saito M. Endodontic Regeneration Therapy: Current Strategies and Tissue Engineering Solutions. Cells. 2025 Mar 12;14(6):422. .
5. American Academy of Pediatric Dentistry. Policy on using harvested dental stem cells. The Reference Manual of Pediatric Dentistry. Chicago, Ill.: American Academy of Pediatric Dentistry; 2024:205-6
6. Kiarashi, Mohammad, et al. "Mesenchymal stem cell-based scaffolds in regenerative medicine of dental diseases." Stem Cell Reviews and Reports 20.3 (2024): 688-721.
7. Inchingolo, Angelo Michele, et al. "Stem Cells: Present Understanding and Prospects for Regenerative Dentistry." Journal of Functional Biomaterials 15.10 (2024): 308.
8. Pilbauerova N, Dasi D, De Souza Araujo IJ, Huang GT. An in vitro tube model for cell biocompatibility study of capping materials for regenerative endodontics. J Endod. 2025 May 8:S0099-2399(25)00246.
9. Aga N, McGregor S, Jones S, Ellis I, Tatullo M, Hassan MEM, Islam M. Efficacy Of Stem Cells In Endodontic Regeneration: A Systematic Review. J Evid Based Dent Pract. 2025 Jun;25(2):102125
10. Sabeti MA, Saqib Ihsan M, Adami D, et al. Cell-based regenerative endodontics for the treatment of irreversible pulpitis: an In vivo investigation. J Endodont. 2024;50(3):344–350. doi:10. 1016/j.joen.2023.11.014.
11. Tan YY, Abdullah D, Abu Kasim NH, et al. Histological characterization of pulp regeneration using decellularized human dental pulp and mesenchymal stem cells in a feline model. Tissue and Cell. 2024; 90:102484. doi:10.1016/j.tice.2024.102484.
12. Zheng C, Jiang P, Hu S, Tang Y, Dou L. Characterization of cells in blood evoked from periapical tissues in immature teeth with pulp necrosis and their potential for autologous cell therapy in Regenerative Endodontics. Arch Oral Biol. 2024;162:105957. doi: 10.1016/j.archoralbio.2024.105957.
13. Brizuela C, Meza G, Urrejola D, et al. Cell-based regenerative endodontics for treatment of periapical lesions: a randomized, controlled phase I/II clinical trial. J Dent Res. 2020;99(5):523– 529. doi:10.1177/0022034520913242.
14. Zhou N, Zhu S, Wei X, et al. 3D-bioprinted hydrogels with instructive niches for dental pulp regeneration. IJB. 2024;10(3):1790. doi:10.36922/ijb.1790.

15. El Moshy S, Radwan IA, Rady D, et al. Dental Stem Cell Derived Secretum/Conditioned Medium: The Future for Regenerative Therapeutic Applications. Stem Cells International. 2020;2020(1):7593402. doi:10.1155/2020/7593402.
16. Kichenbr C, Velot E, Menu P, Moby V. Dental Pulp Stem Cell-Derived Conditioned Medium: An Attractive Alternative for Regenerative Therapy. Tissue Engineering Part B: Reviews. 2018;25(1):78–88.
17. Sarra G, Machado MEdL, Caballero-Flores HV, Moreira MS, Pedroni ACF, Marques MM, et al. Effect of human dental pulp stem cell conditioned medium in the dentin-pulp complex regeneration: A pilot in vivo study. Tissue and Cell. 2021; 72:101536. doi: 10.1016/j.tice.2021.101536.
18. Sarra G, Machado MEdL, Caballero-Flores HV, Moreira MS, Pedroni ACF, Marques MM, et al. Effect of human dental pulp stem cell conditioned medium in the dentin-pulp com-plex regeneration: A pilot in vivo study. Tissue and Cell . 2021;72:101536.
19. Kichenbrand C, Velot E, Menu P, Moby V. Dental Pulp Stem Cell-Derived Conditioned Medium: An Attractive Alternative for Regenerative Therapy. Tissue Engineering Part B: Reviews . 2018;25(1):78–88. doi: 10.1089/ten.teb.2018.0168
20. El Moshy S, Radwan IA, Rady D, et al. Dental Stem Cell- Derived Secretome/Conditioned Medium: The Future for Re-generative Therapeutic Applications. Stem Cells International. 2020;2020(1):7593402. doi: 10.1155/2020/7593402
21. Brizuela C, Meza G, Urrejola D, et al. Cell-based regenerative endodontics for treatment of periapical lesions: a randomized, controlled phase I/II clinical trial. J Dent Res . 2020;99(5):523– 529. doi: 10.1177/0022034520913242
22. Zhou N, Zhu S, Wei X, et al. 3D-bioprinted hydrogels with instructive niches for dental pulp regeneration. IJB . 2024;10(3):1790. doi: 10.36922/ijb.179
23. Zheng C, Jiang P, Hu S, Tang Y, Dou L. Characterization of cells in blood evoked from periapical tissues in immature teeth with pulp necrosis and their potential for autologous cell therapy in Regenerative Endodontics. Arch Oral Biol . 2024;162:105957. doi: 10.1016/j.archoralbio.2024.105957
24. Chueh LH, Huang GT. Immature teeth with periradicular pe-riodontitis or abscess undergoing apexogenesis: a paradigm shift. J Endod . 2006;32(12):1205–1213. doi: 10.1016/j.joen.2006. 07.010
25. Tözüm T.F., Keçeli H.G., Serper A., Tuncel B. Intentional replan-tation for a periodontally involved hopeless incisor by using au-tologous platelet-rich plasma. Oral Surg Oral Med Oral Pathol Oral Radiol endod . 2006;101(6):e119-24. doi:10.1016/j.tripleo. 2005.10.043
26. Sarra G, Machado MEdL, Caballero-Flores HV, Moreira MS, Pedroni ACF, Marques MM, et al. Effect of human dental pulp stem cell conditioned medium in the dentin-pulp com-plex regeneration: A pilot in vivo study. Tissue and Cell . 2021;72:101536. doi: 10.1016/j.tice.2021.101536