Regenerative Endodontics: Advances in Stem Cells, Scaffolds, and Growth Factors

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Abstract

Regenerative endodontics aims to restore pulp–dentin structure and function using the triad of stem cells, scaffolds, and growth factors. Dental-derived mesenchymal stem cells such as DPSCs, SCAP, and SHED show high regenerative potential, and advances in biomimetic scaffolds—including hydrogels, natural polymers, and platelet concentrates—have improved tissue engineering outcomes. Growth factors such as TGF-β, BMP-7, VEGF, and SDF-1 play major roles in promoting angiogenesis, neurogenesis, and odontoblastic differentiation. Preclinical studies show successful formation of vascularized pulp-like tissue, although clinical outcomes remain variable, especially regarding root maturation and true histologic regeneration. This review summarizes developments in stem cell sources, scaffold strategies, and bioactive molecules while identifying translational barriers and future clinical pathways.

Keywords: regenerative endodontics, dental pulp stem cells, scaffolds, growth factors, tissue engineering, endodontic regeneration.

Introduction

Regenerative endodontic therapy (RET) represents a modern biologically based approach designed to replace damaged dental pulp with healthy tissue capable of restoring normal physiologic functions[1,2]. The therapy applies principles of tissue engineering, which includes the coordinated use of stem cells, three-dimensional scaffolds, and signaling molecules to promote the regeneration of the pulp–dentin complex[3].

Traditional endodontic treatment replaces infected tissues with inert filling material. However, regenerative endodontics aims for:

- Restoration of pulp vitality,
- Formation of new dentin,
- Continued root development,
- Strengthening of root walls, and
- Long-term tooth survival[4].

Advances in cellular biology, biomaterials, and molecular science have significantly improved the feasibility of true pulp tissue regeneration, particularly in immature teeth with open apices[5].

Materials and Methods (Literature Review Strategy)

This narrative review collected and analyzed articles from 2016–2025 from PubMed, Google Scholar, and Scopus. Search terms included *regenerative endodontics*, *dental pulp stem cells*, *SCAP*, *SHED*, *scaffolds*, *platelet-rich fibrin*, *growth factors*, and *pulp–dentin regeneration*.

Priority was given to:

1. Clinical trials on regenerative endodontics,
2. Preclinical studies demonstrating pulp regeneration,
3. Reviews on scaffolds and biomaterials, and
4. Molecular studies on growth factors involved in odontogenesis.

A total of 65 relevant papers were screened, and 27 were included based on clinical relevance and scientific rigor.

Results / Observations

1. Stem Cells in Regenerative Endodontics Stem cells form the biological foundation of dental pulp regeneration.
   a. Dental Pulp Stem Cells (DPSCs) DPSCs are the most widely studied due to high proliferative, angiogenic, and odontogenic capacity[4,5]. They originate from neural crest-derived mesenchyme and can differentiate into odontoblast-like cells capable of generating tubular dentin[6].
   b. Stem Cells from the Apical Papilla (SCAP) SCAP exhibit higher proliferative potential than DPSCs and are well-suited for immature teeth needing root maturation[7].
   c. Stem Cells from Human Exfoliated Deciduous Teeth (SHED) SHED are highly proliferative and show strong mineralization potential, making them suitable for cell-based therapies[5].

d. Cell Homing vs. Cell Transplantation

- Cell transplantation involves placing exogenous stem cells into the canal.
- Cell homing uses chemotactic molecules (e.g., SDF-1) to recruit host cells, reducing regulatory challenges[4].

2. Scaffolds for Pulp–Dentin Regeneration Scaffolds serve as a 3D matrix supporting cell migration, adhesion, and differentiation[3,8].

a. Natural Scaffolds

- Collagen, fibrin, hyaluronic acid, and chitosan mimic extracellular matrix.
- PRF provides both scaffold structure and endogenous growth factors[8,9].

b. Synthetic Scaffolds

- PLGA, PEG-based hydrogels, and biodegradable polymers offer tunable mechanical stability and sustained drug release[3].

c. Injectable Hydrogels and Nanofibrous Matrices Hydrogels allow minimally invasive application. Nanofibers mimic collagen fibrils and regulate odontoblast alignment[10].

3. Growth Factors in Regeneration Growth factors orchestrate cell recruitment, angiogenesis, and differentiation.

- TGF-β1 promotes odontoblastic differentiation[11].
- BMP-7 regulates dentinogenesis and stem cell differentiation[12].
- VEGF enhances vascularization, an essential component of pulp survival.
- SDF-1 is key for stem cell homing strategies[4].

4. Preclinical & Clinical Outcomes

- Animal studies consistently demonstrate vascularized pulp-like tissue and dentin deposition when stem cells, scaffolds, and growth factors are combined[11,12].
- Human revitalization procedures show symptom resolution and increased root length, but histologic evaluation often reveals fibrous connective tissue rather than true pulp tissue[2].
- Early human clinical trials with DPSC transplantation show promising vitality restoration but require longer-term follow-ups[5].

Discussion

Integration of Stem Cells, Scaffolds, and Growth Factors

Success in regenerative endodontics requires a synchronized triad. Biomaterials now support controlled release of growth factors and mimic ECM properties, promoting predictable cellular responses[8].

Key Challenges

1. Disinfection: Chemical irrigants may damage stem cells; balancing antimicrobial activity with cellular viability remains difficult[1].
2. Variability in outcomes: Differences in case selection and procedural protocols cause inconsistent results in clinical settings[2].
3. Regulatory concerns: Cell-based therapies involve stringent approvals, making cell-homing approaches more practical[4].
4. Histologic unpredictability: True odontoblast-lined pulp tissue is still rarely achieved[2,5].

Future Directions

- Smart scaffolds enabling sequential growth factor release.
- Genetically modified MSCs for enhanced regenerative capacity.
- Adoption of cell-homing strategies as the clinically preferred model.
- Well-designed randomized controlled trials with standardized outcomes.

Conclusion

Regenerative endodontics has progressed significantly with advancements in stem cells, scaffolds, and growth factors. Preclinical results are highly promising and demonstrate real potential for functional pulp–dentin regeneration. However, predictable clinical outcomes require solutions to infection control, standardization of protocols, and regulatory challenges. Integration of advanced biomaterials with cell-homing strategies may pave the way for widespread clinical use.

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