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Advancements in Regenerative Endodontics: Stem Cell-Based Therapies

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ABSTRACT

Regenerative endodontics is evolving rapidly as an alternative to conventional root canal therapy, aiming not merely to disinfect and fill root canals, but to restore viable pulp tissue with physiological functions such as immune defense, innervation, and dentinogenesis. Central to this paradigm are stem cell–based therapies, which, in concert with scaffolds and signaling factors, offer potential to regenerate the pulp–dentin complex in teeth with necrotic or damaged pulps. This review summarizes the latest progress in the field, focusing on (1) sources of stem cells (e.g. dental pulp stem cells, stem cells from the apical papilla, mesenchymal stem cells of non-dental origin, and induced pluripotent stem cells), (2) scaffold design and biomaterial strategies, (3) delivery of growth factors and bioactive cues, (4) cell transplantation vs. cell homing approaches, (5) in vitro, in vivo, and early clinical evidence, and (6) major challenges and future directions. Evidence from animal studies and limited human trials shows promise in root maturation, vascularization, and functional tissue formation. However, full regeneration of the native pulp–dentin architecture particularly with true odontoblast layer, innervation, and predictable function remains elusive. Key hurdles include controlling stem cell differentiation and proliferation, immune compatibility, standardized protocols, safety (e.g. tumorigenesis risk), and regulatory issues. Emerging innovations such as cell-free secretomes or exosomes, 3D bioprinting of scaffolds, gene engineering for guided differentiation, and smart biomaterials responsive to microenvironment cues may help overcome current limitations. To accelerate translation toward routine clinical use, rigorous multicenter trials with long-term follow-up, development of GMP-grade cell banks, and interdisciplinary collaboration are essential.

Introduction

Conventional endodontic therapy, such as root canal treatment (RCT), has long been the standard for managing infected or necrotic pulp tissues [1]. These procedures aim to remove the diseased pulp, disinfect the canal system, and seal it with inert filling material [2]. While RCT is effective in controlling infection and preserving tooth structure, it does not recreate the biological functions of the pulp sensory perception, immunological defense, nutrition, and ongoing dentin deposition [3]. Over time, teeth become nonvital, more brittle, and susceptible to fracture [4].

The concept of regenerative endodontics (or biologically based endodontic therapy) seeks to shift this paradigm: instead of merely removing debris and sealing canals, the goal is to regenerate a viable, functional pulp–dentin complex. This approach draws on principles of tissue engineering: combining stem cells, scaffolds, and biological signaling molecules to guide regeneration [5]. In certain immature teeth with open apices, successful regenerative endodontic procedures (REPs) have shown thickening of canal walls, continued root development, and restoration of vitality signals (sensibility tests) in some cases [6].

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Yet, many regenerative approaches to date have resulted in repair-like tissues (fibrous connective tissue, cementum-like or bone-like mineralization) rather than true regeneration of the pulp–dentin architecture. Achieving consistent, functional regeneration remains a grand challenge. This review focuses on stem cell–based therapies in regenerative endodontics, cataloguing advances, examining evidence, and outlining unresolved obstacles. The structure is as follows:

- ✓ Stem cell sources and their comparative advantages
- ✓ Scaffold and biomaterial strategies
- ✓ Growth factors and bioactive signaling
- ✓ Approaches for delivering or recruiting cells (transplantation vs. homing)
- ✓ Preclinical and clinical evidence
- ✓ Challenges, safety, and translational barriers [7]
- ✓ Future prospects and research directions

Stem Cell Sources for Pulp Regeneration

A critical component of regenerative endodontics is the selection of an appropriate stem cell population capable of restoring the complex architecture and function of the dental pulp. Effective pulp regeneration requires cells that can survive within the root canal environment, proliferate, migrate, differentiate into odontoblast-like cells, support angiogenesis, and integrate with the host tissue. Over the past two decades, several stem cell sources have been identified and investigated for their potential in pulp regeneration, including dental pulp stem cells (DPSCs), stem cells from the apical papilla (SCAP), mesenchymal stem cells from non-dental origins, and induced pluripotent stem cells (iPSCs). Each source offers distinct advantages and presents unique challenges, shaping their applicability in clinical protocols.

Dental Pulp Stem Cells (DPSCs): DPSCs, first isolated from adult human dental pulp, are multipotent mesenchymal stem cells characterized by clonogenicity, self-renewal, and differentiation into odontogenic, osteogenic, adipogenic, chondrogenic, and neurogenic lineages. Their native origin in the pulp tissue makes them a biologically compatible option for regenerative procedures. DPSCs also secrete antigenic and trophic factors, facilitating vascularization and tissue integration within the pulp chamber. Studies have demonstrated that DPSCs can form dentin-like structures in vitro and in vivo, highlighting their odontogenic potential. Clinically, DPSCs can be harvested from extracted teeth or third molars, providing an autologous source for pulp regeneration. However, challenges include the limited quantity of cells obtainable, donor variability, and reduced proliferative capacity in older individuals, which may restrict their clinical utility in certain populations.

Stem Cells from Apical Papilla (SCAP): SCAP are located at the apical papilla of immature permanent teeth and are particularly relevant in endodontic regeneration of teeth with open apices. SCAP exhibit a higher proliferative rate and greater odontogenic potential than DPSCs, partly due to their more primitive developmental stage and reduced exposure to inflammatory environments. Their capacity to contribute to continued root development, apical closure, and dentin wall thickening has been demonstrated in both animal models and limited human studies. These features make SCAP a preferred cell source in regenerative protocols targeting immature necrotic teeth. However, harvesting SCAP is more challenging than DPSCs and may require extraction or invasive procedures, raising clinical feasibility concerns [8].

Mesenchymal Stem Cells from Non-Dental Sources: Non-dental mesenchymal stem cells, including bone marrow-derived MSCs (BM-MSCs), adipose-derived MSCs (AD-MSCs), periodontal ligament stem cells, and umbilical cord-derived MSCs (UC-MSCs), offer the advantage of greater accessibility and higher cell yields compared to dental-derived populations. These cells exhibit multipotency, immunomodulatory properties, and well-characterized safety profiles in other regenerative contexts. However, their odontogenic potential is generally lower than that of DPSCs or SCAP, necessitating the use of targeted differentiation protocols, scaffold-mediated cues, and growth factor supplementation to induce odontoblast-like differentiation within the pulp environment. While preclinical studies have demonstrated the ability of BM-MSCs and AD-MSCs to contribute to pulp-like tissue formation, clinical translation is limited by regulatory and logistical challenges [9].

Induced Pluripotent Stem Cells (iPSCs): iPSCs, derived by reprogramming somatic cells into a pluripotent state, present a theoretically unlimited, autologous source of regenerative cells capable of differentiating into odontogenic, endothelial, and neural lineages. Their pluripotency enables the potential for complete pulp–dentin complex restoration, including vascularization and innervation. Despite these advantages, iPSCs carry significant safety concerns, including tumorigenicity, epigenetic instability, and incomplete differentiation. Moreover, the clinical use of iPSCs is constrained by high cost, complex manufacturing processes, and stringent regulatory requirements [10].

Endogenous Progenitor Recruitment (Cell Homing): In addition to direct cell transplantation, regenerative endodontics increasingly explores

strategies that recruit endogenous stem or progenitor cells from the apical tissues or periapical region. This cell homing approach leverages chemotactic signals, such as stromal cell-derived factor-1 (SDF-1) and growth factor-enriched scaffolds, to attract native cells into the disinfected canal space. This method avoids the complexities of ex vivo cell expansion, reduces immunogenic risk, and may simplify regulatory approval. Preclinical studies indicate that endogenous progenitors can contribute to vascularized pulp-like tissue formation and dentin deposition, although the efficiency and predictability of this approach remain under investigation.

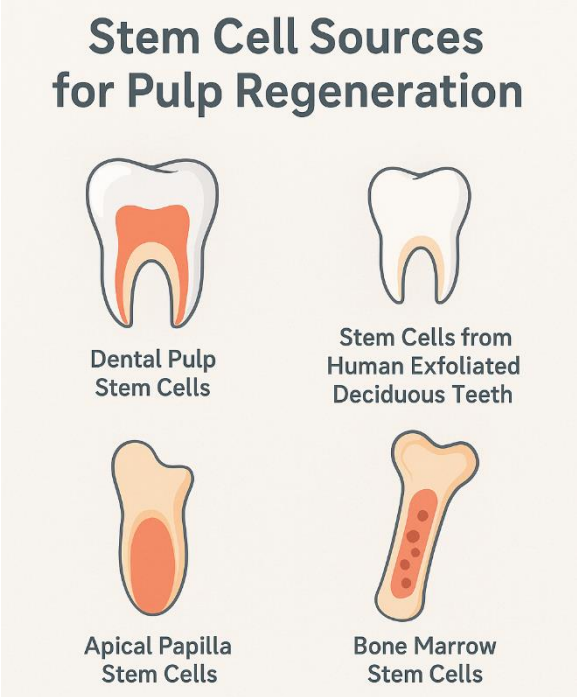

Figure 1. Stem Cell Sources for Pulp Regeneration

Comparative Considerations: The selection of stem cell sources depends on several factors: the patient's age, tooth maturity, availability of tissue, desired regenerative outcomes, and logistical or regulatory considerations. DPSCs and SCAP remain the most biologically suitable for odontogenic regeneration, particularly in immature teeth, while non-dental MSCs and iPSCs may serve as alternatives in specific contexts or advanced regenerative strategies. Cell homing approaches represent a promising adjunct or alternative to transplantation, offering simpler clinical workflows and lower risk profiles. In summary, the diversity of stem cell sources provides a versatile toolkit for regenerative endodontics. Optimal outcomes may require combining the biological advantages of specific cell populations with advanced scaffolds, growth factors, and controlled delivery systems. Continued research is necessary to elucidate the comparative efficacy, safety, and clinical feasibility of these cell sources, aiming to establish standardized protocols for predictable and functional pulp regeneration [11].

Table 1. Types of Stem Cells Used in Regenerative Endodontics

Stem Cell Type	Source	Key Characteristics	Advantages	Limitations
Dental Pulp Stem Cells (DPSCs)	Dental pulp of permanent teeth	Multipotent, easy to harvest	High proliferation rate, odontogenic potential	Limited availability in necrotic teeth
Stem Cells from Human Exfoliated Deciduous Teeth (SHED)	Deciduous (baby) teeth	Immature, highly proliferative	Strong regenerative ability, non-invasive source	Ethical and collection timing limitations
Apical Papilla Stem Cells (SCAP)	Root apex of developing teeth	High mineralization potential	Strong root development potential	Limited to immature teeth

Bone Marrow Mesenchymal Stem Cells (BM-MSCs)	Bone marrow aspirate	Multipotent, osteogenic/antigenic	Well-studied and available	Invasive collection, lower odontogenic tendency
Adipose-Derived Stem Cells (ADSCs)	Adipose tissue	Easy to harvest, abundant	Good proliferation, angiogenesis	Lower odontogenic potential

Analysis:
DPSCs and SHED are currently the most promising for dental pulp regeneration due to their high proliferation and odontogenic differentiation capacity. SCAP is particularly useful for immature teeth with open apices. However, challenges remain regarding source accessibility and maintaining cell viability in necrotic environments.

Dental Pulp Stem Cells (DPSCs)
DPSCs (derived from adult dental pulp) are among the most studied cells for pulp regeneration. They exhibit mesenchymal stem cell (MSC) properties: clonogenicity, self-renewal, multipotency (odontogenic, osteogenic, chondrogenic, adipogenic, neurogenic). They also secrete trophic and antigenic factors that support vascular ingrowth. Advantages of DPSCs include relative ease of harvest (e.g. from extracted nonfunctional teeth), immunomodulatory features, and previous success in animal and limited human studies. However, their limitations include limited cell numbers (especially in older patients), potential donor site morbidity, and variability between donors [12].

Stem Cells from Apical Papilla (SCAP): SCAP are located in the apical papilla of immature permanent teeth and are considered a key cell source in regenerative strategies, especially for teeth with open apices. SCAP have high proliferative potential and the ability to contribute to root lengthening and wall thickening. Because SCAP are more primitive and less exposed to inflammation, they may harbor superior regenerative potential compared to DPSCs in some contexts.

Mesenchymal Stem Cells from Non-Dental Sources: Other MSC sources (bone marrow MSCs, adipose-derived MSCs, umbilical cord MSCs, periodontal ligament MSCs) are also considered owing to their accessibility, larger cell yields, and well-established use in regenerative medicine. The trade-off is that non-dental MSCs may lack strong odontogenic propensity and must be guided by bioactive cues and scaffold environments.

Induced Pluripotent Stem Cells (iPSCs): iPSCs reprogram somatic cells into a pluripotent state and then differentiate them into desired lineages. Thus, they offer a theoretically unlimited, autologous source of cells for regeneration. However, concerns remain about tumorigenicity, incomplete differentiation, epigenetic memory, and immunogenic risk [13].

Other Progenitor or Endogenous Cell Recruitment: Instead of transplanting exogenous cells, one can recruit endogenous progenitor/stem cells (resident in apical tissues or periapical area) through cell homing strategies (see Section 4). This approach avoids many regulatory and immunological issues. In selecting between these options, one must balance ease of harvest, cell potency, immunogenic risk, and clinical practicability. Many current protocols use DPSCs or SCAP, or rely on endogenous homing pathways.

Scaffold and Biomaterial Strategies: Stem cells require a supportive three-dimensional microenvironment that mimics the extracellular matrix (ECM), allows cell adhesion, nutrient diffusion, vascular in-growth, and provides mechanical support. The design of scaffolds is thus a pivotal factor.

Roles of Scaffolds in Regeneration: Scaffolds act as:

- ✓ Structural frameworks guiding cell migration and spatial organization
- ✓ Carriers for cells and growth factors
- ✓ Dynamic matrices that degrade in balance with new tissue formation

They may also deliver cues (biochemical, mechanical, topographical) that steer stem cell differentiation [14].

Table 2. Biomaterials and Scaffolds in Regenerative Endodontics

Scaffold Type	Composition	Function	Biocompatibility	Clinical Relevance
Collagen Scaffold	Natural polymer	Supports cell adhesion and differentiation	Excellent	Widely used; mimics natural ECM
Hydrogel	Synthetic/natural polymers (e.g., alginate, gelatin)	3D matrix, drug delivery	High	Controlled degradation rate
Nanofibrous Scaffold	Electrospun polymers	Mimics ECM structure	Moderate to high	Enhances cell proliferation
Platelet-Rich Fibrin (PRF)	Autologous platelets	Source of growth factors	Excellent	Easy to prepare, enhances healing
Chitosan-Based Scaffold	Polysaccharide	Antibacterial, supports mineralization	Good	Promising for endodontic disinfection and regeneration

Analysis:
Scaffold selection significantly influences stem cell behavior and regeneration outcomes. Natural scaffolds like collagen and PRF are favored for their bioactivity and ease of integration, whereas synthetic options allow for tunable degradation and structural control [15].

Types of Scaffolds
Scaffolds can be classified broadly into natural, synthetic, and decellularized ECM-based materials.
Natural-derived scaffolds: Materials like collagen, gelatin (e.g. GelMA), hyaluronic acid, fibrin, chitosan, silk fibroin, and alginate are biocompatible and often bioactive. They mimic natural ECM, support cell adhesion, and degrade by enzymatic processes. Their limitation may be weaker mechanical strength, faster degradation, and batch-to-batch variability.
Synthetic polymers and hydrogels: Polymers such as poly (lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), poly (lactic acid) (PLA), polyethylene glycol (PEG), and composites/hydrogels allow tunable properties (porosity, stiffness, degradation). Hydrogels are advantageous in minimally invasive delivery (injectable). 3D bioprintable hydrogels offer precise spatial control.
Decellularized extracellular matrix (dECM) scaffolds: These are natural ECM from tissues (e.g. dentin, pulp, periapical tissues) after removing cellular components. dECM provides native biochemical cues and structural microarchitecture. A recent review on histological outcomes with dECM in regenerative endodontics showed promising tissue formation, particularly for vascular and cellular ingrowth.
Scaffold Influence on Clinical Outcomes: A meta-analysis comparing different scaffold options (blood clot, PRP, PRF, synthetic scaffolds) in REPs found no statistically significant difference in clinical success, root lengthening, or wall thickening among scaffold types. This suggests that multiple scaffold options may be clinically viable, and practical considerations (cost, ease, availability) will influence choice. Another systematic review evaluated biomaterial scaffolds for SCAP and DPSCs, observing that ideal scaffolds should possess proper porosity, interconnected pores, biocompatibility, and controlled degradation rates to support pulp regeneration [16].

Advanced Scaffold Strategies

- ✓ **Smart or responsive scaffolds:** materials that respond to pH, enzymes, or stimuli to release growth factors dynamically
- ✓ **Gradient scaffolds:** with spatial variation in stiffness or composition to mimic natural pulp architecture
- ✓ **Nanocomposite scaffolds:** incorporating nanoparticles (e.g. bioactive glass, hydroxyapatite, silica) to enhance mechanical strength and bioactivity
- ✓ **3D bio printing:** precise placement of cells and materials to recreate vascular and neural pathways
- ✓ **Injectable scaffolds with self-assembly or in situ gelation:** for minimally invasive delivery in narrow root canals [17].

Table 3. Growth Factors and Signaling Molecules in Pulp Regeneration

Growth Factor	Function	Source	Role in Regeneration	Challenges
BMP-2 (Bone Morphogenetic Protein-2)	Induces odontoblastic differentiation	Recombinant protein	Promotes dentin-pulp complex formation	Costly, rapid degradation
VEGF (Vascular Endothelial Growth Factor)	Angiogenesis	Platelets, endothelial cells	Enhances vascular supply to regenerated pulp	Requires controlled release
TGF-β1 (Transforming Growth Factor Beta-1)	Cell proliferation & ECM synthesis	Dentin matrix	Stimulates stem cell recruitment	Potential fibrosis if overexpressed
FGF-2 (Fibroblast Growth Factor-2)	Cell proliferation & migration	Various tissues	Promotes pulp tissue growth	Short half-life
PDGF (Platelet-Derived Growth Factor)	Angiogenesis & tissue healing	Platelets	Enhances tissue repair	Unstable under high temperature/pH

Analysis:
A combination of growth factors (VEGF + BMP-2 +FGF-2) can synergistically improve vascularization and odontogenic differentiation. Controlled delivery systems (e.g., hydrogels or nanoparticles) are under research to overcome short half-life and rapid degradation [18].

Growth Factors, Signaling Molecules, and Bioactive Cues
To stimulate stem cell proliferation, migration, differentiation, and vascular ingrowth, growth factors and signaling molecules are essential. Delivery must be controlled in time, dosage, and localization.

Key Growth Factors in Pulp Regeneration

- ✓ Vascular endothelial growth factor (VEGF): crucial for angiogenesis and vascularization
- ✓ Fibroblast growth factors (FGF-2, FGF-8): promote proliferation and differentiation
- ✓ Transforming growth factor-beta (TGF-β) and bone morphogenetic proteins (BMPs, e.g. BMP-2, BMP-7): odontogenic differentiation cues
- ✓ Stromal cell–derived factor-1 (SDF-1 / CXCL12): chemotactic for MSC migration
- ✓ Platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), nerve growth factor (NGF): supporting various lineages
- ✓ Other cytokines or factors embedded in dentin matrix: released by EDTA or demineralization, they can guide cell responses within the canal.

Strategies for Delivery

- ✓ Loading on scaffolds (adsorption, covalent binding, encapsulation)
- ✓ Micro- or nanoparticles / microspheres embedded in scaffolds for sustained release
- ✓ Hydrogels with controlled diffusion profiles
- ✓ Gene-activated scaffolds: DNA plasmids or viral vectors embedded to drive local production of growth factors
- ✓ Layered or sequential release systems (e.g. early release of chemotactic cues, later release of differentiation factors) [19].

Precise spatial temporal control is critical: excessive or prolonged factor release can lead to ectopic mineralization or fibrosis, while insufficient signals may fail to direct regeneration.

Table 4. Clinical and Preclinical Outcomes of Regenerative Endodontic Procedures (REPs)

Study Type	Sample	Method	Results	Limitations
Preclinical (Animal Model)	Dogs, pigs, rodents	DPSCs + collagen scaffold	Root lengthening, pulp-like tissue regeneration	Differences in animal and human healing
Clinical Trial (Human)	Immature necrotic teeth	Revascularization + EDTA + blood clot scaffold	Continued root development, increased dentin thickness	Unpredictable pulp vitality

Clinical Case Series	20 patients	SHED + PRF scaffold	Pulp vitality restored, positive response to cold test	Small sample size
In Vitro	DPSC culture	BMP-2 + Nano fibrous scaffold	Upregulated odontogenic markers	Lacks in vivo environment

Analysis:
Clinical translation is promising but inconsistent. While vitality and root maturation are achievable, true pulp-dentin complex regeneration remains limited. Combining optimized scaffolds, controlled release of bio factors, and patient-derived stem cells may yield more predictable clinical success [20].

Cell Transplantation vs. Cell Homing Approaches
How to bring stem cells into the canal: directly transplant exogenous cells or recruit endogenous cells via chemotactic signaling.
Cell Transplantation: This involves harvesting cells (autologous or allogeneic), expanding them in vitro, seeding into scaffold, and implanting into cleaned canal space. Advantages: controlled cell numbers, pre-differentiation or priming, and spatial distribution. Disadvantages: regulatory hurdles, immunogenic risk, cost, cell survival and engraftment challenges, and handling complexity. Some animal and pilot human studies using DPSCs, SCAP, or MSCs have shown regeneration of vascularized, cellular pulp-like tissue with dentin deposition.

Cell Homing (Endogenous Recruitment): Here, rather than implanting cells, one stimulates migration and recruitment of endogenous progenitor cells using chemotactic factors (e.g. SDF-1) anchored in scaffolds. This avoids cell-handling steps, immunological issues, and regulatory hurdles. Early preclinical data and reviews suggest cell homing is promising for translation.
Combined or Hybrid Approaches: In practice, hybrid strategies may be optimal: modest numbers of transplanted cells plus host recruitment, or scaffolds designed to both deliver cells and attract host progenitors [21].

Choice Considerations
- ✓ In mature teeth with few residual progenitors, transplantation may be needed
- ✓ In immature teeth with remnant apical tissues, homing may suffice
- ✓ Regulatory, cost, and clinical workflow constraints favor homing or acellular approaches (Figure 2).

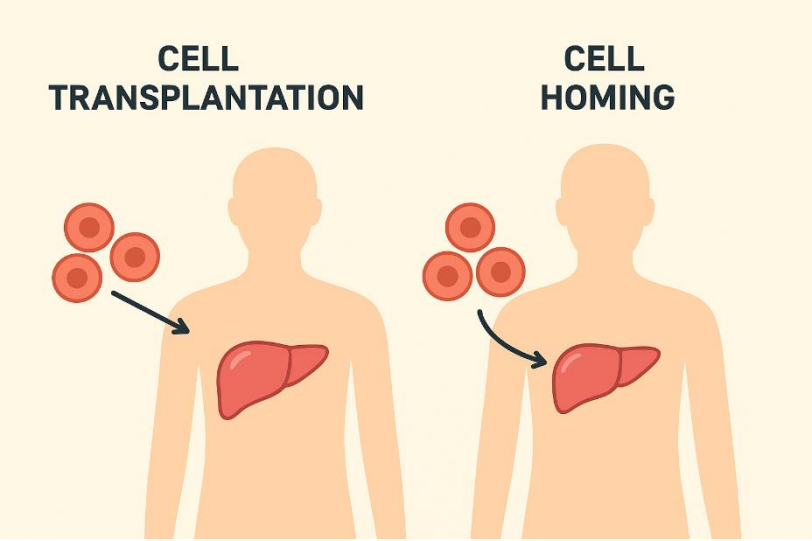

Figure 2. Cell Transplantation vs. Cell Homing Approaches

Evidence from in Vitro and in Vivo Studies
Much of the current knowledge on regenerative endodontics comes from lab (in vitro) and animal (in vivo) models.
In Vitro Studies: In vitro studies evaluate stem cell viability, proliferation, migration, differentiation (e.g. toward odontoblast-like phenotype), mineralization, antigenic potential, and response to scaffold/growth factor materials. Such work helps optimize scaffold formulations, factor combinations, and mechanical parameters before in vivo testing [22-24].

Animal (In Vivo) Models: Animal models (small rodents, dogs, pigs) with pulpal necrosis or created pulp injuries are used to test regenerative protocols. Common end-points include histological identification of pulp-like tissue, vascularization, innervation (nerve fibers), odontoblast-like cell layering, dentin formation, and immunological responses. Many studies show formation of vascularized connective tissue with varying degrees of mineralization. Yet, often what forms is reparative rather than true pulp–dentin. Mineralized tissue may resemble cementum, bone, or osteoid rather than tubular dentin. Differences across species, canal anatomy, disinfection protocols, and immune environment challenge extrapolation to human cases.

A systematic review of dECM scaffolds in animal REPs showed promising histological outcomes with better structural integration and vascularization.

Lessons and Limitations

- ✓ The complexity of root canal geometry and small volumes challenge cell survival.
- ✓ Blood clot as scaffold may not provide optimal microenvironment.
- ✓ Host immune and inflammatory milieu substantially influence outcomes.
- ✓ Animal tooth anatomy and healing differ from human teeth [25].

Clinical Evidence and Human Studies

While preclinical work is substantial, human clinical translation is still in early stages.

Clinical Trials & Case Reports

A systematic review on stem cell therapy in regenerative endodontics included 19 studies (1 RCT, 18 animal) and noted that human outcomes are promising but scarce. One human RCT used umbilical cord MSCs (UCMSCs) + platelet-poor plasma (PPP) in necrotic teeth; favorable results were observed in pulp revascularization and reperfusion. Other case series and pilot studies report positive radiographic healing, apical closure, increased root wall thickness, and even positive sensibility tests after regenerative procedures using stem-cell–augmented protocols. However, methodological limitations abound: small sample sizes, lack of control arms, short follow-up times, and limited histological verification. Many studies also do not strictly differentiate between mere revascularization and true tissue regeneration [26].

Comparative Meta-Analysis

A recent systematic review and meta-analysis compared REPs vs conventional RCT in mature permanent teeth and found that regenerative approaches showed comparable or superior clinical and radiographic healing, with potential restoration of vitality in some cases. The review emphasized, however, that evidence quality is moderate at best, and more high-quality trials are needed. A broader review of regenerative endodontics also notes that, while success rates in terms of symptom resolution and periapical healing are acceptable, formation of biologically functional pulp tissue remains inconsistent [27].

Limitations in Clinical Translation

- ✓ Ethical and regulatory barriers to human cell transplantation.
- ✓ High cost and infrastructure demands.
- ✓ Difficulty in obtaining histological samples in humans.
- ✓ Variation in patient age, tooth anatomy, and disease state.
- ✓ Need for long-term follow-up to assess durability.

Challenges, Safety Concerns, and Translational Barriers

While stem cell–based regenerative endodontics is promising, many hurdles remain before wide clinical adoption.

Controlling Differentiation and Avoiding Ectopic Mineralization: Ensuring that stem cells differentiate into odontoblast-like cells in the correct orientation (lining dentin walls) rather than forming random mineralization or bone-like tissue is a major challenge.

Cell Survival, Engraftment, and Vascularization: Stem cells must survive in a low-nutrient, low-oxygen environment initially and integrate with host vasculature. Hypoxia or necrosis may limit efficacy.

Immune Compatibility and Rejection: Even autologous MSCs can evoke immunologic responses or interact with inflammatory cues unpredictably. Allogeneic transplantation brings more risk.

Tumorigenic or Uncontrolled Growth Risk: Particularly with iPSCs or genetically modified cells, the risk of tumor formation or unwanted proliferation must be addressed with rigorous safety testing.

Standardization and Protocol Variability: Lack of consensus on disinfection regimens, cell dosages, scaffold types, seeding densities, and follow-up criteria hampers comparability among studies.

Regulatory, Manufacturing, and Cost Issues: Producing clinical-grade cells under GMP conditions, transporting them, obtaining regulatory approval, and containing costs are major translational impediments [28].

Ethical Considerations: Use of stem cells, especially from perinatal tissues or genetically

modified sources, raises ethical oversight and public acceptance constraints.

Future Directions and Emerging Approaches

To overcome current barriers, researchers are exploring new strategies:

Cell-Free Therapies: Secretomes, Exosomes, and Conditioned Media: Rather than transporting cells, one can deliver their paracrine factors (e.g. exosomes, growth factor–rich conditioned media). These can modulate host cell behavior, enhance angiogenesis, and avoid many regulatory issues.

Gene Engineering and Genetic Modulation: Introducing genes (e.g. growth factor genes, differentiation transcription factors) into stem cells or surrounding tissues may better guide regeneration. Gene-activated scaffolds are an emerging tool.

Smart and Responsive Biomaterials: Scaffolds that respond to pH, enzymatic activity, electrical stimuli, or mechanical loading to release cues dynamically are under development.

3D Bio printing and Microarchitecture Control: Precise printing of cells and matrix (e.g. multiple cell types, vascular channels, gradients) may better replicate native pulp architecture.

Combined Physical Stimuli: Using adjuncts like low-intensity pulsed ultrasound, electromagnetic fields, or light-based stimulation to enhance proliferation, migration, or differentiation [29].

Larger, Standardized Clinical Trials: Robust multicenter randomized controlled trials with well-defined protocols, long-term monitoring, and standardized endpoints (clinical, radiographic, functional) are urgently needed.

Cell Banking and Allogeneic Off-the-Shelf Products: Development of universal donor MSC lines, cryopreserved cell banks, and off-the-shelf scaffold–cell composites may reduce logistical barriers.

Personalized Approaches: Tailoring regenerative protocols based on patient age, tooth status, residual apical tissues, and diagnostic imaging to optimize outcomes [30].

Discussion

Regenerative endodontics has revolutionized the concept of root canal therapy by shifting from traditional disinfection and obturation toward biologically based tissue regeneration. Stem cell based therapies represent the core of this transformation, aiming to restore the natural structure and function of the dentin–pulp complex rather than merely replacing it with inert materials.

Among various stem cell populations, dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHED), and stem cells from the apical papilla (SCAP) have demonstrated the most promising potential. These cells exhibit strong proliferative capacity, multiline age differentiation, and an inherent affinity for odontogenic pathways. However, challenges related to their harvesting, long-term viability, and controlled differentiation in the inflamed or necrotic environment remain unresolved [31].

Scaffold design also plays a crucial role in the success of regenerative endodontic procedures (REPs). Natural scaffolds, such as collagen and platelet-rich fibrin (PRF), provide a biologically active microenvironment that supports cell adhesion and angiogenesis. Synthetic scaffolds, including hydrogels and Nano fibrous matrices, offer structural stability and customizable degradation rates. The integration of bioactive molecules or nanoparticles into these scaffolds further enhances their regenerative efficiency.

In addition, growth factors such as BMP-2, VEGF, and FGF-2 are essential in modulating stem cell behavior, promoting vascularization, and inducing odontoblastic differentiation. Controlled delivery systems particularly hydrogel-based or nanoparticle-mediated release mechanisms are being developed to overcome limitations like short half-life and rapid degradation of these molecules [32].

Despite significant progress in preclinical and early clinical studies, true regeneration of functional pulp tissue remains a challenge. Many reported cases show partial revascularization or tissue repair rather than complete dentin–pulp complex formation. Future advancements depend on improved stem cell sources (including induced pluripotent stem cells), biomimetic scaffolds, and precise molecular signaling control. Integration of gene editing and 3D bio printing technologies may further enhance the reproducibility and predictability of outcomes.

Overall, stem cell–based regenerative endodontics holds immense promise as a biological alternative to conventional root canal therapy. Continued interdisciplinary collaboration among stem cell biology, materials science, and clinical dentistry will be crucial to translate these laboratory successes into consistent, safe, and long-term clinical results [33] (Figure 3).

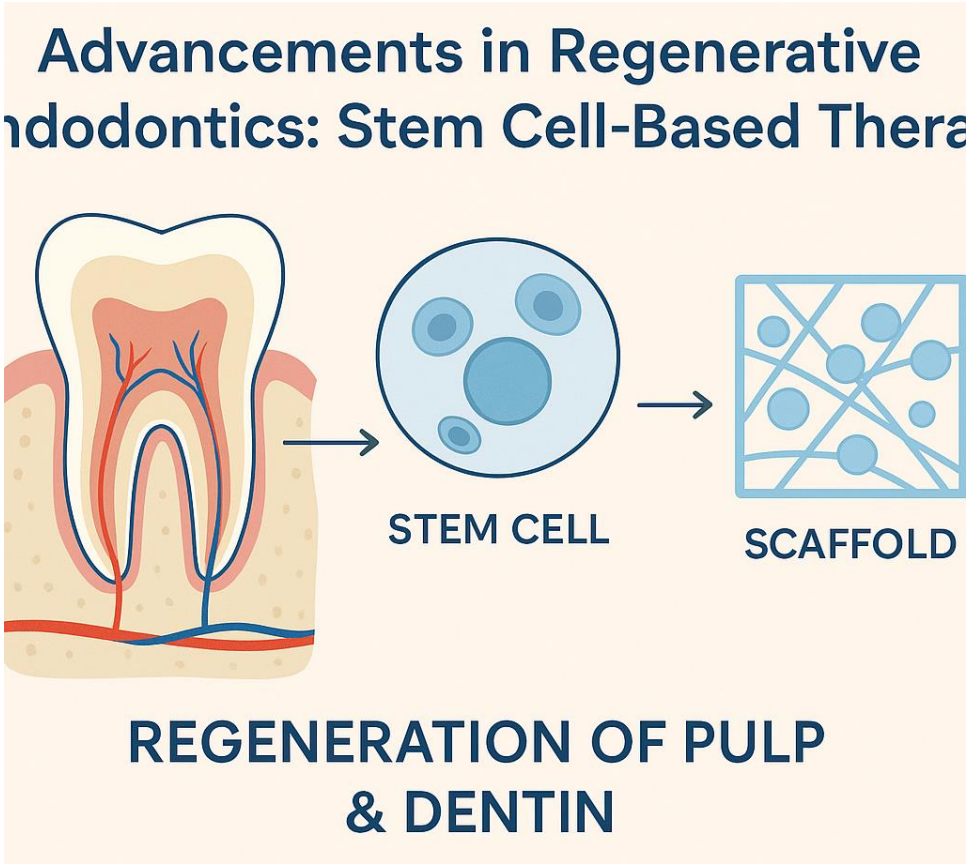

Figure 3. Advancements in Regenerative Endodontics: Stem Cell-Based Therapies

Conclusion

Stem cell–based regenerative endodontics holds transformative potential: restoring living pulp tissue rather than leaving teeth nonvital after root canal treatment. While early successes in animal models and pilot human studies are encouraging, true and consistent regeneration of the pulp dentin complex with proper architecture, innervation, and physiological function has not yet been reliably achieved. The major challenges lie in controlling differentiation, ensuring vascularization, guaranteeing immune compatibility and safety, and designing standardized, translatable clinical protocols. Emerging innovations particularly exosome-based therapies, gene-engineered scaffolds, 3D bio printing, and smart biomaterials may help surmount these obstacles. Yet, translation to mainstream clinical practice will require interdisciplinary collaboration, regulatory pathways, GMP-grade manufacturing, and rigorous, long-term clinical trials.

In summary, regenerative endodontics is no longer a mere speculative concept but a rapidly maturing field. With careful scientific progress and cautious clinical translation, the vision of biologically restoring pulp vitality in necrotic teeth may become a standard of care in future endodontics.

In conclusion, delirium remains a common and serious complication following hip arthroplasty in elderly patients. Advanced age, pre-existing cognitive impairment, and comorbid conditions such as heart failure, hypertension, and chronic kidney disease significantly increase the risk. Delirium not only impairs recovery but also contributes to greater healthcare utilization and poorer short-term outcomes. Early identification and implementation of preventive strategies are critical to improving patient outcomes and reducing the burden on healthcare systems.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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