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Strategies for Dental Pulp Regeneration: An overview of current practices and new development

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ABSTARCT

Irreversible pulpitis is traditionally treated with procedures that have inherent limitations. Pulp regeneration offers a promising alternative by restoring the dentin–pulp complex. Current strategies include apexification and revascularization for immature teeth, with revascularization providing superior root development, and stem cell–based therapies for mature teeth supported by tissue engineering, biomaterials, and growth factors. Despite significant progress, standardized clinical protocols and strong clinical evidence remain elusive. This review summarizes current regenerative approaches, their advantages, limitations, and future prospects.

Keywords: Pulp regeneration, Irreversible pulpitis, Stem cell therapy, Revascularization

INTRODUCTION

Dental pulp is a specialized soft connective tissue enclosed within the pulp chamber and root canals, forming the dentin–pulp complex. It contains blood vessels, nerves, connective tissue, odontoblasts, fibroblasts, and immune cells, and plays a vital role in tooth nutrition, defense, sensation, and dentin formation.[1] Deep caries, trauma, or infection can cause irreversible pulp damage, traditionally managed by root canal treatment. Although effective in

eliminating infection, conventional endodontic therapy removes vital pulp tissue, leaving the tooth non-vital and more susceptible to fracture and reinfection over time.[2] Pulp regeneration has emerged as a biologically based alternative that aims to restore the vitality and function of the dentin–pulp complex. This approach is particularly valuable in immature permanent teeth, where continued root development and apical closure are essential for long-term tooth survival.[3] Regenerative strategies—including revascularization, stem cell therapy, and tissue engineering—utilize the triad of stem cells, biomaterial scaffolds, and signalling molecules to promote regeneration. Dental pulp stem cells, stem cells from the apical papilla, and other mesenchymal stem cells can differentiate into odontoblast-like cells, while bioactive scaffolds and hydrogels support cell proliferation, vascularization, and tissue organization.[4]Despite significant advances, regenerative endodontics still faces challenges, including the lack of standardized clinical protocols, limited long-term clinical evidence, and unpredictable outcomes, particularly in mature teeth.[5] Therefore, this review provides an overview of current dental pulp regeneration strategies, recent advances, existing limitations, and future directions in regenerative endodontic therapy.

STRATEGIES FOR DENTAL PULP REGENERATION

Cell homing-based pulp revascularization is based on the presence of viable residual tissues within the root canal and periapical region, which contribute to the regeneration of pulp tissue. During the procedure, bleeding is intentionally induced in tissues present in periapical region to create regenerative scaffold, mainly composed of a blood clot that serves as a source of growth factors. The procedure is completed by establishing a well-sealed coronal restoration to prevent reinfection [6]. Murray et al. evaluated the clinical effectiveness of platelet-rich fibrin (PRF), platelet-rich plasma (PRP), and the traditional blood clot scaffold in regenerative treatment of immature permanent teeth. PRP and PRF showed superior apical closure, while all three approaches achieved comparable root length increase, periapical healing, and root canal wall thickening. [7] Terranova et al. developed a composite membrane consisting of

a three-dimensional conical nanofiber scaffold integrated with tannic acid microparticles and coated with gelatin. This scaffold was designed to facilitate the migration and colonization of dental pulp stem cells within the root canal system. [8] Another biomaterial, Platelet-rich fibrin (PRF) incorporated into a methacrylated chitosan/methacrylated collagen (ChitMA/ColMA) injectable hydrogel has shown excellent injectability, cytocompatibility, and bioactivity, promoting odontogenic differentiation and pulp–dentin complex regeneration through a cell-homing approach.[9] In mature teeth, cell-homing regenerative procedures demonstrated slightly higher success than conventional root canal therapy, although the difference was not statistically significant.[10] Despite these promising results, complications such as root canal calcification, canal obliteration, and crown discoloration may occur [11], highlighting the need for further long-term clinical studies, particularly in mature teeth.

PULP TISSUE ENGINEERING

Dental Pulp cells exhibit key stem cell properties such as capacity, and multilineage differentiation potential. In vivo, DPSCs can generate pulp -like tissue surrounded by odontoblast-like cells and dentin-like structures. They express classical mesenchymal stem cell markers including CD105, CD73, and CD90 [12], as well as neurovascular-associated markers such as CD31, p75, Snail-1, Snail-2, and SOX-1. [13] Ishizaka et al. demonstrated that $CD31^-$ side population cells show enhanced angiogenic and neurotrophic activity, promoting cell migration and neurite outgrowth. [14] Furthermore, modified DPSCs (MDPSCs) isolated using granulocyte colony-stimulating factor (G-CSF) display strong angiogenic and regenerative potential.[15]

Stem Cells from Human Exfoliated Deciduous Teeth (SHEDs), first identified by Miura et al., exhibit high proliferative capacity and can differentiate into neural cells, adipocytes, and odontoblasts. [16] They express mesenchymal stem cell markers CD44, CD73, CD90, and CD166 and share phenotypic characteristics with dental pulp stem cells (DPSCs). [18] SHEDs combined with Puramatrix™ or recombinant human collagen type I have successfully generated pulp-like tissue

and functional odontoblasts in immunodeficient mice. [19] Additionally, SHED-derived exosomes (SA-Exo) promote angiogenesis through the TGF-β/SMAD2/3 pathway [17] and demonstrate successful pulp regeneration and continued root development in necrotic immature permanent teeth.[20]

Apical Papilla- Derived Stem Cells (SCAPs), first identified by Sonoyama et al., are located in the apical papilla of developing teeth and express markers including STRO-1, CD24, CD29, CD73, CD90, CD105, CD106, CD146, and CD166, with CD24 being a specific SCAP marker. [21] Compared with dental pulp stem cells (DPSCs), SCAPs exhibit greater proliferative and mineralization potential.[22] Growth factors such as VEGF and NGF enhance dentinogenic and neurogenic gene expression, especially under bacterial lipopolysaccharide stimulation.[23] In combination with platelet-rich plasma and bioactive materials, SCAPs have demonstrated excellent biocompatibility and promoted dentin–pulp complex regeneration and mineralized tissue formation. [24]

Bone marrow mesenchymal stem cells (BMMSCs), first described by Friedenstein et al., are multipotent cells capable of differentiating into bone, cartilage, adipose, tendon, muscle, and neural tissues. [25] They express Stro-1, CD271, CD73, CD90, and CD105, while lacking hematopoietic markers CD31, CD34, and CD45. [26] In a regenerative study, rat BMMSCs combined with a bioceramic material and iRoot BP promoted vascularized pulp-like tissue formation after subcutaneous implantation of root fragments. [27]

Adipose-derived stem cells (ADSCs), first isolated by Zuk et al. from human adipose tissue, are mesenchymal stem cells capable of chondrogenic, myogenic, and osteogenic differentiation. [28] They express markers such as CD44, CD146, and CD34, but lack STRO-1.[29] Compared with dental pulp stem cells (DPSCs), ADSCs exhibit similar odontogenic potential but greater proliferation and resistance to cellular aging. [30] Moreover, ADSCs have been shown to generate more pulp-like tissue and extracellular matrix than bone marrow mesenchymal stem cells (BMMSCs) [31]

Induced Pluripotent Stem Cells (iPSCs), first introduced by Takahashi et al., possess embryonic stem cell-like pluripotency and can differentiate into cells of all three germ layers.[32] In regenerative dentistry, co-culture of iPSCs with Hertwig's epithelial root sheath/epithelial rests of Malassez (HERS/ERM) cells generated dental epithelial-like stem cells (EPI-iPSCs) with enhanced odontogenic gene expression and mineralization.[33] Additionally, iPSC-derived cranial neural crest-like cells (CNCLCs) combined with self-assembling peptide hydrogels successfully mimicked dental pulp tissue in experimental models. [34]

Scaffold Materials

Natural Materials play an essential role in tissue engineering because of their biocompatibility and ability to imitate the natural extracellular matrix. **Collagen**, a major extracellular matrix protein, is widely used in tissue engineering and drug delivery due to its excellent biocompatibility. Thant et al. [35] developed The AceCol scaffold, combining acemannan with native collagen, demonstrated superior physical and biological properties over collagen alone, highlighting its potential for dental pulp regeneration.

Chitosan, a natural biopolymer derived from crustacean shells, promotes cell attachment, proliferation, and differentiation. A calcium phosphate cement–chitosan scaffold loaded with metformin enhanced odontogenic differentiation of dental pulp stem cells (DPSCs), increasing dentin-related marker expression, mineralization, and alkaline phosphatase activity. [36] Similarly, PVA/chitosan nanofibers containing ciprofloxacin and IDR-1002 exhibited antimicrobial, antibiofilm, and anti-inflammatory properties, while promoting pulp-like tissue formation in vivo. [37]

Silk fibroin (SF) exhibits excellent biocompatibility and supports cell adhesion and proliferation.[38] A scaffold composed of ultrasmall superparamagnetic iron oxide-labeled hydroxyapatite combined with silk fibroin and loaded with DPSCs was developed for regenerative purposes.[39]

Gelatin, derived from collagen, also demonstrates excellent biocompatibility and supports cell attachment and growth. Gelatin scaffolds can be fabricated

into three-dimensional structures that mimic the architecture of tissues and organs [40] and are also widely used as drug delivery platforms. [41] In dentistry, gelatin–fibrin hybrid scaffolds have been developed, exhibiting improved physicochemical and biological properties compared with scaffolds composed of a single material. These scaffolds enhanced migration, proliferation, and odontogenic differentiation of DPSCs. [42]

Alginate, a natural polysaccharide derived from brown algae, is widely used in drug delivery and tissue engineering because of its controlled release properties and ability to support cell adhesion and growth. [43] Alginate-based hydrogels are also commonly used as bioinks in 3D bioprinting. An alginate–dentin protein bioink supported stem cell survival and promoted the differentiation of SCAPs. [44]

Hyaluronic acid (HA) is a naturally occurring polysaccharide playing a significant role in tissue repair and wound healing. Injectable HA-based hydrogels have been developed for regenerative applications. In vitro studies have shown that these hydrogels enhance odontoblastic differentiation of DPSCs by releasing thymosin-derived peptides (Td) and stimulate vascularization through the release of Rg. [45] Silva et al. developed an injectable hydrogel composed of hyaluronic acid, cellulose nanocrystals, and platelet lysate (HA/CNC/PL), which exhibited improved properties for tissue engineering. [46]

Synthetic Biomaterials, particularly poly(α-hydroxy ester)-based polymers, are widely used for pulp–dentin regeneration due to their tunable mechanical properties and controlled degradation. Polyglycolic acid (PGA), polylactic acid (PLA), and poly(lactic-co-glycolic acid) (PLGA) provide biodegradability, drug delivery, and mechanical stability. [47] PGA–α-MSH conjugates enhanced human pulp fibroblast activation, adhesion, and proliferation, highlighting their potential for regenerative endodontics. [48] A **fibrin hydrogel containing clindamycin-loaded PLA nanoparticles** also showed promise for dental pulp regeneration. [49] Chen et al. developed a PLGA/gelatin electrospun scaffold incorporating dental pulp extracellular matrix and treated dentin matrix, which

promoted odontogenic differentiation and regenerated periodontal tissue and the pulp–dentin complex in a miniature pig model. [50] Seonwoo et al. developed **reduced graphene oxide–polycaprolactone (RGO-PCL) electrospun nanofibers**, which promoted neurogenesis of dental pulp stem cells. [51] Similarly, an electrospun **polycaprolactone (PCL) tubular scaffold** combined with fibronectin or collagen hydrogels enhanced the proliferation and migration of SCAPs

Polyethylene glycol (PEG) is a biocompatible, biodegradable, and non-immunogenic polymer widely used in regenerative medicine. [52] An injectable PLGA/PEG hydrogel enabling controlled release of VEGF and DPSC-derived exosomes promoted angiogenesis and osteogenesis in vitro and in vivo. [53] Additionally, a PEG/PLGA composite scaffold containing TGF-β1-loaded nanoparticles enhanced DPSC adhesion, proliferation, and differentiation, leading to chondrogenic differentiation.[54]

Gelatin methacryloyl (GelMA) is a modified gelatin derivative containing methacryloyl functional groups that allow it to form hydrogels upon exposure to ultraviolet light in the presence of a photoinitiator. This property makes GelMA highly suitable for 3D bioprinting and fabrication of three-dimensional scaffolds for tissue engineering.[55] Several studies have explored GelMA-based hydrogels. For example, researchers developed a GelMA/platelet lysate/Laponite hydrogel microsphere system for endodontic regeneration. [56] This scaffold demonstrated excellent physicochemical characteristics and biocompatibility and enabled sustained release of multiple growth factors.

Growth Factors play a vital role in regenerative endodontics by regulating essential biological processes such as angiogenesis, odontoblast differentiation, and nerve regeneration.

Vascular endothelial growth factor (VEGF) is a key regulator of angiogenesis and tissue regeneration. Injectable hydrogel microspheres and degradable bio-cements delivering VEGF, alone or with TGF-β1, have enhanced odontogenic differentiation, DPSC migration, vascularization, and dentin–pulp–like tissue regeneration. Additionally, the VEGF/MEK1/ERK/ERG pathway promotes

integration of DPSC-derived blood vessels with host vasculature, supporting functional vascular regeneration. [57]

Bone morphogenetic protein-2 (BMP-2) is essential for bone and cartilage regeneration. Sequential delivery of VEGF and BMP-2 via injectable hydrogels enhances DPSC proliferation and mineralization, while BMP2 or DMP1 plasmid DNA incorporated into dentin scaffolds promotes odontoblastic differentiation and dentin–pulp interface regeneration. BMP-2 also stimulates DPSC differentiation and reparative dentin formation through the p38 MAPK/WNT/β-catenin pathway.[58]

Nerve Growth Factor (NGF) stimulates neuronal survival, growth, and synaptic connections by activating intracellular signaling pathways. In dental tissues, NGF signaling has been associated with age-related changes and plays a significant role in odontoblast differentiation, dentin matrix formation, and nerve attraction within the pulp. Zhang et al. demonstrated that the combined application of NGF and bFGF successfully induced neural differentiation of DPSCs. Following induction, the cells showed increased expression of neural-related genes and proteins, a process believed to be mediated through the **ERK and AKT signalling pathways** for achieving functional dental pulp regeneration. [59]

Extracellular Vesicles (EVs) are lipid bilayer–bound particles that mediate intercellular communication by transporting nucleic acids, proteins, lipids, and signaling molecules. Exosomes from odontogenically induced DPSCs promote odontogenic differentiation via the p38 MAPK pathway.[60] Schwann cell–derived extracellular vesicles enhance DPSC proliferation, migration, osteogenic differentiation, angiogenesis, and neurite formation through the SDF-1/CXCR4 pathway.[61] Apoptotic vesicles from SHED-apoVs stimulate endothelial cell proliferation, migration, differentiation, and angiogenesis by activating TUFM/TFEB-mediated autophagy. [62]

Gene therapy is an emerging regenerative approach that modulates gene expression using viral or non-viral vectors. Adenoviral delivery of the hepatocyte

growth factor (HGF) gene into DPSCs has been shown to reduce apoptosis and enhance periodontal bone and vascular regeneration in a swine model. [63]

In Vivo Models for Regenerative Endodontics

Ectopic Regeneration Model

Ectopic transplantation involves implanting cultured cells or tissues at a non-native site. Lee et al. developed an ectopic regeneration model by subcutaneously transplanting a mixture of DPSCs and HA/TCP, with or without preameloblast-conditioned medium (PA-CM) or recombinant human BMP-2, into immunocompromised mice. Findings showed that the addition of PA-CM significantly enhanced the formation of dentin/pulp-like structures.[64]

Semi orthotropic Regeneration Model

The semi orthotopic model is an intermediate approach between ectopic and orthotopic models.Zhang et al. demonstrated that root slices filled with collagen gel containing dental pulp stem cells (DPSCs) and Hertwig's epithelial root sheath (HERS)-derived exosome-like vesicles formed pulp–dentin–like tissues after subcutaneous implantation in mice. [65] Although semi orthotopic models better reproduce the native dental microenvironment, their outcomes may still be influenced by blood flow and organ movement.

Orthotropic Regeneration Model

Orthotopic models involve direct placement of scaffolds, stem cells, or growth factors into animal root canals, closely simulating human pulp regeneration. Due to the small root canals of rodents, larger animals such as pigs, dogs, ferrets, and sheep are typically used. In miniature pigs, hydrogels containing autologous stem cells successfully regenerated vascularized pulp-like tissue and dentin-like structures, although peptide hydrogels with porcine dental pulp cells produced osteodentin rather than true pulp tissue. [66] In dogs, dental pulp extracellular matrix (DP-ECM) promoted vascularized pulp-like tissue and mineralized tissue formation. Ferret studies demonstrated superior hard tissue formation with blood

clot therapy compared with SynOss Putty, which induced limited regeneration and greater inflammation.[67] Together, these in vivo models provide complementary platforms for evaluating dental pulp regeneration and regenerative endodontic strategies.

Challenges and Future Prospects

Pulp regeneration aims to restore the dentin–pulp complex through neurovascular regeneration, but predictable clinical outcomes remain challenging. Cell homing may cause canal calcification and tooth discoloration, while cell-based therapies require adequate stem cell expansion and genetic stability. Cell-free approaches using extracellular vesicles are promising but face production and standardization challenges. Advanced scaffolds, including electrospun and 3D-bioprinted biomaterials, are essential for tissue regeneration; however, achieving functional dentin formation, neurovascular integration, optimal stem cell selection, and clinical translation remain difficult. Further research is needed to develop standardized protocols and optimize stem cell–scaffold–growth factor interactions for successful clinical pulp regeneration.

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