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Advancement in Dental Pulp Stem Technology, Its Implications in Regenerative Technology: Narrative Review

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Abstract

Dental Pulp Stem Cells (DPSCs) are a type of Mesenchymal Stem Cell (MSC) that assists in oral tissue repair and regeneration. The dental pulp contains distinct subpopulations of progenitor cells, each characterized by varying capacities for self-renewal, proliferation, and differentiation. Studies have demonstrated that dental pulp stem cells (DPSCs) can be induced to differentiate into various cell types—including odontoblasts, osteoblasts, chondrocytes, cardiomyocytes, neurons, adipocytes, corneal epithelial cells, melanoma cells, and insulin-secreting beta cells—through the modulation of growth factors, transcription factors, extracellular matrix proteins, and receptor molecules. In addition to their therapeutic applications in dentin regeneration, and the regeneration of periodontal and craniofacial skeletal tissues, dental pulp stem cells (DPSCs) have also been reported to aid in the treatment of neurotrauma, autoimmune disorders, myocardial infarction, muscular dystrophy, and connective tissue injuries.

Ethical concerns surrounding stem cell harvesting, high treatment costs, and the need for extensive clinical trials are among the obstacles that need to be addressed in regenerative dentistry. Dental pulp stem cells (DPSCs) have shown potential in promoting peripheral nerve regeneration by inducing neuronal differentiation and upregulating various neurotrophic factors. CAD and 3D bioprinting have further revolutionised tissue engineering and regenerative approaches, where patient-specific customised constructs can be created with high accuracy and precision. The potential clinical implications are profound, as such therapies could shift the paradigm from conventional endodontic treatments toward biologically based regeneration.

Keywords: Dental Pulp Stem Cells, Deciduous Teeth, Myocardial Infarction, Proliferation

Introduction

The dental pulp is a soft connective tissue primarily responsible for the formation of dentin and the maintenance of its biological and physiological vitality. Additionally, it contains a highly sensitive sensory nervous system that can produce intense pain in response to mechanical trauma, chemical irritation, or microbial invasion[1]. Stem cells are unspecialized cells with a property of self-renewal and further differentiate into various specialized cells[2]. Gronthos et al. first described that DPSCs were initially discovered from the third molar dental pulp, which is later found in other dental pulps including deciduous teeth, permanent teeth, and supernumerary teeth[3]. Studies have demonstrated that dental pulp stem cells (DPSCs) can be induced to differentiate into various cell types—including odontoblasts, osteoblasts, chondrocytes, cardiomyocytes, neurons, adipocytes, corneal epithelial cells, melanoma cells, and insulin-secreting beta cells—through the modulation of growth factors, transcription factors, extracellular matrix proteins, and receptor molecules[4]. Dental Pulp Stem Cells (DPSCs) are a type of Mesenchymal Stem Cell (MSC) that help in oral tissue repair and regeneration. The dental pulp contains distinct subpopulations of progenitor cells, each characterized by varying capacities for self-renewal, proliferation, and differentiation[5].

DPSCs can differentiate into odontoblasts, osteoblasts, endotheliocytes, smooth muscle cells, adipocytes, chondrocytes and neurons. Dental stem cells isolated from different parts of the teeth are a. SHED. b. Adult dental pulp stem cells (DPSC). c. Stem cells from the apical part of the papilla (SCAP). d. Stem cells from the dental follicle (DFSC). e. Periodontal ligament stem cells (PDLSC). f. Bone marrow-derived mesenchymal stem cells (BMSC). In addition to their therapeutic applications in dentin regeneration, and the regeneration of periodontal and craniofacial skeletal tissues, dental pulp stem cells (DPSCs) have also been reported to aid in the treatment of neurotrauma, autoimmune disorders, myocardial infarction, muscular dystrophy, and connective tissue injuries[6].

Therapeutics Application

Dental pulp tissue engineering is an emerging field with the potential to significantly advance oral health care. Depending on specific signals from their environment, DPSCs can either regenerate new stem cells or undergo a differentiation process. In the dental pulp, there are different progenitor cell subpopulations, which differ in terms of self-renewal ability, proliferation rate and differentiation potential. Stem cell therapy is being used in medical sciences for various degenerative diseases other than those of dental origin such as Alzheimer's disease, myocardial infarction, diabetes mellitus, bone defects and spinal cord injuries etc[7].

Role of DPSCs in corneal regeneration

The potential of DPSCs in corneal reconstruction has also been investigated recently. In an animal study by Gomes et al., a tissue-engineered DPSC sheet was transplanted onto the corneal bed and subsequently covered with a de-epithelialized human amniotic membrane[8]. Histological analysis three months postoperatively confirmed the formation of a healthy, uniform corneal epithelium. The study concluded that the tissue-engineered DPSC sheet was effective in reconstructing the corneal epithelium[9].

Role in myocardial infarction

From this perspective, the cardiomyogenic differentiation potential of DPSCs has been investigated by several researchers. Arninam and colleagues were among the first to compare the ability of stem cells derived from bone marrow (BMSCs), adipose tissue

(ATSCs), and dental pulp (DPSCs) to differentiate into cells exhibiting a cardiac phenotype[10]. The therapeutic potential of DPSCs in the repair of myocardial infarction was evaluated by Gandia et al. in 2008, who concluded that human DPSCs secrete multiple pro-angiogenic apoptotic factors[11].

Therapeutic role of DPSCs in Ischemia

Iohora et al. successfully isolated a highly vasculogenic subpopulation of DPSCs from dental pulp, exhibiting characteristics similar to endothelial progenitor cells. These cells demonstrated enhanced proliferation, migration, multi-lineage differentiation, and a strong innate capacity for vasculogenesis—the ability to form blood vessels and related structures[12].

Segregation of DPSCs into muscular tissue

Yang et al. were among the first to use human DPSCs for treating muscular dystrophy in golden retriever dogs, administering the cells through arterial or intramuscular injections. The therapeutic potential of DPSCs to differentiate into dystrophin-producing multinucleated muscle cells can be successfully utilized in diseases like muscular dystrophy which where the body is incapable of producing dystrophin and has the myogenic potential of DPSCs[13].

Neural differentiation of DPSCs

Apel et al. investigated the neuro-protective effect of DPSCs in vitro models of Alzheimer's and Parkinson's disease[14]. It was also found that DPSCs exhibited a neuronal phenotype and secreted neurotrophic factors such as NGF (nerve growth factor), GDNF (glial cell-derived neurotrophic factor), BDNF (brain-derived neurotrophic factor), and BMP2. Additionally, DPSCs supported primary neuron survival and enhanced cell viability[15]. It was demonstrated that DPSCs promoted the regeneration of transplanted axons by directly inhibiting multiple axon growth inhibitors and by preventing of apoptosis of neurons, astrocytes and oligodendrocytes. The DPSCs also differentiated into mature oligodendrocytes to replace cells that were lost.

DPSCs differentiation into Hepatocytes

Ishkitiev and colleagues were among the first to demonstrate that DPSCs can differentiate into cells exhibiting morphological, phenotypic, and functional characteristics of hepatocytes. They further isolated stem cells from dental pulp and proposed that DPSCs possess the potential to differentiate into the hepatic lineage[16].

Differentiation of DPSCs into bone cells

DPSCs, of ectomesenchymal origin, express osteogenic markers that respond to signals inducing osteogenic and odontogenic differentiation. Derived from the neural crest, these mesenchymal stem cells play a vital role in surgical repair and regeneration by migrating, differentiating, and contributing to the morphogenesis of craniofacial structures such as muscle, ligaments, cartilage, bone, periodontal membrane, and teeth. Graziano et al. and Aquino et al. evaluated bone regeneration using DPSCs seeded on a collagen scaffold, assessing outcomes both clinically and radiographically. Their findings showed that complete radiographic bone regeneration was achieved within three months of scaffold colonization[17,18].

DPSCs' considerations for Type 1 diabetes

Chen et al. demonstrated that insulin-producing cells (IPCs) can be derived from both monoclonal and polyclonal DPSCs. Moreover, when following the same IPC induction protocol, the insulin yield from both clonal and polyclonal DPSCs was higher than that of BMSCs. These findings highlight the ability of DPSCs to differentiate into islet-like cell aggregates[19]. Preservation and isolation of DPSCs from the teeth intended for orthodontic extraction, from exfoliated deciduous teeth or extracted impacted teeth can be

advantageous for upcoming regenerative medicine. Moreover, DPSCs can be efficiently cryopreserved, and numerous studies have shown that they retain high viability and functional properties upon thawing. This capability makes them ideal candidates for biobanking, allowing for long-term storage and future use in regenerative therapies, personalized medicine, and research applications[20].

Current Approaches For Pulp Tissue Regeneration

Pulp Revascularization: When the root canal has been cleaned and disinfected, a blood clot is injected in the canal to regenerate the diseased pulp tissue into healthy pulp tissue. This process is known as pulp revascularization. As apical foramina haven't closed in baby teeth, hence this technique can be used on them. Root growth of young teeth can be completed if revascularization is conducted effectively; thus, it has been intensively investigated in the field of traumatology[21]. Pulp revascularization and traditional root canal treatment have a common goal—the elimination of infection—but the two procedures have fundamentally different approaches. Root tip bleeding is employed to introduce mesenchymal stem cells (MSCs) into the root canal. Due to its rich content of growth factors, the resulting blood clot serves both as a biological scaffold and a reservoir of signaling molecules. Many of these growth factors are typically sequestered within dentin, but can be released using ethylenediaminetetraacetic acid (EDTA), promoting DPSC development into odontoblast-like cells[22]. Pulp revascularization has a few restrictions, as this approach can only be utilized on baby teeth and the majority of the tissues formed during pulp revascularization have been shown through histological studies to be different from the original pulp-like tissues; instead, they resemble periodontal, cementum, and bone tissues. So, we need additional study before we can use this method on completely formed teeth and stimulate the growth of pulp-like tissue.

Cell-Homing-Based Regenerative Endodontic Treatment: The concept of cell homing for dental regeneration revolves around the chemotaxis of host endogenous cells to injured pulp tissue via signaling molecules[23]. Blood not only provides a natural scaffold but also serves as a rich source of signaling molecules. The cell homing approach plays a key therapeutic role by recruiting, inducing differentiation, and promoting the proliferation of endogenous stem cells capable of regenerating the pulp-dentin complex, making the identification of native stem cell sources critically important. As local DPSCs are highly homing and have the natural potential to repair pulp dentin in response to specific signaling molecules, a pulpotomy can be accompanied by a cell-homing technique[24]. However, there are constraints associated with the cell-homing approach as root growth in juvenile teeth may be stunted if inflammation and pulp necrosis damage the apical papilla or follicle, which houses stem cells necessary for odontoblast differentiation and dentin production so, it is difficult to anticipate the outcome of treatment when cell-homing based RET is conducted on completely developed teeth.

Cell-Transplantation-Based Regenerative Endodontic Treatment: Pulp tissue regeneration through regenerative endodontic therapy (RET) marked the first application of the classical tissue engineering principle of cell transplantation. Since then, this approach has advanced significantly. Following the standard tissue engineering paradigm, experimental and preclinical animal studies have explored stem cell implantation for pulp regeneration[25]. Notably, the use of autologous dental pulp stem cells (DPSCs) in

combination with Gelfoam scaffolds has enabled the regeneration of pulp-like tissue—complete with dentin-like structures and blood vessels—in immature permanent incisors of canine models. The cell transplantation-based RET approach appears to be the most promising strategy for clinical application. Unlike cell-homing-based RET, which relies on the challenging task of inducing endogenous stem cell recruitment, this method allows for the direct delivery of stem cells with the desired regenerative properties, facilitating the formation of pulp-like tissue more efficiently. While each study used a somewhat different combination of scaffolds and signaling molecules, more investigation into the optimal combination is required.

Allogenic transplant: In this dental pulp is harvested from a healthy, non-infected donor tooth—typically a wisdom tooth or one extracted for orthodontic reasons. Following isolation and culture, dental pulp stem cells (DPSCs) are cryopreserved for future use. During the patient's pulpectomy procedure, these cryopreserved DPSCs or preserved pulp tissues can be expanded as needed. After thorough cleaning of the pulp space, an appropriate scaffold—embedded with signaling molecules and DPSCs—is introduced into the canal to facilitate tissue regeneration[22]. Pulp tissue collection, banking, and clinical application should be standardized and help to save money and streamline the process. By using allogeneic cells, there is a risk of immunological rejection from the host due to an MHC mismatch.

Challenges in Regenerative Dentistry

Ethical concerns surrounding stem cell harvesting, high treatment costs, and the need for extensive clinical trials are among the obstacles that need to be addressed in regenerative dentistry. Additionally, obtaining a sufficient quantity of cells can also be challenging. Therefore, it is essential to explore alternative cell sources and establish stem cell banks to enhance the feasibility of this process. However, translating laboratory research into clinical practice is also a complex process, as patient responses to regenerative treatments can vary widely[26]. Further, the anatomical location of the pulp, which is encased within the dentin tissue and receives its blood supply only from the apical end, establishing vascularity may be difficult in cases where the apical opening is less than 1 mm[27].

Cell homing-based dental pulp regeneration often leads to complications such as root canal calcification and tooth discoloration. Consideration must also be given to the immune response after stem cell implantation and monitoring the cell cycle to ensure genetic stability and to avoid immune reactions associated with cell transplantation. Dental pulp regeneration often involves a lengthy process, so there is a need to reduce the time duration for the procedure. Selecting the ideal regeneration approaches, appropriate cells, growth factors, and scaffolds to meet the requirements for functional dental pulp regeneration remains a challenge. Even though the risk of infection and immune rejection is minimal with the use of heterogeneous cells, the potential risks of undesired tissue formation, tumourigenesis, and metastasis represent a controversial issue that has not yet been resolved[28].

Future Advances

Dental pulp tissue yields great reproductive ability and is rich in varying categories of stem cells with unique differentiation potentials. Dental pulp stem cells (DPSCs) have shown potential in promoting peripheral nerve regeneration by inducing neuronal differentiation and upregulating various neurotrophic factors. When combined with suitable biomaterials, DPSCs represent a promising strategy for neural tissue repair. Their broad therapeutic potential includes applications in conditions

such as peripheral nerve injuries, diabetic neuropathy, and retinal damage[29]. Cryopreserving DPSCs will preserve their ability to differentiate into multiple lineages, including the osteogenic, chondrogenic, dentinogenic, myogenic, neurogenic, and adipogenic lineages. Dental pulp is inherently heterogeneous, comprising various cell types capable of differentiating into distinct lineages. To achieve lineage-specific differentiation, clonal isolation and enrichment of single cell types are performed in culture. These subpopulations are then characterized through immunophenotyping, using molecular and phenotypic markers that govern their differentiation potential. This process is conducted under defined media conditions in either two- or three-dimensional culture systems[30].

CAD and 3D bioprinting have further revolutionised tissue engineering and regenerative approaches where patient-specific customised constructs can be created with high accuracy and precision[31].

Cell sheets, spheroids, and organoids: Cell sheets are a scaffold-free cell therapy that forms high-density sheet structures out of cells and their extracellular matrix. It preserves intercellular and cell-matrix connections and caters to the function of a scaffold by providing strength and support for cells and a 3D structure for cell proliferation and differentiation. The use of in vitro fabricated prevascularized microtissue spheroids of DPSCs has been reported to produce vascular dental pulp-like tissue in immunodeficient mice[31,32]. The development of tooth germ organoids that closely mimic the tissue interactions involved in human tooth development has been explored using dental pulp stem cells (DPSCs). Additionally, dental pulp organoid models have been investigated as platforms for toxicity screening of dental materials[31].

3D bioprinting: The limitations and challenges of organoid fabrication can be overcome in large part by 3D bioprinting, an advanced manufacturing technology capable of producing personalised 3D objects using standardised material. One of the most important aspects of 3D bioprinting is its ability to manipulate the delivery of cells and materials in complex fabricated tissue-like constructs enabling it to maintain cell-to-cell growth interconnectivity for improved tissue regeneration[33].

Exosomes: MSC-secreted exosomes are currently considered a viable, cell-free, therapeutic alternative for the use of cells[31]. Compared to conventional cell therapy, dental stem cell (DSC)-derived exosomes offer several advantages, including low immunogenicity, high drug-loading capacity, biocompatibility, specificity, stability, and minimal cytotoxicity. These exosomes have demonstrated significant potential for dentin–pulp and oral soft tissue regeneration in both in vitro and in vivo models[34].

Biobanking: However, long-term in vitro culture of DSCs may pose potential hazards such as chromosomal abnormalities, senescence, and microbial contamination. Cell banking is used to avoid these risks and to preserve the cells at their most potent stage for future applications[35]. The quality control and maintenance of this multistep process are carried out and followed according to international guidelines to ensure its safety and effectiveness.

Conclusion

The application of stem cells in regenerative medicine has facilitated the advancement of cell transplantation techniques for pulp regeneration. However, to enable clinical translation, further laboratory and clinical research is necessary to optimize large-scale production, storage, and transport of DPSCs while minimizing contamination risks. Additionally, a deeper

understanding of the molecular mechanisms governing DPSC interactions with various biomaterials is needed. Crucially, in the development and clinical use of tissue-engineered dental pulp and scaffolds, factors such as spatial constraints, precise placement, and ease of handling play a vital role, as they directly influence treatment efficacy and success rates.

Regeneration of functional dental pulp tissue may be a viable approach for restoring vitality in necrotic immature permanent teeth. By engineering new pulp tissue, it becomes possible not only to reestablish vascularization and innervation but also to support continued root development and dentin formation. The potential clinical implications are profound, as such therapies could shift the paradigm from conventional endodontic treatments toward biologically based regeneration. Shortly, these advancements may enable the reinforcement and long-term preservation of tooth structure through natural tissue repair and maturation, ultimately improving outcomes for young patients with compromised teeth.

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