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Review Article

Harnessing dental pulp stem cells for endodontic pulp regeneration; Current insights & future directions

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Abstract

Dental pulp stem cells (DPSCs), found within both permanent and deciduous teeth, represent a unique source of ectodermally derived mesenchymal stem cells with notable proliferative ability, self-renewal, and multi-lineage differentiation (including osteogenic, adipogenic, chondrogenic, and neurogenic pathways). Notably, their neurovascular properties and the relatively non-invasive nature of their isolation distinguish DPSCs from other stem cell sources, such as bone marrow-derived MSCs. DPSCs have demonstrated superior odontogenic differentiation and are thus regarded as promising candidates for regenerating the dentin-pulp complex. Recent literature, including a systematic review of 35 studies from PubMed and Google Scholar (2000–present), highlights substantial progress in the application of DPSCs for regenerative endodontic. Growth factors such as BMPs, TGF-β1, and VEGF are critical in directing DPSC differentiation and facilitating pulp regeneration. Various isolation techniques both enzymatic and explant-based are under investigation, yet challenges remain, particularly regarding donor variability and effective cryopreservation. Tissue engineering approaches combining DPSCs with biomaterial scaffolds (collagen, hydroxyapatite-tricalcium phosphate, hydrogels) and signaling molecules have shown considerable promise. Preclinical studies in animal models (rat, dog, pig) confirm that DPSCs can generate vascularized pulp-like tissue and tubular dentin. While the regenerative potential of DPSCs extends into neurology and orthopedics, successful clinical translation faces several obstacles, including inconsistent isolation protocols, post-transplantation survival in hypoxic environments, immunogenicity concerns, and regulatory challenges. DPSCs represent a promising frontier in tissue engineering, with ongoing research poised to overcome current barriers and expand their therapeutic applications.

Keywords: Tissue Engineering, Growth Factors, 3D Bioprinting, Scaffolds, Odontogenic Differentiation, Regenerative Endodontics, Cell Homing, Dental Pulp Stem Cells (DPSCs)

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1. Introduction

Dental pulp stem cells (DPSCs), residing within the pulp tissue of teeth, represent a significant population of adult stem cells with considerable regenerative capacity.[1] Dental pulp stem cells (DPSCs) are derived from neural crest cells during embryonic development, which imparts a unique ectodermal origin to these cells.[2] Dental pulp stem cells (DPSCs) exhibit substantial self-renewal abilities and a notably high proliferative rate, characteristics that position them as valuable assets in regenerative medicine. Their remarkable cellular plasticity enables differentiation into multiple lineages including osteoblasts, adipocytes, and neural-like cells highlighting their versatility within research and clinical contexts. A practical benefit is that DPSCs are typically isolated from extracted teeth, a minimally invasive procedure that enhances their accessibility for both experimental and therapeutic purposes.[2,3]

The neurovascular properties of DPSCs, along with their ease of collection, underscore their promise as candidates for regenerative approaches targeting the dentin-pulp complex

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and, potentially, certain neurological conditions.[4] Recent studies have shown that DPSCs are capable of forming tissue constructs closely resembling native dentin-pulp, with features such as mineralized matrices, dentinal tubule-like structures containing odontoblast-like cells, organized connective tissue, and vascular components similar to natural pulp. Compared to bone marrow-derived stem cells, DPSCs often show a superior capacity for odontogenic differentiation, further supporting their potential in dental tissue engineering and regenerative applications.[4]

DPSCs were first thoroughly characterized by Gronthos and colleagues, who identified similarities to bone marrow stromal cells while also noting unique characteristics. In vitro, DPSCs generally display a spindle-shaped, fibroblast-like morphology, adhere to plastic culture substrates, and demonstrate colony-forming ability. Under appropriate differentiation conditions, these cells can generate adipogenic, chondrogenic, odontogenic, and neurogenic lineages, underscoring their utility and relevance in regenerative research.[5,2]

Phenotypically, DPSCs express mesenchymal stem cell surface markers such as CD29, CD44, CD59, CD73, CD90, and CD146, and lack hematopoietic markers like CD34, CD45, and CD11b.[2] Although some studies suggest that their differentiation range may be more limited compared to bone marrow-derived MSCs possibly due to the relatively static environment of dental tissue other comparative analyses (for example, by Alge et al.) have demonstrated that DPSCs have a higher proliferation rate, greater clonogenic potential, and enhanced mineralization compared to BMMSCs.[1,2] Furthermore, electron microscopy studies have confirmed the formation of odontoblast like cells with cytoplasmic extensions into dentinal tubules when DPSCs are cultured on conditioned dentin surfaces, reinforcing their odontogenic capacity.[1]

Beyond their dental applications, DPSCs show significant osteogenic differentiation, forming bone-related cells and expressing bone-specific proteins such as alkaline phosphatase, osteocalcin, and osteopontin core components in bone matrix formation and mineralization.[1] Their neurogenic properties also support their potential use in neuroregenerative therapies, particularly for nerve injuries and neurodegenerative diseases. Given their high proliferative capacity, multi-lineage differentiation, and ease of isolation, DPSCs are an important cellular resource for advancing therapeutic strategies in dentistry, orthopedics, and neurology.[1] [Figure 1] .

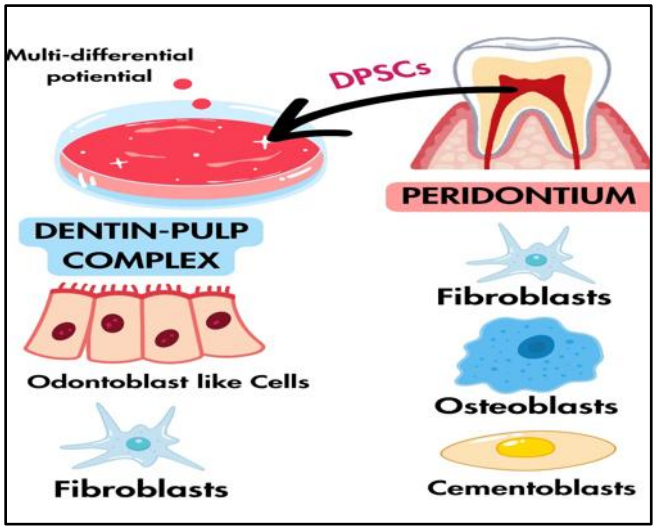


Figure 1: Pluripotent potential of dental pulp stem cells (DPSCs) [Figure created by the author using licensed elements from Canva Pro]

2. Materials and Methods

2.1. Literature review

This review synthesizes recent advances relating to dental pulp stem cells (DPSCs) in the context of regenerative endodontic. The authors conducted a comprehensive literature search using databases such as PubMed and Google Scholar, focusing on publications since 2000 and employing keywords like “DPSCs,” “regenerative endodontic,” “tissue engineering,” “scaffolds,” and “growth factors.” The main aim is to provide an in-depth overview of current DPSC research and discuss its potential implications for regenerative endodontic therapies. Notably, the review highlights innovative developments such as 3D bio printing and gene editing approaches (e.g., CRISPR-Cas9), which may have significant impact on the field.

Initially, 505 articles were identified. These were screened for relevance to DPSC biology, experimental models, clinical applications, and challenges within regenerative endodontics. Non-English and duplicate studies were excluded, leaving 120 full-text articles for detailed assessment. Two independent reviewers evaluated these, ultimately including 35 studies that satisfied the inclusion criteria. The selection methodology is outlined in the accompanying PRISMA flow diagram.

2.2. Inclusion and exclusion criteria

Studies were selected based on the PICO framework:

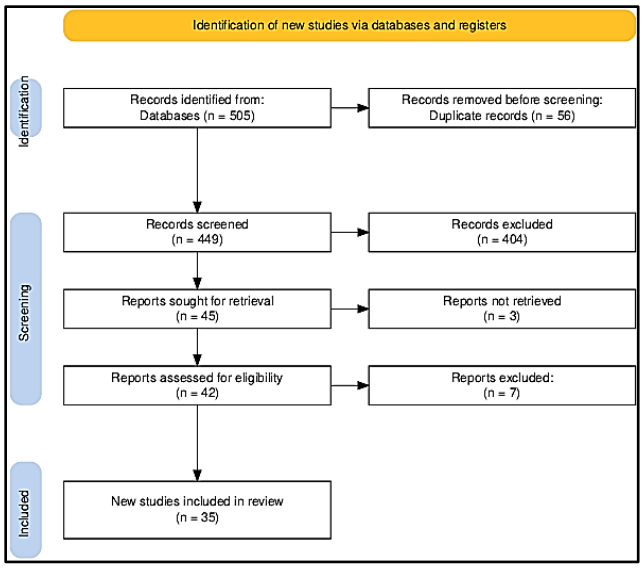
1. ***Population:*** Human dental pulp stem cells (DPSCs) derived from permanent or deciduous teeth, including studies on their isolation, characterization, and differentiation potential.
2. ***Intervention:*** Regenerative strategies such as tissue engineering (scaffolds, growth factors), cell

transplantation, genetic modification (e.g., CRISPR-Cas9), and exosome-based therapies.

3. ***Comparison:*** Efficacy of DPSCs versus other mesenchymal stem cells (e.g., BMMSCs), scaffold types, or differentiation protocols.
4. ***Outcome:*** Key metrics included pulp-dentin complex regeneration, angiogenesis, mineralization, clinical translation challenges, and ethical considerations.

2.3. Inclusion criteria

1. Peer-reviewed articles (original research, reviews, clinical trials) focusing on DPSCs in regenerative endodontics.
2. Studies reporting in vitro, in vivo, or preclinical outcomes.
3. Articles addressing challenges such as donor variability, cryopreservation, and regulatory barriers.



2.4. Exclusion criteria

1. Non-English articles, opinion pieces, or non-peer-reviewed publications.
2. Studies on non-dental stem cells (e.g., ESCs, iPSCs) unless directly compared to DPSCs. Articles unrelated to endodontic applications (e.g., cardiac or neurological studies).

3. Results

3.1. Growth factors signalling molecules in regenerative endodontic

Stimulation of dental pulp stem cells, which reside in the dental pulp, is necessary to regenerate the dentin pulp complex. The stimulated DPSC then divides and produces daughter stem cells, which leads to pulp regeneration. However, the original or parent stem cells remain in place and maintain a stem cell niche. The newly formed daughter stem cells move away to the defective site and participate in dentin bridge and new dental pulp formation.[6]

Growth factors have a major effect on dental pulp tissue regeneration by using DPSCs. There are multiple sources of growth factors which include stem cells themselves, dentin, or scaffold materials. They all work together in regulating the behavior of undifferentiated immature DPSC.[6] The dentin's tubular structure makes it easier for growth factors to flow through dentin matrix that has been demineralized by pulp-capping materials, acidic tooth conditioning treatments, or cavities. It has been demonstrated that calcium hydroxide dissolves dentin and releases bioactive compounds that help in dentin regeneration. These events are DPSC recruitment, their differentiation into odontoblast, and the secretion of matrices.[4]

Research conducted by Govindasamy and colleagues (2012) revealed that dental pulp stem cells (DPSCs) can be effectively extracted from both permanent and primary teeth that have fallen out.[4] Research indicates that stem cells derived from primary teeth exhibit a notably greater proliferative capacity than those sourced from permanent teeth. These primary tooth stem cells also display heightened expression of markers related to pluripotency and neuroectodermal differentiation. Additionally, Huang and colleagues (2008) successfully isolated dental pulp stem cells from supernumerary (extra) teeth, thereby expanding the available sources for regenerative applications.[3]

Earlier studies from the 1990s demonstrated that bone morphogenetic proteins specifically BMP-2, BMP-4, and BMP-7—initiate signaling pathways that promote dentin formation in animal models. It is important to note, though, that BMPs are not the sole agents capable of inducing dentinogenesis; other factors can also stimulate this process.It has been demonstrated that dentin matrix protein (DMP)-1 induces dentin production and nucleates apatite crystals.[5] Furthermore, pulp cells can be stimulated to differentiate into cells that can secrete mineralized matrices in pulp exposure areas by bone sialoprotein (BSP). It's interesting to note that distinct morphologic traits are seen when dentin is generated by various substances (for example, dentin induced by BSP seems to vary from dentin induced by BMP). These findings present the exciting prospect that a particular kind of biological inducer of dentin repair may be chosen in accordance with patients' needs. All these morphogenetic factors possibly be found in the dentin matrix and induce differentiation into odontoblast.[5]

3.2. Isolation of DPSCS.

Dental pulp cells are a good source of stem cells in terms of noninvasive isolation from the dental pulp as compared to bone marrow and adipose tissues.[8] Govindasamy et al. (2012) demonstrated that dental pulp stem cells (DPSCs) can be successfully isolated from both permanent and exfoliated deciduous teeth. Interestingly, their research found that

DPSCs derived from deciduous teeth possess a higher proliferative capacity compared to those from permanent teeth, and also display increased expression of pluripotency and neuroectodermal markers.[4] Further expanding the potential sources for DPSCs, Huang et al. (2008a) reported successful isolation of these cells from supernumerary teeth.[2,4,5] [Figure 2]

3.3. Challenges in isolation of DPSCs

Concerning the challenges associated with DPSC isolation, Lizier et al. (2012) observed that DPSCs can be maintained in culture for up to six months without significant morphological changes or loss of stem cell marker expression.[7] This duration allows for considerable expansion of DPSCs and supports their potential for therapeutic and regenerative applications. One ongoing challenge involves the preservation of teeth prior to cell isolation. Reliable cryopreservation methods would make it possible to establish practical "cell banks," improving accessibility to stem cells as needed. Lee et al. (2010) contributed to this area by demonstrating that dental tissue can be cryopreserved using controlled cooling rates, even in the absence of conventional.[7]

Notably, under these conditions, cells maintained both their viability and expression of stem cell markers, supporting the feasibility of long-term storage and future therapeutic use.[7] This is important because cryoprotectants, while commonly used, are known to sometimes damage cells during the preservation process. Eliminating their use could potentially improve outcomes in the long run.[7]

Nonetheless, a significant challenge remains ensuring that dental pulp stem cells (DPSCs) remain both viable and functional after preservation without these chemical agents. Addressing this issue is essential for advancing the reliability and accessibility of DPSCs in regenerative medicine. As preservation techniques evolve, the prospect of storing and utilizing these stem cells in clinical practice becomes increasingly realistic.[7]

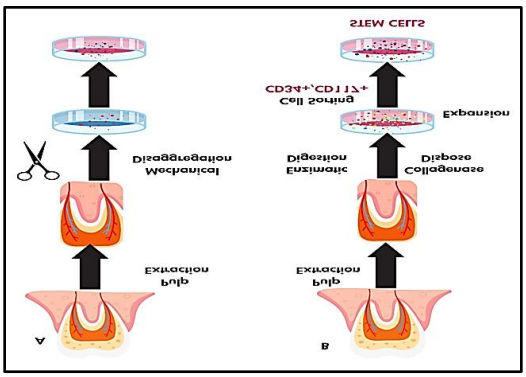


Figure 2: In isolation of dental pulp stem cells DPSCs) [Figure created by the author using licensed elements from Canva Pro]

3.4. Multi-cell lineages of dpsc and their use in regenerative medicine (other than endodontic regeneration)

The results of a study concluded that stem cell populations obtained from either of the methods can differentiate into osteoblasts and chondroblasts, which ultimately suggests that these stem cells can be used therapeutically in the treatment of bone and cartilage.[2]

DPSCs can be used in tooth regeneration and repair. In addition to this DPSC can be clinically applied in other domains. They have multi-lineages differentiation potential as they can differentiate into endothelial cells, and functional neurogenic cells that show the neuron-related surface markers.[2]

It has been shown in studies that DPSCs can differentiate into functional neurons and glial cells but the presumptive conditions should be met. They are also capable of secreting neurotrophic factors that lead to neurite outgrowth.[6,9] **[Figure: 3,4]**

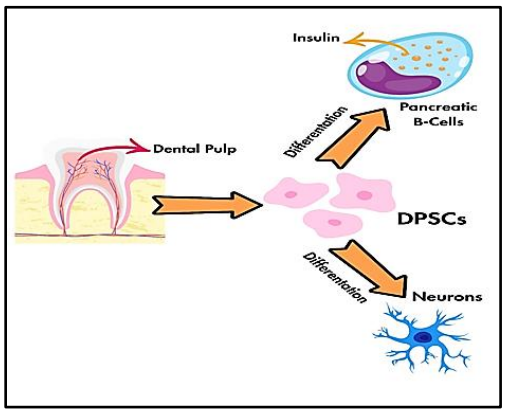


Figure 3: Multi-cell lineages of dental pulp stem cell (DPSC) [Figure created by the author using licensed elements from Canva Pro]

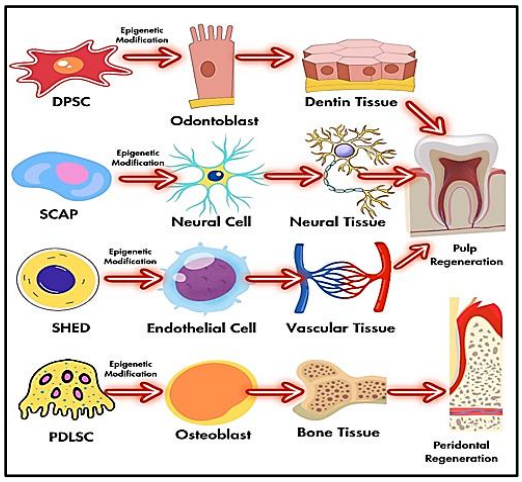


Figure 4: Multi-cell lineages of dental pulp Stem Cell (DPSC) [Figure created by the author using licensed elements from Canva Pro]

3.5. Tissue engineering and experimental models for dental pulp stem cell-based regenerative endodontics

3.5.1. Tissue engineering in endodontics: The triad approach

Regenerative endodontics employs tissue engineering strategies that combine stem cells, biomaterial scaffolds, and signaling molecules to restore pulp function and promote dentin regeneration.[10] Notably, Dental Pulp Stem Cells (DPSCs) have emerged as a leading candidate due to their accessibility and robust regenerative potential. DPSCs exhibit multilineage differentiation capabilities, giving rise to various cell types such as odontoblasts, osteoblasts, and neuron-like cells, which makes them particularly well-suited for engineering dental tissues.[10]

3.5.2. Stem Cells: Role of DPSCs in Pulp Regeneration

DPSCs, originally isolated from third molars and deciduous teeth, account for approximately 1–5% of permanent and 2–9% of deciduous pulp cells. They express mesenchymal stem cell markers such as CD29 and CD105, along with pluripotency genes like Oct4 and Nanog.[11] Two primary strategies are used in DPSC-based therapies: cell transplantation, where exogenous DPSCs are seeded into a scaffold and implanted, and cell homing, where host cells are recruited via signaling molecules and scaffold cues.[11] [Figure 5]

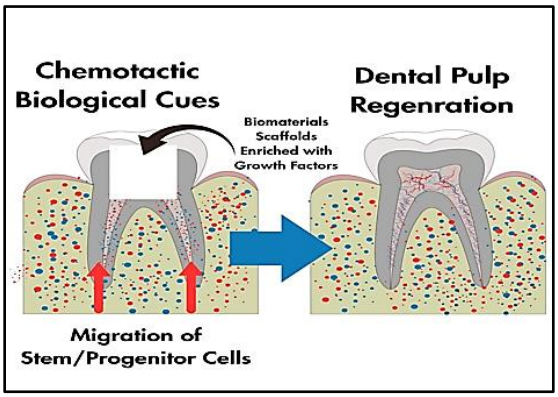


Figure 5: Role of dental pulp stem cells (DPSCs) in Pulp Regeneration [Figure created by the author using licensed elements from Canva Pro]

DPSCs also respond to epigenetic regulation. Agents such as histone deacetylase inhibitors (HDACis)—including TSA, VPA, and SAHA—have been shown to enhance odontogenic differentiation and mineralization in vitro.[12]

3.5.3. Scaffolds: Biomaterials supporting pulp regeneration

Scaffolds act as essential three-dimensional structures that provide the necessary environment for dental pulp stem cells (DPSCs) to proliferate, migrate, and differentiate. Researchers have explored a variety of scaffold systems to optimize the biological behavior of DPSCs.[12] Natural scaffolds such as collagen gels, platelet-rich fibrin (PRF), and decellularized extracellular matrix closely resemble the native tissue microenvironment, supporting cellular activities in a manner that aligns with physiological conditions.[12]

3.5.4. Growth Factors: Signaling molecules in pulp regeneration

Growth factors serve as key molecular signals in the process of pulp regeneration. Bone Morphogenetic Proteins (BMP-2 and BMP-4) are especially significant due to their capacity to stimulate odontogenic differentiation, a process essential for dental tissue development.[13] Transforming Growth Factor Beta 1 (TGF-β1) promotes the proliferation of dental pulp stem cells (DPSCs) and supports production of the extracellular matrix, while Vascular Endothelial Growth Factor (VEGF) is critical for angiogenesis. Additionally, Fibroblast Growth Factor 2 (FGF-2) enhances cell proliferation and tissue formation.[13] Other factors such as Stromal cell-derived factor-1α (SDF-1α) and Granulocyte Colony-Stimulating Factor (G-CSF) further facilitate stem cell recruitment and neovascularization. When these growth factors are integrated into scaffold systems, they establish a microenvironment that supports the development of pulp-dentin-like tissue—demonstrating substantial potential for advancing regenerative endodontic therapies.[13] [Figure 3]

4. In Vitro and In Vivo Studies

Empirical findings from both in vitro and in vivo studies indicate that culturing DPSCs on scaffolds with selected growth factors and histone deacetylase inhibitors reliably triggers their differentiation into odontoblast-like cells. This differentiation is characterized by the deposition of mineralized matrix, increased expression of dentin sialophosphoprotein (DSPP), and formation of tubular dentin structures.[12,14]

Moving from in vitro to in vivo evidence, animal model studies further corroborate the regenerative abilities of DPSCs. In rodents, for instance, researchers consistently observe the emergence of pulp-like tissue and mineralized matrices within a 4–6 week timeframe. Larger models, such as dogs and miniature pigs, extend these findings: within twelve weeks, DPSC transplantation (on suitable scaffolds) leads to pulp regeneration, functional odontoblast formation, neovascularization, and apical closure. These results collectively highlight the robust regenerative potential of DPSCs across species.[12,14]

5. Animal Models in Regenerative Endodontics

Animal studies have been fundamental in validating the regenerative potential of DPSCs in pulp-dentin complex repair. The use of rat, dog, and pig models provides insight into the histological and functional outcomes of various tissue engineering approaches.[14] Rodent models are commonly used in early-stage experiments due to ease of handling and cost-effectiveness. In subcutaneous transplantation studies: DPSCs seeded on biodegradable scaffolds formed dentin-pulp-like tissue within 4–6 weeks.

Histological sections showed layered odontoblast-like cells along the scaffold surface and tubular dentin formation.[14,37] However, the lack of apical foramen closure and non-orthotopic placement (e.g., subcutaneous rather than intra dental) limits the translation of these findings to clinical relevance.[12]

Dog models are more clinically translatable due to tooth size and apical anatomy.[14] In a landmark study by Iohara et al, autologous DPSCs combined with granulocyte colony-stimulating factor (G-CSF) were transplanted into pulpectomized mature dog teeth. Within 28 days, histological analysis showed vascularized pulp-like tissue and new dentin formation. At 12 weeks, regenerated tissue included functional odontoblasts, blood vessels, and nerve bundles. Another study showed that DPSCs with collagen scaffolds led to apical closure and root elongation in immature teeth, mimicking natural development.[14]

Miniature pigs offer a close approximation to human dental anatomy and are suitable for scaling regenerative protocols[14] Zhu et al. (2022) transplanted DPSCs embedded in hydrogel scaffolds into pulpectomized swine molars. By week 4, revascularization and cell infiltration were evident. By week 12, a complete pulp-like structure with vascularity and tubular dentin was observed. CBCT imaging confirmed apical reconstitution and tissue integration, supporting the scaffold's biocompatibility and the DPSCs' odontogenic potential. [Table .1]

Table 1: Comparative insights

Animal Model	Outcome Time frame	Key Findings
Rat	4–6 weeks	Ectopic dentin-pulp-like tissue formation; early odontoblast differentiation.[14,37]
Dog	4–12 weeks	Vascularized pulp regeneration, functional odontoblasts, apical closure.[14]
Pig	4–12 weeks	Full pulp regeneration, angiogenesis, tubular dentin, imaging-confirmed integration.[14]

While each model offers unique advantages, canine and swine studies are more reflective of human clinical conditions due to similarities in root canal anatomy, pulp volume, and healing responses.[13,14]

6. Clinical Findings and Early Human Trials

Clinical application remains limited but promising. A few case reports and early-phase human trials have reported positive outcomes in terms of pulp vitality, apical closure, and radiographic evidence of tissue regeneration using DPSCs and growth factor-enhanced scaffolds.[13] However, ethical limitations around histological validation and variability in treatment protocols still limit widespread clinical adoption.

7. Discussion

7.1. Dental pulp stem cells: Current challenges and future potential

Dental pulp stem cells (DPSCs) hold significant promise in regenerative medicine, particularly for dentin-pulp complex regeneration, owing to their robust proliferative capacity and ability to differentiate into multiple cell lineages. Derived from the pulp tissue of permanent or primary teeth, DPSCs can give rise to various cell types, including odontoblasts, osteoblasts, and cells exhibiting neuronal characteristics.[15,16] Although dental pulp stem cells (DPSCs) possess considerable therapeutic potential, there remain substantial barriers to their broad clinical application. These obstacles include inconsistencies in cell isolation, the limited survival of cells after transplantation, issues related to immunogenicity, the absence of standardized protocols, and complex regulatory requirements.[15,16]

7.2. Variability in isolation, expansion, and stemness potential

The functional quality of dental pulp stem cells (DPSCs) remains highly sensitive to methods of isolation and expansion, with numerous variables impacting both yield and consistency. Donor age, for example, is a significant determinant: DPSCs obtained from younger individuals—especially those sourced from exfoliated deciduous teeth (SHED) consistently demonstrate superior proliferation and differentiation abilities compared to cells derived from permanent teeth or older donors. As donor age increases, the regenerative capacity of DPSCs demonstrably declines.[17,18] Additionally, the health status of the dental pulp at extraction is critical. DPSCs originating from inflamed or infected pulp tissue exhibit compromised viability, reduced differentiation, and altered immunomodulatory functions, which collectively diminish their suitability for clinical use.[19]

An additional challenge appears during in vitro expansion. Repeated passaging and extended culture periods may lead to cellular senescence, morphological alterations, reduced proliferation, and even genetic instability.[16] These issues raise important concerns regarding the safety and therapeutic efficacy of DPSCs. Therefore, the clinical utility of DPSCs is closely tied to careful selection of donor age, tooth condition, and optimization of culture protocols, since each of these parameters substantially affects the quality of the resulting stem cell populations.[16]

7.3.2. Post-transplantation survival and functional integration

Following transplantation, DPSCs face considerable obstacles to survival and functional integration.[21] The post-

transplant microenvironment is often hypoxic and characterized by elevated oxidative stress, both of which threaten cell viability and may induce apoptosis. To address this, approaches such as preconditioning cells under hypoxia or supplementing with specific growth factors have been investigated to enhance resilience and post-transplant survival.[21]

Inadequate vascularization of regenerated tissues further limits successful outcomes. Effective tissue regeneration depends on neovascularization, which provides essential oxygen and nutrients to transplanted cells.[22] Without sufficient vascular integration, tissue necrosis or incomplete regeneration may result. Accordingly, angiogenic growth factors particularly vascular endothelial growth factor (VEGF) are being explored to promote neovascularization and improve DPSC survival after transplantation. While DPSCs hold significant potential for regenerative therapies, substantial further research is necessary to overcome these biological and technical challenges and enable reliable clinical application.[23]

7.3.3. Immunogenicity and safety concerns

Finally, concerning immunogenicity and safety, DPSCs are often described as "immune-privileged" due to their low expression of MHC class II molecules. This characteristic is generally advantageous, as it may reduce the risk of immune rejection following transplantation. Nevertheless, ongoing vigilance regarding safety and immunological compatibility remains essential for clinical translation.[24] Nevertheless, this status is not absolute; chronic inflammatory environments can significantly upregulate MHC expression in DPSCs, thereby heightening the risk of immune rejection particularly in allogeneic transplantation contexts. This dynamic complicates their clinical utility and underscores the need for careful immunological assessment.[25]

Additionally, there remains a significant safety concern tied to DPSC-based therapies: the risk of uncontrolled differentiation or tumorigenesis. Extensive in vitro expansion of these cells may lead to chromosomal instability and genetic mutations, both of which could increase the likelihood of tumor formation post-transplantation.[26] Therefore, rigorous preclinical and in vivo investigations are essential to fully assess the safety profile of these cells before considering clinical use. Ultimately, comprehensive testing is imperative to ensure that new therapeutic risks are not inadvertently introduced.[26]

8. Lack of Standardized Protocols and Regulatory Barriers

A major obstacle to moving DPSCs (dental pulp stem cells) into clinical use is the lack of standardized methods for isolating, culturing, and cryopreserving the cells. At this point, protocols are all over the place labs differ on everything from what's in the culture media to which growth factors they add, and even how they handle the cells.[18] This inconsistency makes it tough to predict the quality of the cells or how well therapies will work. Cryopreservation is a particular sticking point; after thawing, the viability and function of DPSCs can fluctuate a lot depending on the technique used, which really underscores the need for better, agreed-upon protocols.[27]

In addition to these technical issues, regulatory barriers remain a major concern. DPSC-based therapies aren't yet widely approved, in large part because navigating the complex, demanding regulatory environments is a challenge. Rules about stem cell products can differ by country, making approval a moving target.[28] Plus, the strict need for Good Manufacturing Practice (GMP) compliance adds even more time and cost to the process. Taken together, these factors continue to slow down the translation of DPSC therapies into mainstream clinical practice.[28]

9. Future Directions and Potential Solutions

Recent advancements in gene-editing technologies, such as CRISPR-Cas9, offer potential solutions to enhance the regenerative capacity of DPSCs by modulating key signaling pathways involved in differentiation and immune regulation.[29] The development of advanced biomaterial scaffolds that mimic the natural extracellular matrix can improve DPSC transplantation outcomes. Hydrogels, nanofiber scaffolds, and 3D-printed biomaterials are being explored to enhance cell survival, differentiation, and tissue integration.[30] Preconditioning DPSCs with growth factors, hypoxia exposure, or small molecules has been shown to improve their survival, differentiation potential, and immunomodulatory properties, making them more suitable for clinical applications.[21]

10. Future Directions & Emerging Trends

The field of dental stem cells & regenerative medicine is rapidly growing and it has a great potential to both dental & medical applications on a broader scale. Day by Day as more researches are being conducted, we have a lot of promising directions & trends which are emerging in Dental Stem Cells & Regenerative Medicine like Personalized Regenerative Therapies, Expansion of Dental Stem Cells Banking, Bioengineering Whole Tooth Regeneration, Integration with 3D Bioprinting & Scaffold Design, Neural and Bone Regeneration Beyond Dentistry, Immunomodulation & Anti-inflammatory Properties, Clinical Trials & Regulatory Advances, Organoid Development & Disease Modelling.[31]

It has been observed that when CRISPR-Cas9 & other gene editing technologies are integrated into dental pulp stem cells have shown a great advancement in regenerative dentistry.[31] The best thing about these tools is that they are precise, not very expensive & are very efficient in modification of genetic makeup of DPSCs providing great potential to be used in therapeutic applications & disease

modelling such as Correction of Genetic Disorders, the Enhancement of Regenerative Capacity, Resistance to Inflammation and Apoptosis, Disease Modelling.[31] 3D Bioprinting represents a great advancement in regenerative medicine, It's an emerging technique that makes it possible to create complex 3D Structures which incorporate living cells. it helps to create biomimetic pulp tissue constructs using dental pulp stem cells.[32] This latest advancement in technology holds a promise of changing traditional endodontic treatments by offering biologically functional alternatives to Root Canal therapy.[32]

Exosomes have shown a great potiential in promotion of tissue repair & regeneration. They are basically very tiny size extracellular vesicles which are secreted by stem cells , it also include dental stem cells as well which serve as string mediators of intercellular communication by transporting protiens, lipids, and nucliec acid such as mRNAs.[33] They help in promotion of Pulp and Dentin Regeneration, they provide cell free alternative to stem cell therapy, they help in immuno-modulation and have anti-inflammatory effects, due to their natural biocompatibility & ability to cross biological barriers, exosomes are being explored as delivery vehicle for targeted gene therapy or controlled drug release in dental applications.[33] Its an emerging concept in field of dentistry, It involves several approaches that can be helpful for regeneration in endodontics such as Derving Patient own Stem cells for Autologous Therapies, Genomic & Biomarker Based Treatment Planning can be done, Customized Scaffold & Biomaterial Design, Immune Profiling and Personalized Immune Modulation, Microbiome-Driven Regenerative Strategies, AI Artificial Intelligence & Predictive Modelling.[34]

11. Ethical Consideration

The ethical landscape of embryonic stem cell research is, frankly, fraught with complexity. At its core, the issue revolves around the use of human embryos at the blastula stage essentially, the very beginning of human development[35] On the scientific front, embryonic stem cells (ESCs) offer remarkable promise for addressing a wide array of diseases and injuries, given their ability to differentiate into virtually any cell type. Yet, this potential comes tethered to profound moral concerns.[36] One of the central debates centers on the source of these stem cells. Extracting them typically requires the destruction of embryos, which many individuals equate with ending a human life. Some ethicists and members of the public insist that human life—and, by extension, full moral status begins at fertilization. From this perspective, using ESCs in research is morally unacceptable. On the other hand, others argue that a blastula does not constitute a person and, therefore, its use in research is ethically permissible especially when weighed against the potential to alleviate human suffering.[35,36,38]

Further complicating the issue are fears about possible misuse, such as the creation of genetically modified humans or the exacerbation of social inequities in access to advanced treatments.[39] Additionally, stem cell therapies are still relatively novel, and questions remain regarding their safety and effectiveness. The commercialization of stem cell research introduces further ethical dilemmas, particularly concerning the risk of profit-driven exploitation.[40] It is also worth noting that many embryos used in research are created in laboratory settings, which raises additional questions about the acceptability of creating human life specifically for scientific purposes. Ultimately, the debate over embryonic stem cell research reflects enduring disagreements about the moral status of the early embryo and the appropriate boundaries of scientific inquiry.[41]

12. Conclusion

Dental pulp stem cells (DPSCs) have emerged as a particularly promising and accessible source within the broader field of mesenchymal stem cells, demonstrating notable regenerative capacity. These cells, derived from the neuroectoderm, exhibit robust proliferative abilities and have been shown to differentiate into multiple cell types, including odontoblasts, osteoblasts, chondrocytes, adipocytes, and neurogenic lineages. Their application in regenerative endodontics is of significant interest; preclinical studies indicate that DPSCs, when combined with biomaterial scaffolds and appropriate signaling molecules such as BMPs, TGF-β1, and VEGF, can facilitate the regeneration of vascularized pulp-like tissue and functional dentin-pulp complexes. In fact, DPSCs frequently demonstrate superior odontogenic differentiation and mineralization relative to other mesenchymal stem cell sources, such as those from bone marrow.

Despite these advantages, several substantial challenges remain before DPSCs can be widely adopted in clinical practice. Key obstacles include significant donor variability (influenced by factors such as age, tooth type, and pulp health), limited cell survival following transplantation into hypoxic environments, the absence of standardized protocols for cell isolation and cryopreservation, and complex regulatory pathways. Additionally, prolonged in vitro expansion carries risks—including genetic instability and diminished cellular potency—which necessitate rigorous long-term safety assessments.

Ethical concerns, which often complicate stem cell research, are less pronounced with DPSCs, as they are sourced from non-viable (extracted) teeth and thus do not involve the same controversies as embryonic stem cells. As advances in biomaterials, gene editing, and delivery mechanisms continue to progress, DPSCs hold considerable potential not only for endodontic therapy but also in the fields of neurology, orthopedics, and systemic regenerative medicine. Realizing this potential, however, will require coordinated efforts to standardize methodologies, ensure long-term safety, and address regulatory challenges associated with clinical application.

13. Abbreviations

ALP: Alkaline Phosphatase, ASCs: Adult Stem Cells, DMP-1: Dentin Matrix Protein-1, DPSCs: Dental Pulp Stem Cells, dECM: Decellularized Extracellular Matrix, DSPP: Dentin Sialophosphoprotein, ECM: Extracellular Matrix, BMMSCs: Bone Marrow Mesenchymal Stem Cells, BMPs: Bone Morphogenetic Proteins, TGF-β1: Transforming Growth Factor-beta 1, VEGF: Vascular Endothelial Growth Factor, HA-TCP: Hydroxyapatite-Tricalcium Phosphate, MSCs: Mesenchymal Stem Cells, hDPSCs: Human Dental Pulp Stem Cells.

14. Source of Funding

None.

15. Conflict of Interest

None.

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