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Dental Stem Cells: A Gateway to Regenerative Dentistry and Medicine

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Abstract

Dental stem cells (DSCs) have emerged as a pivotal resource in the evolving fields of regenerative medicine and dentistry, owing to their accessibility, ethical acceptability, and multipotent to pluripotent capabilities. Sourced primarily from dental pulp, exfoliated deciduous teeth, and periodontal tissues, DSCs demonstrate robust potential to differentiate into various cell lineages, including osteoblasts, neurons, hepatocytes, insulin-producing cells, and cardiomyocytes. This review explores the origin, classification, and biological properties of embryonic, fetal, and adult stem cells, with a dedicated focus on DSCs. It discusses the current and potential therapeutic applications of DSCs in treating neurological disorders, cardiovascular diseases, diabetes, liver conditions, ocular defects, and bone regeneration. The manuscript also emphasizes the significance of DSC banking, technological advances in their isolation and application, and the molecular mechanisms underpinning their regenerative capacity. By integrating recent findings and clinical insights, the study underscores DSCs as a promising, minimally invasive, and patient-specific tool for future personalized regenerative therapies.

Keywords: dental stem cells, regenerative dentistry, regenerative medicine, stem cell banking, stem cell therapy

Introduction

Stem cells are a unique group of undifferentiated cells possessing the ability to self-renew and differentiate into specialized cell types, playing a vital role in tissue homeostasis and repair. These cells form the biological foundation for regenerative medicine due to their capacity to restore or replace damaged tissues. The concept of stem cells was first introduced in the late 19th century by German biologist Ernst Haeckel, and further established when Alexander Maximow, in 1909, proposed the existence of a common precursor for blood cells–paving the way for modern stem cell biology.[1]

Stem cells are broadly classified based on origin (Embryonic Stem Cells (ESCs), Fetal and Extra-Embryonic Stem Cells, Adult stem cells) and potency (Totipotent, Pluripotent, Multipotent and Unipotent) (Figure 1). By origin, they include ESCs, derived from the inner cell mass of the blastocyst during early embryonic development, are pluripotent cells capable of differentiating into all three germ layers, ectoderm, mesoderm, and endoderm except for placenta and umbilical cord tissues. They possess unique properties such as indefinite self-renewal, high proliferative capacity due to a shortened G1 phase, and the potential to form diverse cell types, making them valuable in regenerative medicine, tissue replacement, and research on development and diseases. However, their use is limited by ethical concerns surrounding embryo destruction, the risk of immune rejection, limited functional integration in tissues like the heart, and the potential formation of tumor such as teratocarcinomas, raising significant safety and ethical considerations for clinical application.[2]

Fetal stem cells, the third major stem cell class, originate from the fetus proper and extra-embryonic structures such as the placenta, amniotic fluid, amniotic membrane, and Wharton's jelly. These perinatal tissues, often discarded after birth, are rich sources of various stem cells, including hematopoietic stem cells (HSCs) and mesenchymal stromal cells (MSCs). Fetal stem cells are characterized by high plasticity, survival in low oxygen environments, and secretion of angiogenic and trophic factors that promote tissue regeneration. Extraembryonic stem cells, in particular, offer ethical and practical advantages due to their non-invasive sourcing and lower immunogenicity, making them attractive for therapeutic use. However, their limited differentiation potential, lower proliferative capacity, and the need for further research on their applications restrict their current clinical utility.[3] (Table 1)

Adult stem cells, derived from adult tissue. Also known as somatic stem cells or resident stem cells. The adult stem cells have the ability to self-renew themselves, and can be differentiated into a limited number of mature cell types.[4] Adult stem cells include: hematopoietic stem cells, epidermal stem cells, adipose stem cells, neural stem cells, limbal stem cells and hepatic stem cells and mesenchymal stem cells, including dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHED), periodontal ligament stem cells (PDLSCs), and stem cells from apical papilla (SCAPs) and are widely used in therapeutic applications due to lower ethical concerns and immune compatibility.[5]

Since adult stem cells are multipotent cells they are reprogrammed to acquire pluripotent state, the stem cells formed are called Induced Pluripotent Stem Cells (iPSCs). these cells were similar to human ESCs and they could differentiate into cell types of the 3 germ layers *in vitro*.[7] and are a powerful tool in personalized regenerative therapies, albeit with ongoing concerns about genomic instability and tumor risk.[6]

In terms of potency, stem cells may be Totipotent, can differentiate into both embryonic and extraembryonic tissues (e.g., zygote). Pluripotent, can form all cells of the three germ layers (e.g., ESCs, iPSCs). Multipotent, limited to cell types within a lineage (e.g., MSCs, HSCs) and Unipotent, which can generate one cell type (e.g., skin stem cells), with self-renewal ability.[7]

The advent of regenerative medicine has ushered in a transformative era for tissue repair and organ replacement, with stem cells at its core. Among the various sources of stem cells, DSC have garnered increasing attention due to their non-invasive harvesting, immunomodulatory functions, and multilineage differentiation potential, especially for craniofacial, neurological, and orthopaedic regeneration.[8] Compared to other MSC sources such as bone marrow or adipose tissue, dental stem cells are younger in origin, exhibit higher proliferative rates, and retain epigenetic plasticity that enhances their regenerative utility.[9]

Emerging research also highlights the feasibility of using DSC in neurodegenerative diseases, such as Parkinson's and Alzheimer's, due to their neurotrophic

factor secretion and differentiation into functional neurons *in vitro* and *in vivo*.[5] Moreover, ongoing developments in biomaterials, scaffolding, and 3D bioprinting are accelerating the clinical translation of DSC based therapies.[10] As DSC bridge the interface between dental practice and advanced cell-based therapies, they represent a strategic, ethical, and scalable solution for personalized regenerative applications. This review presents DSCs as a promising avenue for future personalized regenerative medicine.

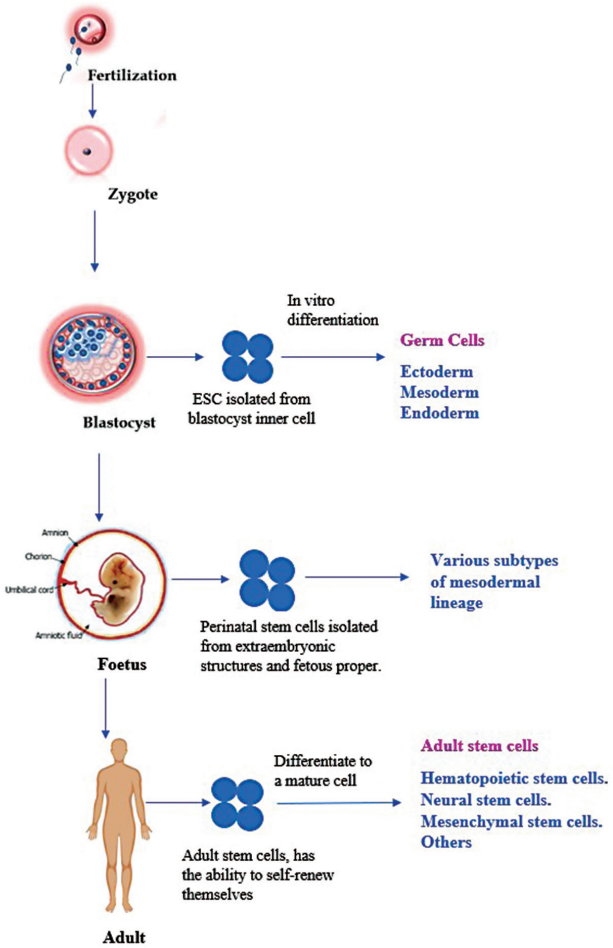

Figure 1: Origin of stem cells.

Dental stem cells

Unlike bones, human teeth have very limited ability to heal or regenerate after injury or disease. Enamel, the outermost layer of the tooth, is acellular and cannot regenerate. However, other dental tissues like dentin, pulp, cementum, and periodontal ligament have some regenerative capacity, depending on conditions.[11]

DSC are a type of adult stem cell found in various parts of the tooth. They can be easily collected from extracted teeth or naturally shedding baby teeth, making them a convenient and minimally invasive source. They are less likely to cause immune reactions or tumors compared to ESCs.[12] Interestingly, stem cells can also be isolated from inflamed or diseased teeth, and these still retain similar regenerative abilities as those from healthy teeth. This suggests that even damaged teeth can be a valuable source of stem cells.[13-15]

DSCs are derived from ectomesenchyme (a mix of ectoderm and mesoderm origin), giving them the ability to form both epithelial (like enamel-producing ameloblasts) and mesenchymal cells (like dentin-producing odontoblasts, cementoblasts, and bone-forming osteoblasts). This dual potential makes them especially useful for full tooth regeneration or repair in the future.[16]

Although dental tissues such as exfoliated deciduous teeth, impacted third molars, and orthodontically extracted premolars are widely recognized as rich sources of MSCs, it must be emphasized that the harvested cellular populations from these tissues are inherently heterogeneous and do not exclusively comprise stem cells.[17] These tissues contain a mixture of various cell types including fibroblasts, endothelial cells, immune cells, and progenitor cells, necessitating rigorous methodologies to isolate and characterize the true stem cell fraction.[18]

Table 1: Stem cells isolated from extra embryonic structures.

Extra embryonic structures	Stem cells
Amniotic membrane	Amniotic epithelial stem cells Amniotic mesenchymal stem cells Amnion-derived stem cells
Amniotic fluid	Amniotic fluid mesenchymal stem cells Amniotic fluid derived - stem cells
Wharton's jelly	Umbilical cord matrix mesenchymal stem cells
Placenta	Placenta derived stem cells

To accurately identify MSCs within these mixed populations, standard protocols typically begin with enzymatic digestion, such as collagenase and dispase treatment, followed by *in vitro* culture under MSC-supportive media.[19] Following isolation, surface marker profiling remains a critical step, with cells required to express positive markers like CD73, CD90, and CD105 while lacking hematopoietic markers such as CD34 and CD45, in accordance with the International Society for Cellular Therapy (ISCT) criteria.[20] Additional validation involves functional assays including colony-forming unit fibroblast (CFU-F) assays, trilineage differentiation into osteogenic, adipogenic, and chondrogenic lineages, and assessments of proliferation and immunomodulatory capacity.[21,22] Only cell populations meeting these phenotypic and functional benchmarks should be classified as dental MSCs or dental stem cells.[23]

Classification of dental stem cells

To date, seven distinct types of human dental stem or progenitor cells have been isolated and characterized, including DPSCs[11], SHED[24], PDLSCs[25], dental follicle progenitor cells (DFPCs)[26], and SCAP.[27] Among these, PDLSCs and DFPCs are classified as periodontium-related stem cells[28], while DPSCs, SHED, and SCAP are considered dental pulp-related stem cells. In addition, subsequent research has identified other DSCs, such as human natal dental pulp stem cells (NDP-SCs) [29] and gingival mesenchymal stem cells (GMSCs).[30] (Figure 2)

Dental pulp stem cells

DPSCs, first identified in 2000 by Gronthos *et al*., are a type of adult MSC found in the pulp tissue of permanent teeth.[11] They possess high self-renewal capacity and can differentiate into multiple cell types including odontoblasts, osteoblasts, neurons, adipocytes, chondrocytes, myocytes, and even melanocytes. DPSCs are easily accessible from extracted teeth and even from inflamed pulp tissues, making them a convenient and promising source for regenerative therapies.[31] They can be isolated using either enzymatic digestion or a simple outgrowth method, and they retain their regenerative potential even after long-term preservation. To understand and identify these cells, researchers look for specific surface and intracellular markers.

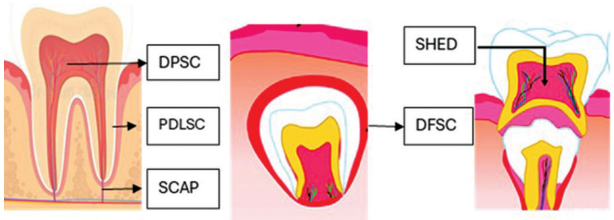

Figure 2: Different DSC types and where they are found in related tissues DPSCs-dental pulp stem cells, PDLSc- periodontital ligament stem cells, SCAP-stem cells from apical papilla, DFSc- dental follicular stem cells, SHED- stem cells from human exfoliated deciduous teeth, are used.

They express classical MSC markers like CD73, CD90, and CD105[32], while lacking hematopoietic markers such as CD34 and CD45.[32] Intracellular pluripotency markers like OCT-4, NANOG, and SOX2 suggest their stemness and multipotent nature.[33] Recent research highlights a regenerative subpopulation marked by CD24a and Sp7 with enhanced dentin-forming ability.[34] Additionally, perivascular markers such as CD146 and NG2 support their role in vascular and neural repair.[35] Upon differentiation, they express markers like ALP, DMP-1, BSP, and OPN, indicating odontogenic and osteogenic potential. These insights affirm DPSCs as a versatile tool for tissue engineering and regenerative dentistry.[36]

Stem cells from human exfoliated deciduous teeth

SHED are a population of highly proliferative, multipotent stem cells derived from the pulp of naturally shed deciduous teeth, first described by Miura *et al*., in 2003.[17] These cells possess the capacity to differentiate into various lineages including odontoblasts, osteoblasts, adipocytes, chondrocytes, neural cells, and hepatocyte-like cells, making them a valuable source for regenerative therapies.[37] SHED is easily accessible during physiological tooth exfoliation, providing a non-invasive and ethically acceptable route for stem cell procurement.[37] Compared to other DSCs, SHED show higher proliferation rates and enhanced telomerase activity, contributing to their superior regenerative potential.[38]

SHED express a typical MSC profile, including surface markers such as CD29, CD44, CD73, CD90, CD105, CD166, and STRO-1, while lacking hematopoietic markers like CD14, CD34, CD45, and HLA-DR.[39,40] They also show expression of pluripotency-associated markers including OCT-4, NANOG, and SSEA-4.[41] Their strong

neurogenic potential is reflected by the spontaneous expression of neural markers such as nestin, βIII-tubulin, SOX1, SOX2, CD271, MAP2, GFAP, CD56, and doublecortin (DCX), even before neurogenic induction.[41,35] Flow cytometric studies indicate consistently high expression rates (70-95%) for CD73, CD90, and CD105, supporting their MSC identity.[41] These findings further validate SHED as a potent source for tissue engineering, particularly in neural and craniofacial applications.

Periodontal ligament stem cells

PDLSCs were first identified by Seo *et al*., in 2004 from the periodontal ligament tissue of extracted human third molars.[18] They are mesenchymal progenitors located in the ligament that connects the tooth root to the alveolar bone. PDLSCs exhibit high clonogenicity, proliferation, and multipotent differentiation into osteoblasts, cementoblasts, chondrocytes, and adipocytes, making them excellent candidates for periodontal and alveolar bone regeneration.[42] They can be non-invasively harvested, cultured, and preserved, offering great potential in regenerative dentistry.

PDLSCs express a standard MSC surface marker profile including CD29, CD44, CD73, CD90, and CD105, along with the perivascular marker CD146, while lacking hematopoietic markers CD34 and CD45.[43] Uniquely, they also express periodontal-specific extracellular matrix proteins like asporin, osteopontin (OPN), and osteocalcin, which are not typically seen in bone marrow or adipose tissue-derived MSCs.[42] These markers support their specialized role in osteogenic and periodontal tissue regeneration.

Dental follicle progenitor cells

DFPCs were first isolated and characterized by Morsczeck *et al*., in 2005 from the dental follicle tissue that surrounds unerupted tooth germs.[19] These progenitor cells are essential precursors for periodontal tissues such as cementum, alveolar bone, and periodontal ligament. DFPCs exhibit fibroblast-like morphology, high migratory capacity, and the ability to differentiate into various lineages, including osteogenic, cementogenic, adipogenic, and neurogenic types–making them promising candidates for periodontal and craniofacial tissue engineering.[43]

Phenotypically, DFPCs express mesenchymal stem cell markers such as CD105, CD44, CD29, CD73, CD90, CD146, STRO-1, Notch1, and HLA-ABC, while lacking hematopoietic and endothelial markers like CD34, CD45, CD14, CD31, and CD117.[44] Their ability to form periodontal tissues has been supported through both *in vitro* and *in vivo* studies, reinforcing their role in tissue regeneration and their relevance in therapeutic applications.[44]

Stem cells from apical papilla

SCAP were first identified by Sonoyama *et al*., in 2006 from the apical tissue of immature permanent teeth.[20] These cells reside in the apical papilla at the root tips of developing teeth and play a crucial role in root maturation and dentinogenesis. Compared to DPSCs, SCAP exhibit faster proliferation, higher colony-forming efficiency, and superior mineralization potential, making them especially valuable for regenerative endodontics and craniofacial tissue engineering.[45]

SCAP express classical mesenchymal stem cell markers such as STRO-1, CD29, CD73, CD90, CD105, CD106, CD146, and CD166, while lacking hematopoietic lineage markers like CD34, CD45, and CD14.[39] A defining feature of SCAP is the expression of CD24, a specific marker not shared with other DSCs, which aids in their identification and confirms their unique lineage commitment. The co-expression of STRO-1 and CD146 is associated with a highly regenerative subpopulation, especially relevant in dental tissue repair.[39]

Human natal dental pulp stem cells

NDP-SCs are derived from the pulp tissue of natal teeth–teeth present at birth or erupting within the first month of life. These cells were first isolated and characterized by Miura *et al*., in 2003, who identified them as a unique subpopulation of MSCs with embryonic-like origin and broad regenerative potential.[22] NDP-SCs exhibit higher proliferative capacity and broader differentiation potential than adult dental stem cells like DPSCs, showing capabilities for osteogenic, adipogenic, chondrogenic, and neurogenic differentiation. Their accessibility at birth and non-invasive collection procedure makes them a promising and ethically favourable source for regenerative medicine and tissue engineering applications.

NDP-SCs express typical MSC markers such as CD73, CD90, and CD105 while lacking hematopoietic markers CD34 and CD45. They also show elevated

expression of pluripotency-associated genes including OCT-4 and NANOG, suggesting more primitive stem-like characteristics compared to DPSCs. Their high proliferation rate, multipotency, and immunomodulatory abilities underscore their potential in bone, neural, and dental tissue regeneration.[46]

Gingiva-derived mesenchymal stem cells

GMSCs were first identified by Zhang *et al*., in 2009 from the lamina propria of gingival tissue.[23] They are easily harvested from healthy or inflamed gingiva, making them highly accessible and minimally invasive for clinical use. GMSCs show robust proliferation, self-renewal, and immunomodulatory properties, which make them suitable for soft tissue regeneration, autoimmune diseases, and even systemic disorders.[47] These cells have demonstrated multilineage differentiation into osteogenic, chondrogenic, adipogenic, and neurogenic cell types, underlining their potential in regenerative medicine and tissue engineering.[47]

GMSCs express common MSC markers such as CD73, CD90, CD105, CD29, and CD44 while lacking hematopoietic markers like CD34 and CD45.[39] They also show elevated levels of CD146 and STRO-1, markers indicative of their perivascular origin. Notably, GMSCs possess unique immunoregulatory capabilities through cytokine release and T-cell suppression, distinguishing them from other oral MSC populations.[39] These traits highlight GMSCs as a promising, practical stem cell source for both dental and systemic therapeutic applications.

Dental stem cells in regenerative dentistry

In regenerative dentistry, DSCs have emerged as a promising therapeutic tool for restoring damaged dental and craniofacial structures. Their ability to differentiate into odontogenic, osteogenic, chondrogenic, and neurogenic lineages underpins their application in regenerative endodontics, periodontal regeneration, craniofacial bone repair, implantology, and experimental tooth regeneration. Preclinical and clinical studies have demonstrated their capacity to promote pulp-dentin complex formation, regenerate functional periodontium, repair critical-size bone defects, and enhance implant osseointegration. These translational advances highlight the growing clinical relevance of DSC-based therapies in modern dental practice.[48] (Table 2)

In pulp–dentin complex regeneration, preclinical and early clinical studies demonstrate that autologous or allogeneic DPSCs, when combined with scaffolds and bioactive factors, can regenerate dentin–pulp-like tissue, restore vascularity, and partially reinstate sensory function. Zhang *et al*.,[49] reported both preclinical and pilot human evidence indicating safety and functional improvement in pulp vitality using DPSC transplantation, highlighting their potential in regenerative endodontic therapies (RETs). Recent systematic reviews (2024-2025) conclude that cell transplantation and cell-homing approaches consistently outperform traditional apexification, though large-scale clinical trials remain limited.[50,51]

In periodontal regeneration, PDLSCs have demonstrated robust potential in restoring periodontal ligament, cementum, and alveolar bone. A 2024 study by You *et al*.,[52] showed that PDLSC injections not only promoted periodontal tissue repair in animal models but also modulated the oral microbiome by increasing beneficial taxa. Scaffold-free, three-dimensional PDLSC pellet constructs have recently been shown to facilitate alveolar ridge preservation and periodontal ligament-like complex formation without the need for synthetic scaffolds, indicating a promising translational strategy.[53] Reviews from 2023-2025 also highlight PDLSC-derived exosomes as a cell-free alternative with significant immunomodulatory and antimicrobial potential.[54]

For alveolar and jaw bone regeneration, systematic reviews of preclinical studies (2025) have found that DPSCs and SHED, combined with scaffolds, significantly enhance bone volume fraction, bone mineral density, and osteogenic marker expression compared to scaffolds alone.[55] In the clinical domain, ongoing randomized controlled trials are evaluating the use of autologous oral-derived MSCs with biomaterials for alveolar ridge augmentation and implant site preparation.[56]

Salivary gland regeneration is another emerging field, particularly for xerostomia secondary to Sjögren's syndrome or radiotherapy. Hu *et al*.,[57] demonstrated that DPSC-derived exosomes could restore salivary flow and glandular function in a NOD mouse model via the GPER-cAMP/PKA/CREB signalling pathway. Recent organoid and 3D bioprinting advances have enabled the creation of salivary tissue biorepositories, with oral-derived progenitors playing a key role in developing implantable salivary units.[58]

Beyond cell-based strategies, cell-free therapies involving DSC-derived exosomes and secretome products have gained traction due to their reduced immunogenicity, ease of storage, and capacity to deliver trophic, angiogenic, and antimicrobial signals. These vesicles have demonstrated efficacy in multiple animal models for pulp regeneration, periodontal healing, and salivary gland rescue, representing a scalable translational approach. Collectively, while DSC-based regenerative dentistry has matured substantially in preclinical research, clinical translation remains at an early stage. The next decade will likely focus on controlled multicentre trials, advanced biomaterial integration, and regulatory pathways to enable routine clinical application.

Dental stem cells in regenerative medicine

The definition of regenerative medicine is an emerging field of multidisciplinary research and clinical applications that focuses on the replacement, repair, or regeneration of tissues, cells, or organs to restore impaired function resulting from any cause, including ageing, disease, trauma, or congenital defects. In 1985, Y.C. Fung, a trailblazer in the fields of biomechanics and bioengineering–which are actually subfields of regenerative medicine–first used the term "tissue engineering." According to Langer and Vacanti (1993), tissue engineering is an interdisciplinary field that uses the concepts of biology and engineering to design biological replacements that preserve, enhance, or restore tissue function. Medical applications involving heart therapies[59], brain tissue regeneration[60], muscular dystrophy therapies[61], bone regeneration[62], and application in liver disease, diabetes mellitus, regenerative ocular therapy are all possible with dental stem cells.[63]

Dental stem cells as a substitute for heart tissue regeneration

DSCs have been identified as a potential option for heart regeneration due to their juvenile nature and inclination towards the cardiac lineage through the PI3-Kinase/Akt signalling pathway. Dental tissues contain stem cells or progenitors that can differentiate into a variety of cell types, including neurons, bone, cartilage, fat, and smooth muscle. They also have a high proliferative capacity and are clonogenic *in vitro*. It may be able to use multipotent stem cells in allogeneic situations because numerous research has shown that these cells are not rejected by the immune system. Furthermore, these amazing cells are readily available in large quantities and require a less intrusive isolation process than bone marrow aspiration.[64]

Medications such as anti-hypertensive or anti-arrhythmias, which primarily function to halt the progression of heart failure, are used as part of current therapy for cardiovascular illnesses. Additional cutting-edge therapies include bypass and stent surgery, which restores blood flow to the heart during ischemia in order to preserve the cardiomyocytes that remain.[65] However, the drawback

Table 2: The main biological properties of DSCs.

No.	Type of DSCs	Location	Differentiation Potential	
			In vitro	*In vivo*
1.	DPSCs	Dental pulp of permanent tooth	Odontogenic, Osteogenic, Neurogenic, Adipogenic, Myogenic, Chondrogenic	Dentin/pulp-like complex
2.	SHED	Dental pulp of deciduous tooth	Odontogenic, Osteogenic, Neurogenic, Adipogenic, Myogenic, Chondrogenic	Dentin formation, new bone formation by recruiting host murine cells
3.	PDLSCs	Periodontal ligament	Osteogenic, Cementogenic, Adipogenic, Chondrogenic, Insulin-producing cells	Cementum/periodontal ligament structure
4.	DFPCs	Dental follicle of developing tooth	Osteogenic, Adipogenic Neurogenic, Chondrogenic	Mineralized tissue structure
5.	SCAP	Apical papilla of developing tooth	Odontogenic, Osteogenic, Adipogenic, Chondrogenic, Neurogenic	Dentin/pulp-like complex
6.	GMSCs	Gingiva	Osteogenic, Adipogenic, Chondrogenic, Neurogenic, Endothelial	Connective-like tissue
7.	NDP-SCs	Dental pulp of newborn	Osteogenic, Adipogenic Chondrogenic, Myogenic Neurogenic	Pulp regeneration

of these treatments is that they are intrusive in nature and do not promote tissue regeneration. As a result, the need for innovative therapeutic strategies to lower cardiovascular disease mortality and mobility is critical. In this case, cell replacement therapy appears to be a viable option for heart repair. Moreover, a number of studies have revealed that adult cardiomyocytes are produced throughout life[66], disproving the long-held belief that the heart is a tissue devoid of the ability to regenerate itself. Nonetheless, compared to epithelial and bone marrow cells (BM), cardiomyocyte production is much lower. This led to an ongoing hunt for a different source of cells with the ability to regenerate cells. Despite genetic modification and ethical debates surrounding their use in therapeutic settings, iPSCs and ESCs have long been regarded as the best options for heart regeneration.[67] Of all the adult/ MSCs, the most research has been done on BM-MSCs. DSCs derived from dental tissue have emerged as a promising option for regenerative medicine. A number of distinct types of DSCs have now been identified in dental origin, including SHED, DPSCs, buccal mucosa, apical papilla and PDLSCs. The discovery of DSCs was initially reported by Gronthos *et al*.[68,69] Compared to isolating BM-MSCs, obtaining these cells is less invasive, simpler, and ethically acceptable. DSCs have been shown to differentiate into odontoblast/osteoblast-like cells[70], also differentiate into functional active neurons, mature melanocytes[71,72], smooth muscle cells[73], islet-like aggregates[74], and hepatic cells[75] in addition to these other known cell lineages. DSCs' remarkable potential to develop into cardiomyocytes *in vitro* and to stimulate angiogenesis in pre-clinical models[76] has recently been documented.

DSCs, particularly stem cells from SHED, show promising pluripotent capabilities due to the expression of key transcription factors like Oct-4, Sox-2, and Nanog, as well as involvement in key signalling pathways such as Wnt, TGFβ/Activin/Nodal, and BMP. These pathways play significant roles in early development and tooth formation, indicating the primitive nature of DSCs and their ease of reprogramming into iPSCs. Additionally, components like C-kit+ cells in DPSCs hint at their potential for lineage-specific applications. The PI3K-Akt signalling pathway, known for regulating cell survival, proliferation, and angiogenesis, also appears critical in guiding DSCs toward cardiomyocyte differentiation. Studies have shown that hypoxia can enhance the angiogenic capacity of DPSCs, and their intramyocardial injection in animal models improved cardiac function, likely due to angiogenesis. Furthermore, the expression of cardio genesis related genes like HAND2, GATA6, and KDR in DSCs supports their potential for cardiac regeneration, highlighting their promise as a therapeutic tool for myocardial repair. (Figure 3)

Dental stem cells as a substitute for brain tissue regeneration

DPSCs are derived from the cranial neural crest and exhibit neural traits such neurotrophin expression.[77] The diffusible peptides secreted by neurons and neuron-supporting cells (DPSCs) function as growth factors for the development, maintenance, repair, and survival of specific neuronal populations. Specifically, it has been demonstrated that neurons in the central nervous system

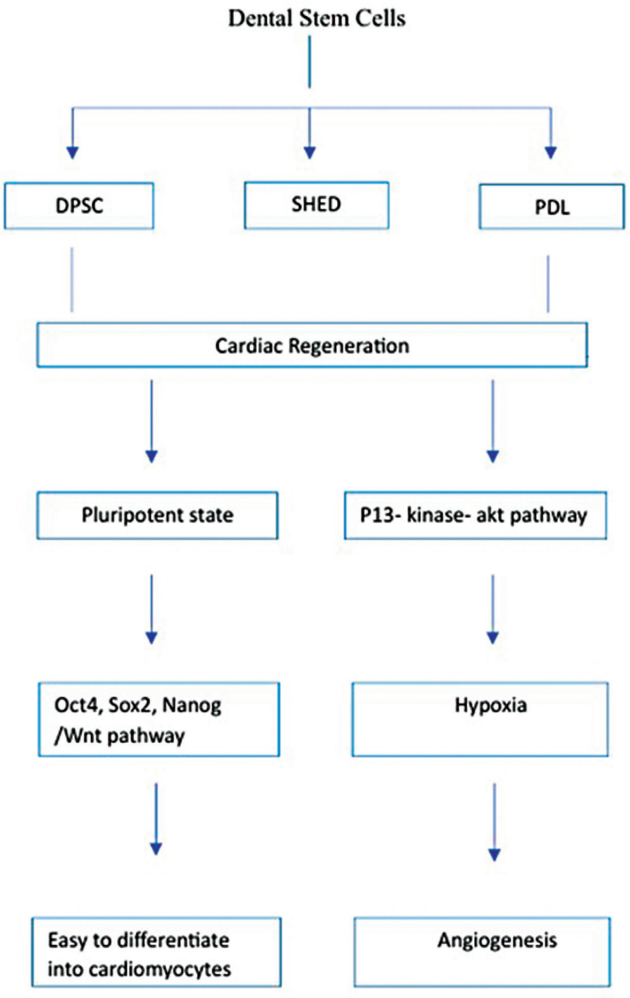

Figure 3: Diagram showing the possible therapeutic benefits of stem cells from human teeth on myocardial infarction.

(CNS), including motor neurons and dopaminergic neurons of the substantia nigra, are significantly influenced by brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and glial-cell-derived neurotrophic factor (GDNF) produced by DPSCs.[78] DPSCs have the power to affect the natural recruitment of neural stem cells and the development of neurospheres.[79] As a result, DPSCs could be a useful source for neurological diseases cell treatment.[80]

The use of DPSCS and SHEDs in models of spinal cord injury has demonstrated that the microenvironment of transplanted stem cells influences their ability to differentiate; an injured spinal cord has elevated levels of pro-inflammatory mediators that may initiate the differentiation cascade specific to oligodendrocytes. The full transected adult rat spinal cord showed a notable recovery of hind-limb locomotor capabilities upon transplantation of hDPSCs. Neuroregenerative activity were demonstrated by the hDPSCs.[81]

A cerebral artery blockage causes ischemia in a specific area of the central nervous system, which can result in stroke. By transferring differentiated neural stem cells extracted from tooth pulp, motor impairment was ameliorated and the extent of the infarct was decreased. Promising results were found in 86 therapeutic translation studies using DPSCs to treat stroke in a mouse cerebral ischemia model.[82] Porcine CD31/CD146 side population (SP) cell transplantation boosted neuronal regeneration and hastened the ischemic zone's neovascularization. The peri-infarct region was reached by Sugiyama *et al*., 88 transplanted pig CD31/CD146 SP cells, which also secreted neurotrophic factors and encouraged the migration and differentiation of neural progenitor cells in the subventricular zone. Forelimb sensorimotor function in a mouse model of focal cerebral ischemia was significantly improved by intracerebral transplantation of hDPSC. Function improvements seemed to be mediated by paracrine actions that are dependent on DPSC.[82] Following an optic nerve crush injury caused by surgery, the therapeutic advantage of implanting rat DPSCs into the vitreous body of the eye enhanced axon regeneration and neurotrophin-mediated survival of rat ganglion cells.[83]

A neurodegenerative condition known as Parkinson's disease is typified by the progressive loss of substantia nigra dopaminergic neurons, which causes a localised decrease in striatal dopamine (DA) levels. Using an indirect co-culture approach with mesencephalic cell cultures, Nesti *et al*.,[84] examined the neuroprotective effects of DPSC against MPP+ and rotenone in an *in vitro* model of Parkinson's disease. They discovered that the co-culture with DPSCs greatly reduced the toxicity caused by MPP+ or rotenone. This was likely due to the neuroprotection provided by soluble factors like NGF and BDNF that are released by DPSC. Therefore, it is possible to consider DPSC as a potential subject for research on cell-based therapy in neurodegenerative diseases.

In a rat model of spinal cord injury, DPSC showed that dental pulp-derived cell transplantation increased the survival of injured motor neurons. Neurotrophic factors, including as NGF, GDNF, and BDNF, were generated and secreted by DPSC from rats and humans, and these helped dopaminergic and sensory neurons survive. Ninety DPSC showed neuroprotective effects in *in vitro* models of Parkinson's and Alzheimer's disease. The capacity to generate and release growth factors is crucial because these factors have the power to stimulate endogenous cell types to differentiate into the specific cell types needed at the site of injury or to secrete additional neurotrophic factors from those cells in order to promote tissue regeneration. When DPSC were loaded onto poly(dl-lactic-co-glycolic acid) (PLGA) collagen and the scaffold was inserted in a model of facial nerve injury, the system allowed the reconnection of damaged axons, demonstrating its applicability also at the peripheral nervous system level for nerve injury treatment.[85]

Dental stem cells as a substitute for bone regeneration

The differentiation profiles exhibited by DPSCs resembled those observed during bone development, which makes them an intriguing model to investigate osteogenesis and the connection to scaffolds. Both *in vitro* and *in vivo*, the osteogenic differentiation capacity of DPSC has been amply proven, as evidenced by the expression of markers unique to bone within freshly produced bone and strong ALP results.[86] Immobilisation led to increased mineralization, protein secretion, and an upregulated osteo-related gene profile. Interestingly, immobilisation also caused DPSC to differentiate into osteogenic tissues without the need for induction agents in the medium.

When DPSCs were inserted into the granular depro-

teinized bovine bone (GDPB) scaffold, there was a propensity to raise the bone mineral density. In a rat calvarial critical defect model, Rat DPSCs was used in conjunction with a GDPB or beta tricalcium phosphate (βTCP) scaffold. GDPB bone scaffolds combined with DPSC demonstrated the ability to improve the process of bone regeneration when it comes to reconstructing calvarial lesions.[87] DFSCs from impacted teeth were utilised by Lucaciu *et al*.[87] To enhance bone regeneration on titanium implant surfaces. They came to the conclusion that DFSCs might be utilised to enhance bone regeneration on titanium implant surfaces after observing a spontaneous predisposition for osteogenic differentiation. DPSCs were also applied in a rat calvarial critical-sized defect model by Maraldi *et al*.[88] After eight weeks, hDPSC-seeded collagen sponges demonstrated nearly complete defect bridging. For cell treatments and regenerative medicine to be used clinically, regulation of DPSC differentiation is essential. To do this, biomaterials' topographical designs may be enhanced. The relationship between changes in pillar topography and the surface topographical parameters during DPSC attachment, morphology, proliferation, and osteogenic differentiation demonstrated increased mineralization. The results of the *in vitro* and *in vivo* investigations indicated that there is a lot of promise for the clinical use of DPSC added to scaffolds in bone restoration.[88]

Dental stem cells application for liver diseases

A permanent fibrotic alteration of the liver, liver cirrhosis can have major side effects include portal hypertension, hepatocellular cancer, and decreased liver function. The only way to stop cirrhosis from taking a more severe clinical course is still through liver transplantation. As innovative therapeutic alternatives to whole organ allografts, cell-based therapies have gained interest. SHED is a viable cell source for MSC-based therapy for patients with liver failure, both paediatric and adult. Third-molar stem cells were cultured into hepatocytes and avoided liver fibrosis and elevated albumin and bilirubin levels in an animal model of liver illness. Melatonin modulates the BMP, p38, ERK, and NF-kB pathways to enhance the hepatic development of hDPSC, as revealed by Cho *et al*.[89] Thus, they came to the conclusion that treating liver cirrhosis with melatonin and transplanted hDPSCs would be a feasible strategy.[89]

Dental stem cells application for diabetes mellitus

Diabetes is characterised by persistent hyperglycaemia, which is caused by either impaired sensitivity to insulin or autoimmune destruction of pancreatic β-cells. An alternative to the standard insulin-based therapy for diabetes may be the use of differentiated stem cells or islet transplantation to replace the lost insulin-producing cells. It has been revealed that DPSC have the capacity to develop into pancreatic cell lineages that resemble islet-like cell aggregates. According to Carnevale *et al*., insulin, pancreatic, and duodenal homeobox-1 genes are expressed by hDPSCs in response to suitable stimuli, which are linked to pancreatic β-cell formation and function. In diabetic mice, islet-like cell clusters (ICCs) generated from hDPSC and SHED were transplanted, as shown by Kanafi *et al*.[90] In experimentally diabetic mice, they observed the restoration of hyperglycaemia to the normal level. These findings raised the possibility of using dental pulp to treat diabetic patients using autologous stem cells.[90]

Dental stem cells as a substitute for regenerative ocular therapy

DSC has been effectively evaluated in corneal blindness as an autologous stem cell source. Due to the comparable embryonic origins of the cornea and DPSC, the latter successfully developed into keratocytes *in vitro*, producing a tissue-engineered corneal stromal-like tissue construct and functioning as keratocytes *in vivo* without causing overt rejection. In mouse corneal stroma, DPSC cultivated on aligned nanofiber substrate-generated tissue-engineered, stromal-like constructions recapitulated the original stromal tissue's tightly packed, aligned, parallel fibrillar collagen. These results show promise for the therapeutic use of DPSC in tissue engineering or cellular treatments for corneal stromal blindness. SHED have been found in studies to have promising effects when used for corneal epithelial regeneration. In rabbit models with complete limbal stem cell deficit, the introduction of cell sheets made of SHED, both with and without the inclusion of amniotic membrane, led to the regeneration of the corneal epithelium. SHED also express markers that are similar to those of corneal limbal stem cells. Retinal cell differentiation was observed in stem cells isolated from the periodontal ligament upon suppression of Wing-

less- related integration site (Wnt) and bone morphogenetic protein signalling, according to Huang *et al*. Third-molar-derived adult DPSCs possess the ability to develop into keratocytes, which are corneal stoma cells. Following *in vitro* differentiation, DPSC produced keratocyte-specific molecules, including keratocan and keratan sulphate proteoglycans, at both the gene and protein levels. After optic nerve damage in mice, intravitreal DPSC transplantation significantly increased neurotrophin-mediated retinal ganglion cell survival and axon regeneration.[91]

Dental stem cells banking

DSC banking requires a standardized workflow comprising donor eligibility screening, aseptic tissue handling, validated isolation/expansion, quality control, cryopreservation, post-thaw assessment, and adherence to regulatory standards (Figure 4). Proper isolation is critical for viability and purity, with methods including enzymatic digestion, explant culture, and magnetic-activated cell sorting (MACS).[92] Advances in cryopreservation media, serum-free systems, and international frameworks are enhancing safety and clinical translation.

In tissue engineering, earlier approaches relied on polymer scaffolds with dissociated tooth germ cells in animal models. Recent strategies combine DSCs with biomaterials and extracellular matrices, providing superior outcomes in dental structure regeneration.[93] Collectively, these advancements emphasize the importance of standardized isolation, storage, and banking protocols to ensure long-term clinical utility of DSCs in regenerative dentistry.

Step 1: Tooth/Tissue collection and transfer

Donor eligibility requires systemic and oral health screening to exclude bacterial or viral infections. Tooth type and developmental stage determine the suitability for banking.

• SHED: Collected from primary incisors/canines with one-third root remaining or early-extracted primary molars; excluded if necrotic, infected, or exfoliated outside clinic.

• DPSCs: Extracted from healthy impacted or orthodontically removed permanent teeth; excluded if necrotic or diseased.

• DFSCs: Obtained from developing tooth organs or impacted teeth without pathology.

• SCAP: Harvested from immature permanent teeth; excluded if roots are complete.

• PDLSCs: Isolated from periodontal ligament of freshly extracted permanent teeth.

Before extraction, antiseptic preparation with chlorhexidine is recommended. During transfer, samples must be kept moist and viable. Transport solutions include PBS, α-MEM with serum, HypoThermosol, or commercial kits, with storage ideally at 4°C. Viable yields are best when processed within 120 hours.[94]

Step 2: Cell isolation and propagation

Upon arrival in a Grade A cleanroom, samples undergo serial disinfection (PBS, povidone-iodine, sodium thiosulfate). Tissue is then dissected: pulp for DPSCs/SHED, follicles for DFSCs, apical papilla for SCAP, and ligament tissue for PDLSCs.

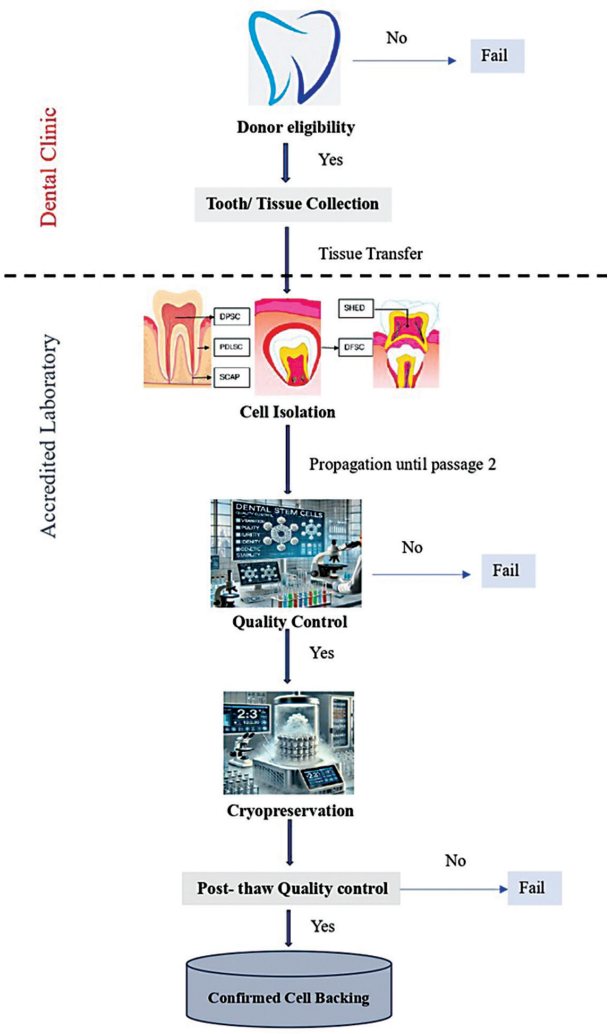

Figure 4: The outlines of dental tissue derived stem cells banking.

Two main methods are used:

• **Explant method:** Favored for clinical translation, as it reduces enzymatic stress and contamination risk.

• **Enzymatic digestion:** Uses collagenase/dispase or trypsin-EDTA for higher single-cell yield.

Cells are expanded in culture media such as α-MEM, DMEM, or DMEM/F12. α-MEM supports superior proliferation and reduced senescence. Serum-free or xeno-free formulations are preferred for clinical use.[95]

Step 3: Quality control and characterization

According to International Society for Cell & Gene Therapy (ISCT) and European Medicines Agency (EMA) guidelines, DSCs must demonstrate:

• Plastic adherence in standard culture.

• Immunophenotype: ≥95% CD105/CD73/CD90; <2% hematopoietic markers (CD45, CD34, CD14, CD19, HLA-DR).

• Trilineage differentiation into osteogenic, chondrogenic, and adipogenic lineages.

Quality control includes:

• **Viability:** ≥80% post-thaw, assessed via trypan blue, mitochondrial assays, or apoptosis markers.

• **Purity:** Sterility testing for bacteria, fungi, mycoplasma, and viral pathogens.

• **Identity:** STR profiling to avoid misidentification.

• **Genetic stability:** G-band karyotyping to confirm chromosomal integrity.[96-99]

Step 4: Cryopreservation

Several factors influence the cryostability of DSCs. The choice of cryoprotectant is critical, with conventional media consisting of 90% fetal bovine serum (FBS) and 10% dimethyl sulfoxide (DMSO). However, due to safety concerns in clinical applications, alternatives such as human serum or serum-free cryoprotectants (e.g., BAMBANKER) are being explored. Controlled cooling rates of approximately −1°C/min, followed by storage at −196°C in liquid nitrogen, are considered optimal to prevent intracellular ice crystal formation and ensure long-term viability. Thawing protocols also play an essential role in reducing cryoinjury. Advanced methods, including serum-free cryoprotectants and vitrification, have been introduced to improve cryostability and enhance the clinical translation of DSC banking.[94]

Studies have demonstrated that DPSCs and SHED retain high viability and multipotency after long-term storage. For instance, Ma *et al*.,[95] reported that DPSCs preserved for up to 24 years in liquid nitrogen maintained >70% viability and osteogenic/adipogenic differentiation potential upon thawing. Similar findings were observed in SHED, where cells cryopreserved for more than a decade showed preserved stemness markers (OCT4, NANOG) and immunomodulatory capacity.[96]

Emerging evidence also highlights the importance of epigenetic stability during long-term storage. A recent study demonstrated that DPSCs retained normal DNA methylation profiles and telomere length after >10 years of cryopreservation, supporting their functional integrity for regenerative therapies.[97] Collectively, these findings confirm that DSCs can be effectively stored long-term with preserved viability, differentiation, and epigenetic stability, strengthening their clinical relevance in regenerative dentistry.

Step 5: Post-thaw quality control

Thawing is usually performed in a 37°C water bath, though dry-heat methods reduce contamination risk. CPA removal must be gradual to reduce cytotoxicity. Post-thaw assessments include viability (>80%), metabolic assays, doubling time, and apoptosis markers, ensuring recovery for therapeutic applications.[98]

Step 6: Standardization and accreditation

DSC banks must comply with ISO 9000, Good Manufacturing Practice (GMP), ICH guidelines (Q7, Q9, Q10), FDA, and WHO regulations. These ensure consistency, sterility, safety, and traceability in therapeutic banking.[99]

Step 7: Documentation

Comprehensive records including donor data, culture history, quality assessments, and cryostorage tracking are mandatory for accreditation and regulatory approval.[99]

Conclusions and Future Directions

Dental stem cells (DSCs) represent a highly versatile, ethically accessible, and clinically promising cell population with demonstrated potential in regenerative dentistry and broad systemic applications. As summarized in this review, DSCs including DPSCs, SHED, PDLSCs, DFPCs, SCAP, NDP-SCs, and GMSCs–exhibit robust proliferative

capacity, multilineage differentiation, immunomodulatory functions, and compatibility with advanced biomaterials. Their translational relevance is increasingly supported by preclinical and early clinical evidence in pulp-dentin regeneration, periodontal repair, craniofacial bone engineering, neuroregeneration, cardiomyocyte induction, liver and pancreatic repair, and ocular therapy. Advances in DSC isolation, characterization, exosome-based therapies, 3D bioprinting, and standardized cryopreservation workflows further strengthen their role as a future cornerstone of personalized regenerative medicine. However, despite significant progress, long-term clinical validation, standardized GMP-grade banking protocols, multicentre clinical trials, and clear regulatory pathways remain essential to ensure safety, reproducibility, and therapeutic efficacy. Future research should therefore focus on large-scale human studies, molecular optimization of DSC differentiation, integration with next-generation scaffolds and organoid systems, and development of cell-free therapeutic platforms to accelerate safe clinical translation of DSC-based therapies.

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