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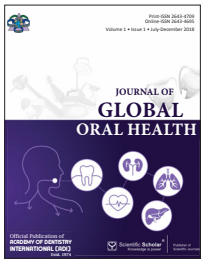

Review Article

Human dental pulp stem cells and its applications in regenerative medicine – A literature review

Saravana Priyan GL, Subachanya Ramalingam, Yogeshwari Udhayakumar

Balaji Dental and Craniofacial Hospital, Chennai, Tamil Nadu, India.

***Corresponding author:**
Dr. Saravana Priyan GL
Balaji Dental and Craniofacial Hospital, No.30, KB Dasan Road, Teynampet,
Chennai- 600 018,
Tamil Nadu, India.

drsaravanapriyangl@gmail.com

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ABSTRACT

Human dental pulp-derived stem cells have varied applications in regenerative medicine. Dental pulp stem cells (DPSCs) are considered to be neural crest cells. They are known to have higher regenerative potential than the bone marrow-derived mesenchymal stem cells. DPSCs have multipotency, immunomodulatory function, and self-renewal capacity. They are highly proliferative, clonogenic and are capable of differentiating into adipocytes, neural cells, odontoblasts, and various other cells. DPSCs are effective for various diseases, such as spinal cord injuries, Parkinson's disease, Alzheimer's disease, cerebral ischemia, myocardial infarction, muscular dystrophy, diabetes, liver diseases, eye diseases, immune diseases, and oral diseases. This article provides an overview of properties and regenerative applications of human DPSCs.

Keywords: Human dental pulp-derived stem cells, Dental pulp stem cells neural crest cells, Regenerative medicine

INTRODUCTION

Stem cells are clonogenic cells capable of self-renewal and multi-lineage differentiation**.** Post-natal stem cells/adult stem cells were first isolated from bone marrow. They were later isolated from the neural tissue, retina, and even the skin.[1] The bone marrow-derived stem cells are most widely researched and utilized in clinical settings.

Dental pulp stem cells (DPSC) were first discovered in the year 2000, from an extracted impacted third molar by Gronthos *et al.*[2] DPSCs are considered to be cranial neural crest cells (CNCCs). A group of NCCs migrate from the neural crest and is temporally formed between ectoderm and neural plate during neural tube formation. They play an important role in embryo development. During the migration, the NCCs translate into mesenchymal cells.

The CNCCs concentrate in facial and pharyngeal arches they form sensory VII, IX, X cranial nerves, thymus, thyroid follicular cells, parathyroid, and cornea. They also form the orofacial mesenchymal organs including facial skeleton such as maxilla, mandible, dentin/pulp complex, cementum, periodontal ligament (PDL), and alveolar bone.[3]

The natural function of DPSCs in the production of odontoblasts to create reparative dentin aids in the regeneration of tooth structures. However, they are also effective in the repair of tissues outside the tooth. The ease of isolation of DPSCs from discarded or removed teeth offers a promising source of autologous cells, and their similarities with bone marrow stromal cells (BMSCs) suggest applications in musculoskeletal regenerative medicine.[4]

DPSCs are effective for various diseases, such as spinal cord injuries (SCIs), Parkinson's disease (PDs), Alzheimer's disease, cerebral ischemia, myocardial infarction, muscular dystrophy, diabetes, liver diseases, eye diseases, immune diseases, and oral diseases.[5]

Other types of human dental pulp-derived stem cells (HDPSCs) include dental pulp of human exfoliated deciduous teeth, root apical papilla of human teeth, and dental pulp of human supernumerary teeth, namely, stem cells from human exfoliated deciduous teeth (SHED), stem cells from apical papilla (SCAP), and human supernumerary tooth-derived stem cells (SNTSCs) were identified in the year 2003, 2006, and 2013 retrospectively [Figure 1]. In addition to this, stem cells can be isolated from various tissues, including oral parts such as alveolar bone, PDL, dental follicle, oral mucosa, and gingival.

Recently, cryopreservation of human cells and tissues is proving to be a reliable and feasible approach for stem cell storage.[6]

PROPERTIES OF HUMAN DENTAL PULP-DERIVED STEM CELLS

The HDPSCs share the common properties of mesenchymal stem cells. They have undifferentiated lineage with long-term self-renewal capacity. They also have the ability to develop into progenitor cells. They can differentiate into mesodermal, ectodermal, endodermal, osteogenic, chondrogenic, and adipogenic lineages.[7]

The properties of HDPSCs include:

Multipotency

Stem cell technology enables to induce HDPSCs into ectodermal lineage cells such as neural cells;[2,8] mesenchymal lineage cells such as odontoblasts, osteoblasts, chondrocytes, adipocytes, and mycocytes;[9] endodermal lineage cells such as vascular endothelial cells,[9] hepatocytes,[10] and pancreatic islet-insulin-producing β cells[11] [Figure 2].

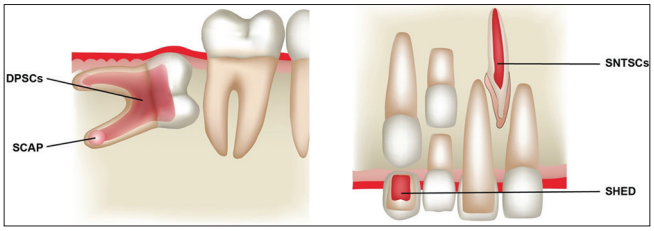

Figure 1: Types of human dental pulp derived stem cells.

High proliferation activity

Population doubling assay shows HDPSCs express higher proliferative ability (3–4 times higher) than human bone marrow-derived mesenchymal stem cells (BMMSCs).[2,8-13] In addition, HDPSCs also express higher telomerase activities.[12,14]

Self-renewal capacity

HDPSCs represent a novel adult stem cell that possesses high proliferative potential with long-term self-renewal capacity.[1,2,8-13]

In vivo tissue regeneration capacity

When HDPSCs are subcutaneously transplanted with hydroxyapatite/tricalcium phosphate (HA/TCP) powders as carrier, into the dorsal surface of immune compromised mice, individual HDPSCs expressed a specific and unique regeneration capability.[2,8-13] DPSCs and SCAP not only regenerate dentin[2,13] but are also able to induce dental-pulp-like tissues containing blood capillary vessels and dense collagen fibers surrounded by the newly formed dentin. Thus, DPSCs and SCAP can reconstruct *de novo* dentin/pulp complex *in vivo,* thereby proving that DPSCs and SCAP are effective cell sources to regenerate dentin/pulp complex structures.

SHED and SNTSCs express a unique *in vivo* bi-potency. *In vivo* transplantation of SHED and SNTSCs with HA/TCP not only form dentin/pulp complex-like structures but also reconstruct bone/bone marrow units. These findings suggest that they might consider a unique cell source to regenerated dentin/pulp complex and bone/bone marrow unit.[8,12]

Colony-forming unit-fibroblasts forming ability

HDPSCs form adherent colonies that consist of spindle-shaped cells, called colony-forming unit-fibroblasts (CFU-F). Amazingly, CFU-F analysis shows that human dental pulp contains abundant MSCs than human bone marrow stem

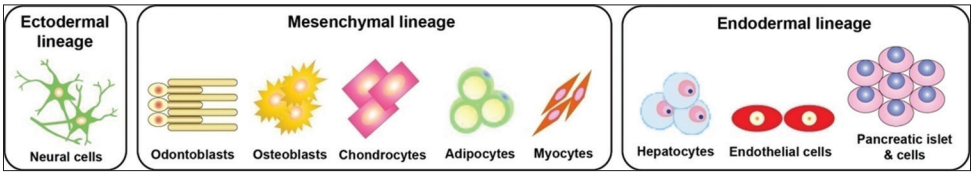

Figure 2: Multilineage differentiation of human dental pup-derived stem cells.

cells. (CFU-F capacity of DPSCs is 5 times higher than human bone marrow-derived MSCs).[2,8-13]

Expression of cell-surface markers

HDPSCs express negative to hematopoietic cell-surface markers including CD34, CD45, and CD14. On the other hand, dental pulp-derived stem cells express positive to STRO-1, CD146 (melanoma cell adhesion molecule), CD105 (endoglin or SH2), and CD73 (5'-nucleotidase [5'-NT] or SH3/4), as well as CD90 (Thy-1) and CD29 (integrin beta-1).[2,8-13] These markers are known as specific markers for MSCs. In addition, HDPSCs express not only markers of embryonic stem cells, stage-specific embryonic antigen-4, Nanog, and Octamer 4, but also markers of NCCs, Nestin, Notch1, and CD271 (p71 neuritrophin receptor or low-affinity nerve growth factor receptor).[12,14] Interestingly, CD24 is expressed only on SCAP among four types of HDPSCs.[13]

Immunomodulation

HDPSCs can affect the immune cells such as T cells directly or indirectly.[15,16] HDPSCs are able to inhibit the proliferation of T cells, downregulate proinflammatory interleukin (IL) 17-secreting helper T cells, and upregulate regulatory T cells.[14,17,18] HDPSCs regulate T cell proliferation through releasing of transforming growth factor-β1 (TGF-β), hepatocyte growth factor, and indoleamine 2, 3-dioxygenase (IDO).[15] HDPSCs express Fas ligand to induce apoptosis of T-cells.[17,18]

APPLICATIONS OF HUMAN DENTAL PULP-DERIVED STEM CELLS

The various applications of HDPSCs based on recent studies with respect to tissue regenerative capacity, multipotency, and immunomodulatory factors [Figure 3].

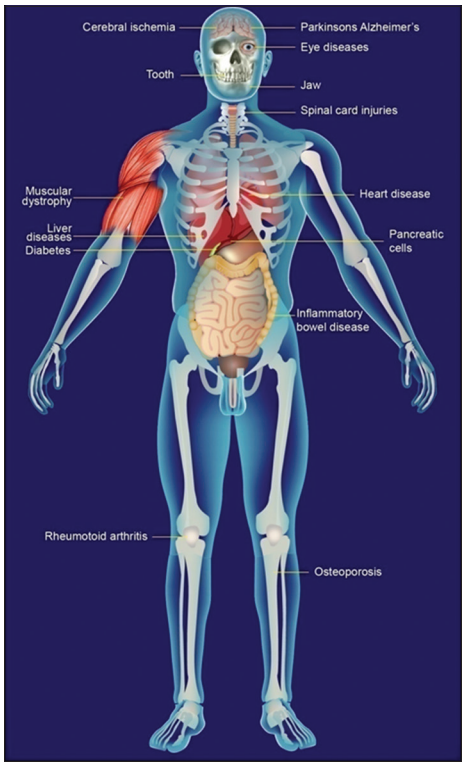

Figure 3: Various applications of human dental pulp-derived stem cells.

Tissue engineering

Regeneration of dentin/pulp complex

The regeneration of dentin pulp complex is based on vascularization. Vascular endothelial growth factor administration promotes vascularization but has a short half-life. This can be increased by binding to heparin.[19] Treating stem cells under hypoxic conditions induce the cells to secrete vascularizing agents.[20] Stem cells differentiate into various types of cells; hence, they have to be controlled using growth factors like soluble protein of the dentin matrix. DPSCs were mixed with a carrier and filled in a root canal treated extracted tooth, and the DPSC filled tooth was transplanted into dorsal surface of immune-compromised mice. Regenerated dentin deposited along to existing dentin and connective tissues beneath the *de novo* dentin contains blood vessels.[21]

Autologous transplantation of DPSCs is clinically tried to regenerate the dentin-pulp complex. Tubular dentin formation was observed when human pulp stem cells with scaffold (HA/tricalcium phosphate) were implanted in immunocompromised mice.[1] Reparative dentin formation on amputated pulp was found when stem cells were combined with recombinant human bone morphogenetic protein 2 in experimental studies on animal models.[22]

Periodontal regeneration

Kawaguchi *et al.* used BMSCs for their ability to produce alveolar bone, PDL, and *in vivo* cementum after implantation into the periodontal defects thereby proving to be an alternative source in the treatment of periodontal diseases.[23,24] Marei *et al.* in their experiment on goat was able to regenerate periodontal tissues around titanium implant using autologous bone marrow stem cells with the scaffold.[25] Transplantation of PDL derived cells into animal models was shown to regenerate periodontal tissue.[26]

Iwata *et al.* harvested and expanded primary canine PDL cells *in vitro* and also made into transplantable constructs containing PGA scaffold and PDL cell sheets. The transplantable constructs in combination with porous

b-tricalcium phosphate induced regeneration of periodontal structures, including alveolar bone, cementum, and periodontal fibers.[27]

Liu *et al*. regenerated periodontal tissue in miniature swine using scaffolds seeded with PDL derived stem cells (PDLSCs).[28] PDLSCs can differentiate into cells that can colonize on the biocompatible scaffold, suggesting an easy and efficient autologous source of stem cells for regeneration of dental tissues.[29]

Root regeneration

SCAP has remarkable cell migration activity; which is considered to involve root growth in tooth development. When SCAP-immersed root-formed HA/TCP carriers were subcutaneously grafted into the dorsal surface of immune-compromised mice, dentin/pulp-complex-like structure is formed in the root-formed carrier. In addition, when a root formed carrier containing SCAPs covered with PDLSC-immersed absorbable gelatin sponge is implanted into a socket of the mandibular bone of a swine, the root-form carrier is reconstructed with newly formed dentin/pulp-complex and is surrounded by regenerated PDL on *de novo* cementum. The regenerated tooth root-like structure works functionally as a masticatory organ likely natural porcine teeth.[10]

Bone regeneration

TH [4-(4-methoxyphenyl)pyrido[40,30:4,5]thieno[2,3-b] pyridine-2-carboxamide], a helioxanthin derivative, induces osteogenic differentiation of preosteoblastic and mesenchymal cells[30] *in vitro* and *in vivo*,[31-33] and the optimal concentration for producing the osteogenic effects of TH on MC3T3-E1 and C3H10T1/2 cell lines is 10^{-6} M.[33]

d'Aquino *et al*. evaluated bone regeneration by DPSCs both clinically and radiographically, using a collagen scaffold. Their results showed that within 3 months of colonization on the scaffold, complete radiographic bone regeneration could be observed.[34] de Mendonça Costa *et al*. evaluated the capacity of human DPSCs to reconstruct large cranial defects in non-immunosuppressed rats and found that a more mature bone was formed in the cranial defects, supplied with collagen membrane and HDPSCs.[35] Chadipiralla *et al*. studied the osteogenic differentiation of stem cells derived from human PDLs and the pulp of human exfoliated deciduous teeth and suggested that PDLSC is a better osteogenic stem cell source.[36]

Lymper *et al*. suggested that positioning of a biocomplex of collagen sponge filled with DPSCs in the extracted site of mandibular third molar resulted in a higher rate of mineralization and cortical levels leading to complete regeneration. The samples also showed a well-organized and vascularized bone with a lamellar architecture surrounding the Haversian canal was observed.[37] They also prove to be a useful tool for the treatment of degenerative diseases involving the maxilla and mandible.[37]

Tooth regeneration

Duailibi *et al*., in their experimental studies, were able to form tooth structures from single-cell suspensions of cultured rat tooth bud cells. They demonstrated bioengineered rat teeth developed in 12 weeks with PGA and PLGA scaffold.[38] Honda *et al*. developed tissue-engineered teeth when implanted into omentum of the rat using porcine tooth bud cells and PGA fiber mesh scaffold resembling odontogenesis. Histological analysis showed that the pattern of tissue-engineered odontogenesis was similar to that of natural tooth development with significant regeneration of enamel, dentin, and cementum.[39]

Cell transplantation

The efficiency of cell transplantation of HDPSCs in various diseases is discussed.

Central nervous system

The CNS typically has a poor ability to repair and regenerate new neurons because of its limited pool of precursor cells.[40] Exogenous stem cells (DPSCs) will lead to both regeneration of new neural precursor cells and their enhanced neuronal and glial differentiation. They will also lead to survival and maintenance of existing neural cells through secretion of trophic factors.[41,42]

SCI

SCI involves an initial primary tissue disruption (e.g., mechanical damage to nerve cells and blood vessels) and then a secondary injury caused by neuroinflammatory responses (e.g., excitotoxicity, blood-brain barrier disruption, oxidative stress, and apoptosis).[43] DPSCs differentiating into neuron-like and oligodendrocyte-like cells that may promote axonal regeneration and tissue repair after SCI.[44-46] DPSCs also reduce secondary inflammatory injury, which facilitates axonal regeneration and reduces progressive hemorrhagic necrosis associated with IL-1β, ras homolog gene family member A, and sulfonylurea receptor 1 expression.[47] DPSCs when transplanted together with artificial scaffolds like chitosan promotes motor functional recovery and inhibits cell apoptosis after SCI by secreting BDNF, GDNF, and NT-3 and reducing the expression of active-caspase 3.[48,49]

Stroke

Stroke is an ischemic cerebrovascular condition that leads to brain damage, long-term disability, and even death. DPSCs promote functional recovery after ischemic stroke

by immunomodulation. Some *in vivo* studies have shown that transplantation of DPSCs into the ischemic areas of middle cerebral artery occlusion in Sprague-Dawley rats promoted locomotor functional recovery and decreased infarct areas by their differentiation into dopaminergic (DA) neurons and secretion of neurotrophic factors.[50,51] DPSC transplantation into ischemic areas of focal cerebral ischemia in rats led to the expression of proangiogenic factors that supported dense capillary formation and renormalization of blood flow.[52] Intracerebral transplantation of DPSCs into regions of focal cerebral ischemia in rodent models promoted forelimb sensory and motor functional recovery at 4 weeks post-treatment.[53] DPSCs also provided cytoprotection for astrocytes by reducing reactive gliosis and preventing free radical and IL-1β secretion within *in vitro* ischemic models.[54]

Parkinson's

PDs is a progressive neurodegenerative condition associated with loss of nigrostriatal DA neurons leading to muscle rigidity, bradykinesia, postural instability, and resting tremor.[55] Intrathecal transplantation of DPSCs into the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced old-aged mouse model of PD, promoted recovery of behavioral deficits, restored DA functions, and attenuated MPTP-induced damage by reducing the secretion of proinflammatory factors such as IL-1α, IL-1β, IL6, IL8, and tumor necrosis factor (TNF)-α and by upregulating the expression levels of anti-inflammatory factors such as IL2, IL4, and TNF-β.[56] DPSCs also showed neuroimmunomodulatory activity in an *in vitro* model of PD by reducing MPTP-induced deficits associated with reactive oxygen species, DNA damage, and nitric oxide release.[57]

Alzheimer's

Alzheimer's disease (AD) is a progressive neurodegenerative condition caused by the loss of neurons, intracellular neurofibrillary tangles, and deposition of insoluble β-amyloid peptides in the brain.[58] Clinical symptoms of AD include memory loss, cognitive deficits, and linguistic disorders.[59] DPSCs promoted neuronal repair and regeneration by restoring cytoskeletal structure, protecting microtubule stability, and reducing tau phosphorylation in the okadaic acid-induced cellular model of AD.[60] DPSCs can also reduce amyloid-beta (Aβ) peptide-induced cytotoxicity and apoptosis in the AD cellular model by secreting higher levels of VEGF, fractalkine, RANTES, fms-related tyrosine kinase 3, and monocyte chemotactic protein 1.[61,62]

Retinal injury

The retina is a part of the CNS and is composed of photoreceptors, bipolar cells, and retinal ganglion cells (RGCs).[63] Head injuries can cause traumatic optic neuropathy while ocular chronic degenerative diseases such as glaucoma lead to the slow loss of RGCs.[64] DPSC transplantation into the vitreous of optic nerve injury rat model could promote axonal regeneration and RGC survival by a neurotrophin-mediated mechanism.[65] Intravitreal transplantation of DPSCs in an animal model of glaucoma maintained visual function up to 35 days after treatment by preventing RGC death.[66]

Peripheral nerve injury

Peripheral nerve injury caused by traumatic accidents and iatrogenic damage often accompanies physical disability and neuropathic pain. Autologous nerve grafting is the preferred treatment choice for a long gap of peripheral nerve deficits. Studies suggest that DPSC-embedded biomaterial nerve conduits such as polylactic glycolic acid tubes have the ability to promote regeneration of injured facial nerve and to improve functional recovery comparable to that of autografts.[67] Collagen conduits loaded with Schwann-like cells induced from DPSCs *in vitro* have facilitated repair and regeneration of 15 mm sciatic nerve defect.[68]

Autoimmune diseases

The major mechanisms may involve the secretion of soluble factors, such as prostaglandin E2, IDO, TGF-β, and human leukocyte antigen G5, and interactions between MSCs and immune cells such as T cells, B cells, macrophages, and dendritic cells.[69] SHED has significant effects on inhibiting T helper 17 cells compared to BMMSCs. SHED transplantation was capable of effectively reversing systemic lupus erythematosus (SLE)-associated disorders in SLE-like mice.[14] DPSCs could inhibit acute allogeneic immune responses by the release of TGF-β as a result of allogeneic stimulation of T lymphocytes.[70]

Systemic transplantation of SHED and DPSC in autoimmune disease mice model including SLE and inflammatory bowel disease ameliorated the tissue damages induced by hypersensitive immune response.[14,17,18]

Bone diseases

Systemic transplantation of mesenchymal stem cells could ameliorate bone loss and autoimmune disorders in a MRL/lpr mouse SLE mode by suppression of Interleukin-17 and maintaining a regular positive bone metabolism.[11] Systemic transplantation of SHED through the tail vein ameliorates ovariectomy (OVX)-induced osteopenia by reducing T-helper 1 and T-helper 17 cell numbers in the recipient OVX mice.[71]

Liver diseases

Terai *et al*.[72] administered bone marrow cells derived from GFP-labeled mice to carbon tetrachloride (CCl4)-induced

liver injury model mice and found that these bone marrow cells engrafted in the injured liver, resulting in the absorption of fibrosis and the improvement of prognosis. The tooth germ progenitor cells prevented the progression of liver fibrosis in the liver of CCl4-treated rats and contributed to the restoration of liver function, as assessed by the measurement of hepatic serum markers aspartate aminotransferase and alanine aminotransferase.[12] Engraftment of DPSCs and SHED morphologically and functionally ameliorate acute and chronic injury of livers in CCl4-treated rats.[73]

Muscular

DPSCs can differentiate into dystrophin-producing multinucleated muscle cells and can be utilized in disorders such as muscular dystrophy, wherein, the body is unable to produce dystrophin. Utilization of myogenic progenitor cells derived from dental pulp produced more dystrophin as compared to the heterogeneously present stem cells.[74] Thereby proving to be a potential alternative for stem cell therapy in muscular dystrophy patients. Kerkis *et al*. used human DPSCs for the treatment of muscular dystrophy in golden retriever dogs, transplanted by arterial or muscular injections.[75]

Diabetes

Diabetes is a chronic degenerative disease. One of the treatments for diabetes includes transplantation of pancreatic islet cells. Chen *et al*. demonstrated that insulin-producing cells can be derived from monoclonal and polyclonal DPSCs.[76] Govindasamy *et al*. demonstrated that DPSCs have the capacity to differentiate into islet-like aggregates.[77]

Infertility

The potential of DPSCs can also be used in the treatment of infertility. Leake and Templeton isolated HDPSCs and injected them into the testes of live male mice. The mice were killed at various intervals after the injection, and their testes were examined to see whether the stem cells survived. It was found that stem cells settled in the testes and also differentiated into cells that were producing viable sperm.[78]

Cell bank for human dental pulp-derived stem cells

SHED isolated from the cryopreserved deciduous pulp tissues for over 2 years (SHED-Cryo) owned similar stem cell properties including clonogenicity, self-renew, stem cell marker expression, multipotency, *in vivo* tissue regenerative capacity and *in vitro* immunomodulatory function to SHED isolated from the fresh tissues (SHED-Fresh).[6] Induced pluripotent stem cells are constructed from dental pulp-derived stem cells and hold a great promise for regenerative medicine and other aspects of clinical applications.[79]

CONCLUSION

HDPSCs are useful in the treatment of various diseases as shown in this article. They have great potential and is a very powerful tool in regenerative medicine. They can be obtained safely and easily without significant morbidity or ethical concerns; however, the challenge of understanding the mechanisms underlying the therapeutic effects of DPSCs requires more research. The future treatment modality will be regenerative based; however, further studies are needed to test the various other applications of DPSCs with long-term follow-up.

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Conflicts of interest

There are no conflicts of interest.

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