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Archives of Stem Cell Research

Review Article

Properties and Possibilities of Human Dental Pulp-Derived Stem Cells

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Abstract

Fifteen years have been passed after the first discovery of human dental pulp-derived stem cells. Now, four types of stem cells are isolated from human dental pulp tissues, and are identified as dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHED), stem cells from apical papilla (SCAP), and human supernumerary tooth-derived stem cells (SNTSCs). Recent investigations accumulate diverse evidence regarding to human dental pulp-derived stem cells to understand their properties, especially the multipotency of the stem cells. Therefore, many investigators have focused on human dental pulp-derived stem cells to apply regenerative therapy for dental and systemic diseases. This review provides insights into properties of human dental pulp-derived stem cells and current application of human dental pulp-derived stem cells into translational researches for local and systemic diseases.

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Submitted: 04 July 2015

Accepted: 29 July 2015

Published: 31 July 2015

Keywords

- Human dental pulp-derived stem cells
- Mesenchymal stem cells
- Translational research
- Tissue engineering
- Cell transplantation

ABBREVIATIONS

DPSCs: Dental Pulp Stem Cells; **SHED**: Stem cells from Human Exfoliated Deciduous teeth; **SCAP**: Stem Cells from Apical Papilla; **SNTSCs**: human Supernumerary Tooth-derived Stem Cells; **CNCCs**: Cranial Neural Crest Cells; **NCCs**: Neural Crest Cells; **BMSCs**: Bone Marrow Stromal Cells; **HSC**: Hematopoietic Stem Cell; **CFU-F**: Colony-Forming Unit-Fibroblasts; **MSCs**: Mesenchymal Stem Cells; **HLA**: Human Leukocyte Antigen; **MCAM**: Melanoma Cell Adhesion Molecule; **5'-NT**:5'-NucleoTidase; **HA/TCP**: Hydroxyapatite/Tricalciumm Phosphate; **SLE**: Systemic Lupus Erythematosus; **iPS:** induced Pluripotent Stem.

INTRODUCTION

In 2000, dental pulp stem cells (DPSCs) were discovered stem cells in human dental pulp tissues of extracted impacted third molars for the first time in the world by Songtao Shi and Stan Gronthos [1]. Later, Shi' group has successively identified other types of human dental pulp-derived stem cells from 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) [2], stem cells from apical papilla (SCAP) [3], and human supernumerary tooth-derived stem cells (SNTSCs) [4], respectively. Since the discovery of them, many investigators have focused on the properties and functions of the human dental pulp-derived stem cells.

Origin of dental pulp-derived stem cells is considered to be cranial neural crest cells (CNCCs). A group of neural crest cells (NCCs) migrates from neural crest, which is temporally formed between ectoderm and neural plate during neural tube formation, and home to various places to play a significant role in embryo development. During the migration, NCCs translate into mesenchymal cells (epithelial-mesenchymal transition). Particularly, CNCCs concentrate in facial and pharyngeal arches, and form not only sensory VII, IX, X cranial nerves, thymus, thyroid follicular cells, parathyroid, and cornea, but also most of orofacial mesenchymal organs including facial skeleton such as maxilla and mandible, dentin/pulp complex, cementum, periodontal ligament, and alveolar bone. Concurrently with the finding of DPSCs, an existence of CNCCs is demonstrated in dental germ mesenchyme in Wnt1-LacZ transgenic micewith lineage tracing analysis by Yang Chai [5]. Wnt1 is known to express only in neural tube to regulate NCCs in fetal life. Chai's group manipulated expression of the embryonic gene well in mice, and succeeded in confirming the existence of LacZ positive cells in dental pulp cells and odontoblasts. Their findings strongly support that dental pulp-derived stem cells such as DPSCs and SHED derives from CNCCs.

In 1970's, Russian stem cell biologist Alexander J. Friedenstein discovered bone marrow stromal cells (BMSCs), which differ from hematopoietic stem cells (HSCs), in bone marrow. BMSCs express 1) an ability of adhering on a plastic culture dish, 2) fibroblast-like spindle shape, 3) a capacity of forming adherent

clonal colonies called colony-forming unit-fibroblasts (CFU-F), 4) *in vitro* differentiation into osteogenic cells, and 5) *in vivo* formation not only of bone-like tissues, but also of bone marrow like tissues [6]. Finally, Arnold Caplan named CFU-F population mesenchymal stem cells (MSCs) [7], because BMSCs are explored further multi differentiation capacities such as chondrogenesis and adipogenesis.

Recently, human MSCs are successively isolated from a variety of mesenchymal tissues expect for bone marrow, such as adipose tissue [8], umbilical cord blood [9], umbilical cord [10], dental pulp [1,2] and periodontal tissue (periodontal ligament, gingival connective tissue) [11,12]. In 2006, International Society for Cellular Therapy (ISCT) stated minimal criteria for defining human MSCs (**Table 1**) [13]. The ISCT's statement requires human MSCs to meet three criteria, 1) adhesive cells, 2) immunological phenotypes positive to CD105, CD73, and CD90 and negative to CD34, CD45, CD14/CD11b CD79a/CD19, and human leukocyte antigen (HLA)-DR, 3) multipotency into osteoblasts, chondrocytes, and adipocytes. However, definitive criteria to identify human MSCs have been controvertible because human MSCs exhibit huge and hierarchal characteristics.

Characteristics of human dental pulp-derived stem cells

All types of human dental pulp-derived stem cells including DPSCs, SHED, SCAP, and SNTSCs commonly share characteristics as MSCs.

(1) Biological characteristics of dental pulp-derived stem cells

Based on current accumulated knowledge, human dental pulp-derived stem cells express following characteristics.

1. Self-renewal capacity

Human dental pulp-derived stem cells express a fundamental and specific characteristic as stem cells, self-renewal capacity [1-4,14,15].

2. CFU-F forming ability

Human dental pulp-derived stem cells form adherent colonies that consist of spindle shaped cells, called CFU-F [1-4]. Amazingly, CFU-F analysis shows that human dental pulp contains abundant MSCs than human bone marrow (CFU-F capacity of DPSCs show five times than human bone marrow-derived MSCs) [1-4].

3. High proliferation activity

This activity is also common in stem cells. Population doubling assay shows human dental pulp-derived stem cells express higher proliferative ability than human bone marrow-derived MSCs(population doubling scores of DPSCs and SHED show three and four times than human bone marrow-derived MSCs [BMMSCs]) [1-4]. In addition, human dental pulp-derived stem cells express higher activity of telomerase than human BMMSCs [4, 15].

Table 1: Minimal criteria for defining human MSCs.

1. Adhesive cells
Adherence to a plastic culture dish in standard culture condition
2. Immunological phenotype
Positive (≥ 95%); CD105, CD73, CD90.
Negative (≤ 2%); CD45, CD34, CD14 or CD11b, CD79a or CD19, human leukocyte antigen-DR
3. Multipotency
in vitro differentiation into osteoblasts, chondrocytes, and adipocytes
Modified from Dominic et al., 2006

4. Expression of cell-surface markers

Human dental pulp-derived stem cells express negative to hematopoietic cell-surface markers including CD34, CD45, and CD14 [1-4]. Because human dental pulp tissues contain a rich blood supply, dental pulp-derived stem cells should express these hematopoietic markers negative. On the other hand, dental pulp-derived stem cells express positive to STRO-1, CD146 (melanoma cell adhesion molecule [MCAM]), CD105 (endoglin or SH2), and CD73 (5'-nucleotidase [5'-NT] or SH3/4), as well as CD90 (Thy-1) and CD29 (integrin beta-1) [1-4]. These markers are known as specific markers for MSCs. In addition, human dental pulp-derived stem cells 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) [4,15]. Interestingly, CD24 is expressed only on SCAP among four types of human dental pulp-derived stem cells [3].

5. Multipotency

Human dental pulp-derived stem cells are known to differentiate into mesenchymal lineage cells including odontoblasts, osteoblasts, chondrocytes, adipocytes, and myocytes (**Figure 1**) [1-4,16,17]. Recent advantage of stem cell technology enables to induce human dental pulp-derived stem cells both into ectodermal lineage cells, such neural cells [1-4], and into endodermal lineage cells, such vascular endothelial cells [16], hepatocytes [16,18], and pancreatic islet-insulin-producing β cells [19] (**Figure 1**).

6. *In vivo tissue regeneration capacity*

When human dental pulp-derived stem cells are subcunaneously transplanted with hydroxyapatite/tricalciumphosphate (HA/TCP) powders as carriers into the dorsal surface of immune compromised mice, individual human dental pulp-derived stem cells express a specific and unique regeneration capability [1-4]. DPSCs and SCAP regenerate only dentin in the implant tissues [1,3]. In addition, they are able to induce dental-pulp-like tissues containing blood capillary vessels and dense collagen fibers surrounded by the newly formed dentin, suggesting that DPSCs and SCAP can reconstruct *de novo* dentin/pulp complex *in vivo*. These findings suggest that DPSCs and SCAP are effective cell source to regenerate dentin/pulp complex structures. On the other hand, 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 to a uniquecell source to regenerated dentin/pulp complex and bone/bone marrow unit [2, 4].

7. Immunomodulation

Human dental pulp-derived stem cells display immunomodulatory properties by affecting directly and indirectly to immune cells such as T cells [20,21]. Human dental pulp-derived stem cells are able to inhibit proliferation of T cells, downregulate proinflammatory interleukin 17-secreting helper T cells, and upregulate regulatory T cells [15,22,23] (**Figure 1**). Human dental pulp-derived stem cells regulate T cell proliferation via releasing of transforming growth factor-β1, hepatocyte growth factor and indoleamine 2, 3-dioxygenase to [20]. Human dental pulp-derived stem cells express Fas ligand to induce apoptosis of T cells [22,23]. Human dental pulp-derived stem cells interplay directly or indirectly with T cells.

Human dental pulp-derived stem cell-based regenerative therapies

Recently, many researchers have expected whether human dental pulp-derived stem cells can apply for regenerative therapies based on recent accumulated knowledge regarding to their multipotency, tissue regenerative capacity, and immune modulatory properties (**Figure 2**).

(1) Tissue engineering with human dental pulp-derived stem cells

1. Regeneration of dentin/pulp complex

DPSCs were mixed with a carrier and filled in a root canal of extracted tooth after root canal treatment, 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 [24]. Recently, autologous transplantation of DPSCs from healthy dental pulp is clinically tried to regenerate dentin/pulp complex [25].

2. Root regeneration

When compared to other human dental pulp-derived stem cells, SCAP displays remarkable cell-migration ability. This capacity is considered to involve root growth in tooth development. For this reason, SCAP is a feasible cell source for dental root regeneration.

When SCAP-immersed root-formed HA/TCP carriers were subcutaneously grafted into 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 mandibular bone of a swine, the root-form carrier is reconstructed with newly formed dentin/pulp-complex, and is surrounded by regenerated periodontal ligament on de novo cementum [3]. Furthermore, the regenerated tooth root-like structure works functionally as a masticatory organ likely natural porcine teeth after the root-like structure is installed a porcelain crown [3].

3: Bone regeneration

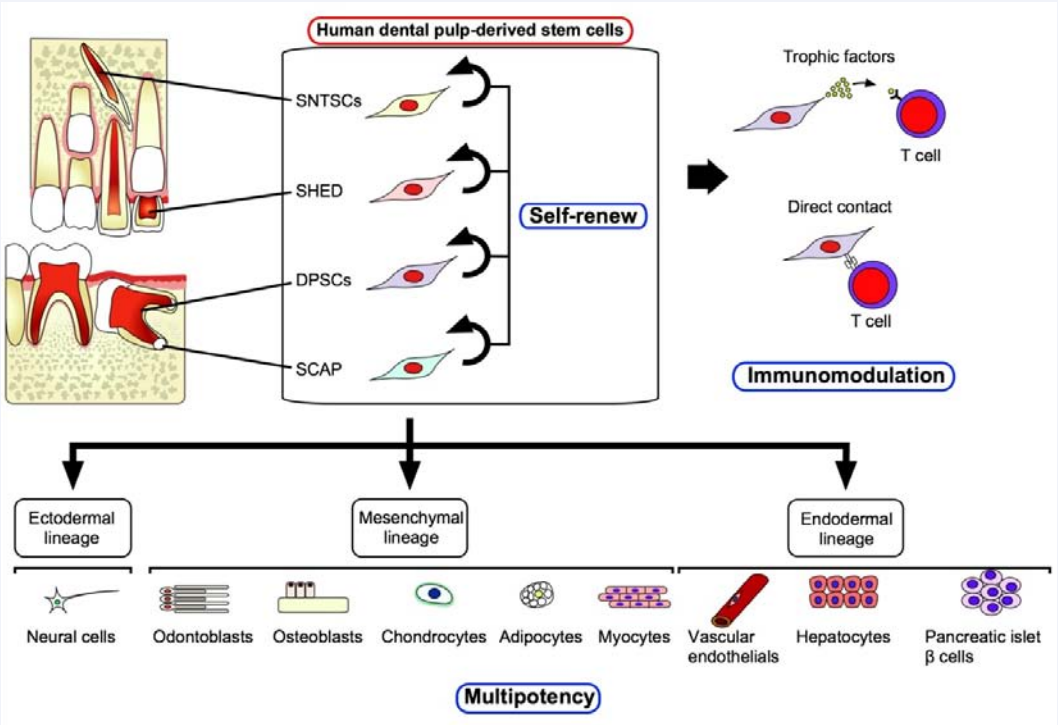

Figure 1 Origin, multipotency, and immunomodulatory function of human dental pulp-derived stem cells. Recent stem cell technology develops isolation and culture of human dental pulp-derived stem cells from permanent teeth including impacted third molars, exfoliated deciduous teeth, and supernumerary teeth. Human dental pulp-derived stem cells express a differentiation capacity not only into mesenchymal cell lineage, but also into ectodermal and endodermal cell lineages. Human dental pulp-derived stem cells exhibit to interplay with immune cells such as T lymphocytes. DPSCs: dental pulp stem cells, SCAP: stem cells from apical papilla, SHED: stem cells form human exfoliated deciduous teeth, SNTCs: supernumerary tooth-derived stem cells.

SHED displays a unique bi-potency to regenerate dentin and bone. Applying this property, efficiency of SHED for bone regeneration was showed in skull of mice and bone defect model of swine [26,27].

(2) Cell transplantation with human dental pulp-derived stem cells

The efficiency of cell transplantation of human dental pulp-derived stem cells has been studied in several disease models.

1. Neural diseases

Since SHED has remarkable differentiation capacity for neural cell, it has been considered to treat neural disease [2]. When SHED are transplanted into hippocampus of mice, the undifferentiated cells are differentiated into neural cells *in situ*, suggesting a treatment possibility of SHED to Alzheimer's disease. Transplantation of human dental-pulp derived stem cells showed a treatment efficacy on Parkinson's disease [28,29]. In a spinal cord injury model rats, local implantation of SHED ameliorates the motor function [30]. In cerebral infarction model animals, systemic infusion of SHED recovers the neural symptoms [31]. DPSCs promote peripheral axon regeneration through trophic functions via activating Schwann cells [32].

2. Autoimmune diseases

Systemic transplantation of SHED and DPSC in autoimmune disease model mice including systemic lupus erythematous (SLE) and inflammatory bowel disease ameliorated the tissue damages induced by hypersensitive immune response [15,22,23].

3. Bone diseases

Systemic transplantation of SHED ameliorates the early stage of osteoporosis in ovary-ectomized postmenopausal osteoporosis model mice [33]. SHED transplantation also prevents secondary osteoporosis in SLE model mice [16].

4. Liver diseases

Engraftment of DPSCs and SHED morphologically and functionally ameliorate acute and chronic injury of livers in CCl_4-treated rats [18,34]. Recent our investigation confirms an *in vivo* trans differentiation capacity of SHED into human hepatocytes, as well as the therapeutic efficacy to liver cirrhosis, in CCl_4-treated mice [35].

5. Other diseases

In many transplant therapies, short of donors has been a serious problem. Since SHED show capacities to differentiate into insulin-producing cells and myocytes, transplantation of SHED has been considered to use for type one diabetes [19], cardiac ischemia[17].

(3) Cell Bank for human dental pulp-derived stem cells

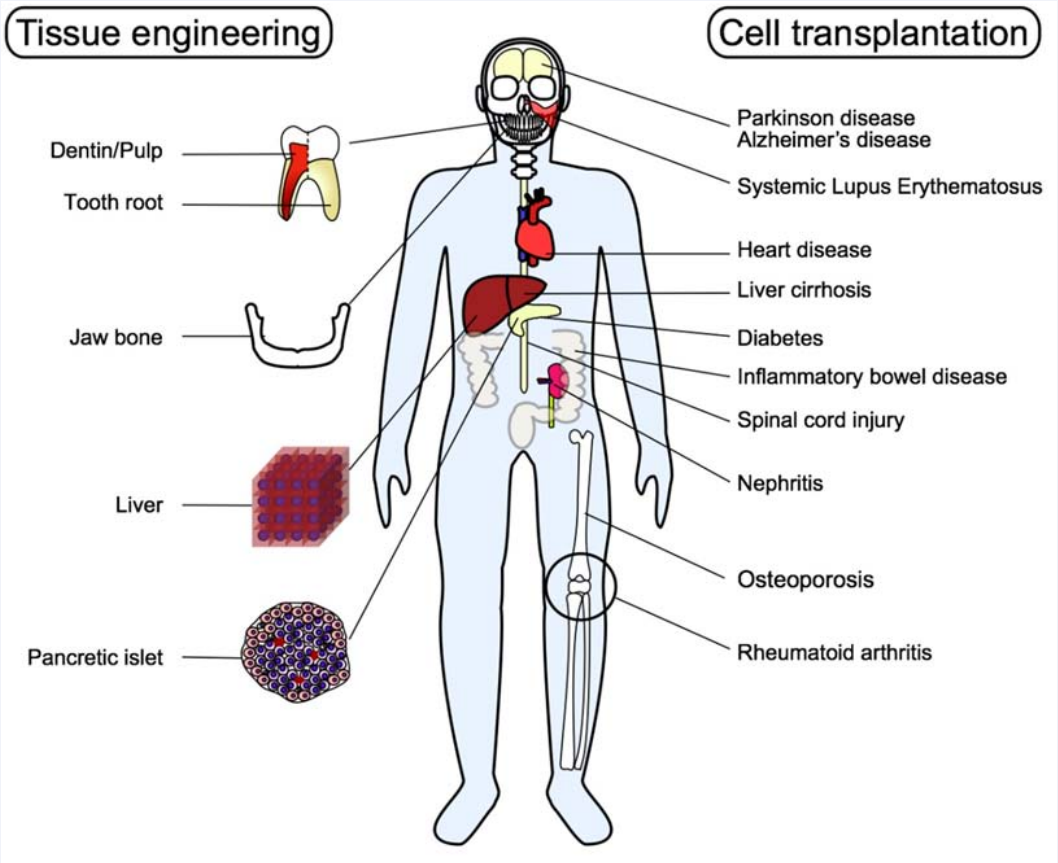

Figure 2 A perspective of human dental pulp-derived stem cell-based regenerative medicine. Human dental pulp-derived stem cells are considered to a promising stem cell source in tissue engineering and cell transplantation to treat diverse human diseases in future.

Since cryopreserved human dental pulp tissues maintain the stem cells, human dental pulp-derived stem cell-bank is structured gradually [36,37]. On the other hand, induced pluripotent stem (iPS) cells are constructed from dental pulp-derived stem cells [38,39].

Therefore, human dental pulp cells are also considers as a cell bank for iPS cells [40]. Human dental pulp-derived iPS cell-modified hepatocytes ameliorate fulminant hepatic failure in mice [41].

(4) Other therapy

Trophic factors from human dental pulp-derived stem cells cultures are known to display therapeutic efficacy in spinal cord injury model rats [29], cerebral infarction model animals [30], acute lung injury model mice [42], and bone regeneration [43]. Exosomes derived from human dental pulp-derived stem cells are also considered to show therapeutic effects [44,45].

CONCLUSION

Recent studies suggest that human dental stem cell-based therapy may provide a therapeutic option for patients who would obtain benefits of tissue regeneration in the future. Sufficient understanding regarding to the characteristics and relationship with immune cells of human dental stem cells will improve therapeutic effects on human dental stem cell-based therapy.

ACKNOWLEDGEMENTS

This work was supported by grants from the Japan Society for the Promotion of Science, including Grant-in-Aid for Scientific Research (B) (Grant Number 25293405 to TY), Grant-in-Aid for Challenging Exploratory Research Project (Grant Number 24659815 to TY).

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Cite this article

Sonoda S, Tomoda E, Tanaka Y, Yamaza T (2015) Properties and Possibilities of Human Dental Pulp-Derived Stem Cells. Arch Stem Cell Res 2(2): 1012.