ISSN 1948-0210 (online)

World Journal of *Stem Cells*

World J Stem Cells 2024 February 26; 16(2): 54-227

Published by Baishideng Publishing Group Inc

World Journal of Stem Cells

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World Journal of Stem Cells

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NAME OF JOURNAL
World Journal of Stem Cells

ISSN
ISSN 1948-0210 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Shengwen Calvin Li, Carlo Ventura

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https://www.wjgnet.com/1948-0210/editorialboard.htm

PUBLICATION DATE
February 26, 2024

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World J Stem Cells 2024 February 26; 16(2): 54-57

DOI: 10.4252/wjsc.v16.i2.54

ISSN 1948-0210 (online)

EDITORIAL

Human dental pulp stem/stromal cells in clinical practice

Mohammed E Grawish

Specialty type: Cell and tissue engineering

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Wu HT, China; Yang RL, China

Received: October 16, 2023
Peer-review started: October 16, 2023
First decision: December 5, 2023
Revised: December 28, 2023
Accepted: January 30, 2024
Article in press: January 30, 2024
Published online: February 26, 2024

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Abstract

Dental pulp stem/stromal cells (DPSCs) are fibroblast-like, neural crest-derived, and multipotent cells that can differentiate into several lineages. They are relatively easy to isolate from healthy and inflamed pulps, with little ethical concerns and can be successfully cryopreserved and thawed. The therapeutic effects of DPSCs derived from animal or human sources have been extensively studied through *in-vitro* and *in-vivo* animal experiments and the findings indicated that DPSCs are effective not only for dental diseases but also for systemic diseases. Understanding that translational research is a critical step through which the fundamental scientific discoveries could be translated into applicable diagnostics and therapeutics that directly benefit humans, several clinical studies were carried out to generate evidence for the efficacy and safety of autogenous or allogeneic human DPSCs (hDPSCs) as a treatment modality for use in cell-based therapy, regenerative medicine/dentistry and tissue engineering. In clinical medicine, hDPSCs were effective for treating acute ischemic stroke and human exfoliated deciduous teeth-conditioned medium (SHED-CM) repaired vascular damage of the corpus cavernous, which is the main cause of erectile dysfunction. Whereas in clinical dentistry, autologous SHED was able to regenerate necrotic dental pulp after implantation into injured teeth, and micrografts enriched with autologous hDPSCs and collagen sponge were considered a treatment option for human intrabony defects. In contrast, hDPSCs did not add a significant regenerative effect when they were used for the treatment of post-extraction sockets. Large-scale clinical studies across diverse populations are still lacking to provide robust evidence on the safety and efficacy of hDPSCs as a new treatment option for various human diseases including dental-related problems.

Key Words: Dental pulp stem/stromal cells; Human clinical studies; Regenerative medicine; Regenerative dentistry; Cell-based therapy

Core Tip: The need for new alternative therapeutic strategies is of paramount importance to improve the cure rate and quality of patients' lives. Human dental pulp stem/stromal cells and human exfoliated deciduous teeth are promising candidates for regenerative medicine and dentistry as they have been used clinically to treat acute ischemic stroke, erectile dysfunction, traumatized teeth with necrotic pulps, and intrabony defects.

Citation: Grawish ME. Human dental pulp stem/stromal cells in clinical practice. *World J Stem Cells* 2024; 16(2): 54-57
URL: https://www.wjgnet.com/1948-0210/full/v16/i2/54.htm
DOI: https://dx.doi.org/10.4252/wjsc.v16.i2.54

INTRODUCTION

Dental pulp is the loose connective tissue that resides in the central part of the tooth and is surrounded by a mineralized specialized tissue, known as dentin. It is derived from the ectomesenchyme of the dental papilla. Morphologically, it is composed of pulp horn(s), pulp chamber or coronal pulp, root canal(s) or radicular pulp, and accessory or lateral canal(s). From the dentin-pulp junction to the central part of the tooth, the pulp has four distinctive histological zones known as the odontoblastic zone, cell-free zone, cell-rich zone, and pulp core. The odontogenic zone of the pulp includes odontoblasts, the cell-free zone, the cell-rich zone, and the parietal plexus of nerves. Histologically, the pulp is composed of cells, fibers, ground substances, nerves, blood, and lymphatic vessels. Dental pulp cells include odontoblasts (most distinctive), fibroblasts (most abundant), defensive cells (macrophages and other immunocompetent cells), and undifferentiated ectomesenchymal or progenitor cells[1].

Undifferentiated mesenchymal cells or dental pulp stem/stromal cells (DPSCs), are adult stromal cells that regulate the homeostatic function of the dentin-pulp complex and play a crucial role in the regenerative processes of the pulp. They are fibroblast-like, neural crest-derived, multipotent cells that are located specifically in the perivascular niches of the cell-rich zone and the pulp core. They possess multilineage differentiation potential, capacity for self-renewal, high proliferation rate, and high frequency of colony formation with the capacity of terminally differentiating into odontogenic, osteogenic, chondrogenic, adipogenic, myogenic, and neurogenic cells[2]. They are relatively easy to collect from discarded teeth with little ethical concerns, can be cryopreserved while retaining their stem cell properties, and could be harvested from naturally lost or surgically removed teeth. The first mesenchymal stem cells isolated from the oral cavity were DPSCs which could be isolated from dental pulp tissues of human-extracted permanent teeth and deciduous teeth. The most widely used method for isolating DPSCs is enzymatic digestion of tissues or outgrowth from tissue explants. These cells express mesenchymal stem cell markers such as CD13, CD29, CD73, CD90, CD106, CD146, and Stro-1. However, they do not express hematopoietic stem cell markers such as CD34, CD45, and CD11b[3].

Our *in-vitro*[4-7] and other *in-vivo* studies performed on animal models[8-10], considered DPSCs to be the most promising stem cell types for regenerative therapies. As animals are not simply small humans and to produce valid and scientific results, clinical studies have been developed to ensure reliable and optimal conditions[11]. In the past five years, few clinical studies have been conducted to assess the safety and effectiveness of human DPSCs (hDPSCs) for the treatment of various human diseases including dental-related problems. Clinically, hDPSCs have been used to treat acute ischemic stroke and erectile dysfunction, and to regenerate necrotic dental pulp tissues and improve clinical parameters of periodontal regeneration. In contrast, hDPSCs did not add a significant regenerative effect when they were used for the treatment of post-extraction sockets. Unfortunately, some studies had been registered in the ClinicalTrials.gov but the results have not yet been released.

ANALYSES CONDUCTED

There is no clear evidence so far as to whether hDPSCs are effective in treating various human diseases including dental-related problems. Conflicting feedback from clinical studies have been reported and some published studies showed the feasibility and effectiveness of hDPSCs as a treatment option while others revealed a non-significant effect. Among the clinical studies that reported positive feedback was one designed to treat acute ischemic stroke as a systemic disease. The study evaluated the efficacy and safety of JTR-161 as allogeneic hDPSCs for treating patients with acute ischemic stroke, compared to placebos. JTR-161 is a 5.0 mL vial containing 1.0×10^8 hDPSCs isolated from sound-extracted teeth, manufactured by JCR Pharmaceuticals with good manufacturing practices. Intravenous administration of JTR-161 provided a novel therapeutic option for the treatment of patients with ischemic stroke due to the wider therapeutic time window for hDPSCs transplantation[12]. A second study with promising results was designed to evaluate the efficacy of human exfoliated deciduous teeth-conditioned medium (SHED-CM) in erectile dysfunction patients. Direct injection of SHED-CM into the corpus cavernosum successively repaired vascular damage, which is the main cause of erectile dysfunction. The repair mechanism was attributed to the beneficial effect of SHED-CM in treating pathological damage of vascular endothelial cells of the corpus cavernosum[13].

From the dental viewpoint and compared to an apexification group, when the autologous aggregates containing a total of 1×10^8 SHED was implanted into traumatized permanent incisors this led to the regeneration of three-dimensional pulp tissue equipped with sensory nerves and blood vessels. The regenerative capacities of the aggregates increased the

length of the root and reduced the width of the apical foramen without any adverse events[14]. Another promising study was carried out to evaluate the effect of a biocomplex formed from micrografts enriched with autologous hDPSCs and a collagen sponge scaffold as a treatment option for human chronic periodontitis presenting with one deep intrabony defect. Compared to the control defects that were filled only with collagen sponge, the defects filled with micrografts seeded onto collagen sponge showed that the application of hDPSCs significantly improved clinical and radiographic parameters of periodontal regeneration after one year of treatment as it reduced probing depth, increased clinical attachment level and bone defect fill[15].

Contrary to the above-mentioned studies, it has been reported that hDPSCs did not add a significant regenerative effect when they were used for the treatment of post-extraction sockets. The clinical and radiographic parameters were evaluated for the effectiveness of micrografts enriched with hDPSCs combined with leukocyte-platelet-rich fibrin (L-PRF) membranes on the periodontal status of the lower second molars after placing them into the extraction sockets of impacted mandibular third molars. The hDPSCs did not significantly contribute to the results compared to L-PRF therapy alone as there were no improvements in the probing pocket depth, clinical attachment levels, vertical bone loss, and relative bone density distal to the lower second molars[16]. Moreover, when the autologous hDPSCs were delivered in a collagen matrix for post-extraction socket healing, after a 6-month follow-up period, autologous hDPSCs were unable to reduce socket bone resorption after lower third molar extraction. Computed tomography and an advanced display platform were used to record extraction socket density (HU) and height (mm) of the distal interdental bone septum of the second molar[17].

On the other hand, there are some studies registered on ClinicalTrials.gov but unfortunately, the results have not yet been released. The goal of one study was to evaluate the safety and feasibility of autologous hDPSCs therapy in patients with a chronic disability after stroke. They designed the study to determine the maximum tolerable dose of autologous hDPSCs therapy and if this maximum tolerable dose is safe and feasible in chronic stroke. Advanced magnetic resonance, positron emission tomography neuroimaging, and clinical assessment were the chosen tools to determine any change afforded by stem cell therapy in combination with rehabilitation[18]. Moreover, another study aimed to assess the safety and efficacy of allogeneic hDPSCs in treating severe pneumonia caused by COVID-19. The authors reported that they will enroll twenty serious COVID-19 patients to be randomized into two equal groups as certain patients will receive an intravenous injection of 3.0×10^7 hDPSCs suspended in 30 mL saline solution on days 1, 4, and 7 whereas patients in the control group will receive an equal amount of saline on the same days. Laboratory and clinical observations are considered the tools for analysis of each case in this 28-d study[19].

PERSPECTIVE

Currently, progress in the field of stem cells is very attractive and promising with reports of clinical success in treating certain diseases. The hDPSCs have been used in clinical studies to treat acute ischemic stroke, regenerate dental pulp tissues, and promote periodontal tissue regeneration. Unfortunately, most of the performed clinical studies were designed as phase I which involved a small group of participants. It is well known that phase I studies are concerned with determining a safe dose of the drug being studied as well as its potential side effects. Therefore phases II, III, and IV of large-scale studies are required to determine the time of the treatment's effectiveness, to compare with standard treatments and for approval of the new treatments by the Food and Drug Administration. In addition, long-term follow-up in the form of patient surveys or periodic health examinations and multiregional clinical studies across diverse populations is mandatory to produce strong evidence on the feasibility and effectiveness of hDPSCs as a treatment option. Before conducting such clinical studies, simplified protocols of hDPSCs' isolation, expansion, cryopreservation, techniques, and related application methods should be established. In addition, problems such as the risk of contamination by microorganisms, high treatment costs, and ethical treatment policies should be overcome to obtain the benefits of using hDPSCs in clinical studies.

CONCLUSION

To gain the full beneficial effects of hDPSCs-based treatment, harvesting hDPSCs from inflammatory tissues, expanding-free strategies, and applying hDPSCs-CM or hDPSCs-small extracellular vesicles should be studied, as they have strong application potential and research value. Taken together, hDPSCs-based therapy is a promising tool for the treatment of various diseases and can be further promoted.

FOOTNOTES

Author contributions: Grawish ME designed, analyzed, and wrote the manuscript.

Conflict-of-interest statement: The author reports no relevant conflicts of interest for this article.

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S-Editor: Wang JJ
L-Editor: Webster JR
P-Editor: Zhao YQ

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