Am J Stem Cells 2022;11(2):28-36
www.AJSC.us /ISSN:2160-4150/AJSC0141324

Review Article

The therapeutic effects of stem cells from human exfoliated deciduous teeth on clinical diseases: a narrative review study

Fariba Naderi[1], Mohsen Mehdiabadi[1], Farideh Kamarehei[2]

[1]*Pediatric Dentistry Department, Faculty of Dentistry, Hamadan University of Medical Sciences, Hamadan, Iran;*
[2]*Department of Microbiology, Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran*

Received December 25, 2021; Accepted April 25, 2022; Epub April 25, 2022; Published April 30, 2022

Abstract: Introduction: Stem cells isolated from human dental pulp tissue are different from other sources of Mesenchymal stem cells because of their embryonic neural crest sources and neuro-trophic potential. These stem cells consist of dental pulp stem cells from human permanent teeth and stem cells from human exfoliated deciduous teeth. Aim: In this study, we survey the advantages and disadvantages of these stem cells with therapies attitude. Main text: Stem cells from human exfoliated deciduous teeth with a high proliferation rate could distinguish into a wide types of cells. After stem cell banking appearance, stem cells from human exfoliated deciduous teeth can preserve and use for treatment, especially in regenerative medicine. But the crucial health hazards related to stem cell transplantation, such as immune rejection reactions and the interaction with other tissues, should not be neglected. Conclusion: Further experiments are required to approve the impact of these stem cells on different human disorders.

Keywords: Stem cells, tooth, deciduous, transplantation

Introduction

Different types of Stem cells interrelate together to protect homeostasis or growth, and the interconnections are intricate and broad. There are different human dental mesenchymal stem cells derived from human permanent and temporary teeth. Stem cells from human exfoliated deciduous teeth (SHED) effects on wound healing. Mesenchymal stem cells (MSCs), multipotent somatic stem cells, are existent in various tissues, such as funiculus umbilicalis, bone marrow and adipose tissue. MSCs could renovate themselves with proliferation and also could differentiate into various tissues such as osteoblasts, osteoclasts, chondrocytes, myocytes, adipose cells and also connective cells. Therefore, MSC treatment may be very useful for osteogenesis, diabetes, neurological, cardiac, autoimmune, and cartilage diseases. Nowadays, MSCs usually isolated from bone marrow sources. But the bone marrow aspiration is a harmful and invasive method. So, the discovery and recognition of another basis of exploring of MSCs are pending. Our study aimed to survey SHED effect on different degenerative diseases in comparison with dental pulp stem cells (DPSCs) and bone marrow mesenchymal stem cells (BMMSCs) [1].

Therapeutically researches of stem cells have performed for various states such as neurodegenerative diseases like Parkinson's disease and multiple sclerosis, diabetes, liver, cardiac, musculoskeletal, and autoimmune disorders, and also for nervous system renewal after brain or spinal cord damage. Nowadays, the stem cells are used for treating patients who suffer bone breakage, cancer and spondylodesis surgery. Besides, the stem cells are used in leukemia, myelodysplastic syndromes, myeloproliferative, lymphoproliferative disorders, histiocytic and phagocyte diseases, hereditary erythrocyte disorders, Lysosomal storage, hereditary immunity diseases, hereditary platelet dysfunctions, plasma cell abnormalities and also malignancies therapy [2].

In this study, we reviewed the efficiencies of SHED and its therapeutic capacities in different diseases.

Table 1. The comparison of SHEDs and DPSCs characteristics

Criteria	SHEDs	DPSCs	Methods	*P* value
Proliferation rate	79.5±3.98%	47.6±1.47%	Colony Forming Unit	<0.05
Proliferation rate	Day 7	Day 1	MTT Assay	<0.05
percentage of cells in S + G2M phases	50.94%	42.66%	Flowcytometry	<0.05
proliferation marker Ki67	50.68±3.23%	28.95±5.66%	Immunostaining analysis	<0.05
Osteogenic differentiation capability after 14 days	High lipid clusters formed	Low lipid clusters formed	Staining with Alizarin Red O	<0.05
Capability of mineralization after 14 days	High number of mineralization nodules	Low number of mineralization nodules	Staining with Alizarin Red O	<0.05
Expression of inflammatory cytokines (MMP1, MMP2 and IL6)	Relative mRNA Level (~2)	Relative mRNA Level (~1)	Real Time PCR	<0.05
Expression of Col I, ALP, Runx2 and proliferating cell nuclear antigen (PCNA) genes	Relative mRNA Level (~1.5)	Relative mRNA Level (~1)	Real Time PCR & PCNA Assay	<0.05

The isolation and tracking of SHEDs

SHEDs have to successfully and carefully extracted and identified. In the *in vivo* experiments, SHEDs usually extract from exfoliated deciduous teeth and transplant with an infusion by the tail vein. SHEDs were marked by the PKH26 red fluorescent cell linker mini kit to follow their traces. SHEDs have to be approved using flow cytometry [3].

The comparison of SHEDs with DPSCs and BMMSCs

SHED is a novel origin of stem cells, recognized as a population of postnatal stem cells. MSC specifications like fibroblastic shape, and the MSC antigens exhibit in DPSCs, SHED, and BMMSCs isolated cells. SHEDs in comparison with DPSCs are similar to pericytes. The dividing rate of SHED was significantly more than DPSCs and BMMSCs. There are 2.0-fold or more expression rate of 4386 genes by an altered expression among DPSCs and SHED cells that has been revealed by gene expression profiles using DNA microarray analyzer. The genes participated in cell division and extracellular matrix, such as various cytokines like fibroblast growth factors and tumor growth factor beta, had more expression in SHED. It is concluded that SHEDs are better because of their superior proliferation ability, plentiful cell stock, and a noninvasive stem cell collecting method. So it is a favorable choose as a cell origin for treatment use [4].

Differentiation characteristics and differences in the growth between SHED and DPSCs showed in **Table 1**. SHED and DPSCs were evaluated for their cell markers and multiplication by calculating the cell division cycle, growth rates, Ki67-positive effects, and cell colonies. The differences between them were demonstrated by alizarin red and oil red O and real-time PCR in vitro. The mineralization ability of the cells was investigated using ceramic bovine bone implanted into the immune-compromised mice for eight weeks, *in vivo*. A 3 dimensional pellet culture method was used to recreate the biological microenvironment like a regenerative milieu in SHED and DPSCs. The expression rates of inflammatory cytokines such as matrix metalloproteinase (MMP) 1, 2, tissue inhibitors of metalloproteinase 1, 2 and interleukin (IL)-6 were assessed. Overall, it is concluded that SHED is a feasible, available and possible source of tissue regeneration [5].

The comparison of SHEDs with hematopoietic stem cells

SHEDs are a complementary for cord blood stem cells. SHEDs are capable to renewal rigid tissue types but the hematopoietic stem cells could not repair the connective, dental, nervous and bone tissues. Although, hematopoietic stem cells are invaluable for the refinement of blood cells.

The effects of low-level laser therapy on SHEDs

The low-level laser break the total energy and release with single or several radiations could induce SHEDs renewal. Cell viability with MTT assay, trypan blue exclusion test, and crystal violet and also cell density determination with sulforhodamine B test had been performed at

24, 48, and 72 h after the first irradiation. The use of laser releasing fractionated total energy (2 or 3 times of 2.5 J/cm^2) stimulated cell proliferation after 2 days, but one radiation with 2.5 J/cm^2 could not induce metabolic function and the viability. Also, the 5.0 and 7.5 J/cm^2 single doses and the 3 time uses of 2.5 J/cm^2 protected the cells and induced division of SHED after 3 days [6].

The effects of SHEDs on inflammation

Temporomandibular joint osteoarthritis (TMJ-OA) is an inflammation disorder in joints. Exosomes secreted by SHEDs (SHED-Exos) have an anti-inflammation effect on TMJOA by miRNA (microRNA)-100-5p/mTOR. They had confirmed using western blot and transmission electron microscope examinations and also nanoparticles tracking. The anti-inflammatory effects of SHED-Exos were verified using western blotting and RT-qPCR. The miRNA expression of SHED-Exos, was determined by miRNA array analysis. Cartilage cells were recovered with a miR-100-5p emulation or rapamycin. The molecular effect of the exosomal miR-100 target, mTOR was detected by a luciferase reporter test. The results revealed that MiR-100-5p would be in the SHED-Exos, abundantly. SHED-Exos down-regulated the expression of IL-6, IL-8, MMP1, MMP3, MMP9, MMP13, and disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5). Cartilage cells recovered by the miR-100 emulation revealed low levels of MMP1, MMP9, MMP13, ADAMTS5, and mTOR. But, the expression of the MMPs and mTOR were increased. Rapamycin therapy enhanced miR-100 and suppressed MMPs and ADAMTS5. So, the luciferase reporter assay showed that miR-100-5p exactly selected the mTOR 3' untranslated region and SHED-Exos miR-100-5p down-regulated mTOR gene. It is revealed that SHED-Exos has anti-inflammatory effects on TMJ cartilage cells and so, SHED-Exos has therapeutic effects on TMJOA [3].

The effects of SHEDs on hair regeneration

The evidence revealed that mesenchymal-epithelial interrelations in the primary differentiation steps of teeth and hair follicles have numerous homologies. SHED extracted from 8 to 12 years old child accelerate the hair regeneration cycle and enhance and aggregate the skin cells, *in vitro*. SHED and dermal cells of C57 mice were administrated to nude mouse, *in vivo*. So, hair was appeared from dermal cells sans SHED. For the molecular mechanism exploration, the epidermal and dermal cells were exploited and cultured with SHED. After that, many ligands in regenerated hair follicle were indicated. Also, the levels of Sonic Hedgehog (Shh) and Glioma-associated oncogene 1 (Gli1) were increased. So, SHED might promote the generation of hair with increasing Shh/Gli1 levels that is a revolution in tissue regeneration and improvement of injured cell [7].

Medical use of SHEDs in dentistry

The capacities of SHEDs were investigated by tissue engineering and regenerative medicine. Some recognized main principles of these investigations are restoration of perfusion in a necrotic root canal using disinfectant following establishment of bleeding in the canal with many instruments. The use of root canal irritants (NaOCl and chlorhexidine) with the antibiotics (ciprofloxacin, metronidazole, and minocycline), for many days, are major steps in root canal disinfection and enhancement of perfusion in the tissue. So, there are not immune rejection and pathogen transmission in revascularization because of insider blood cells involved in this regeneration [5]. When the apex is open, post-natal stem cells derivative from derma, buccal mucosa, adipose, and bone tissue are transplanted in the dis-infected canal system for pulp implantation. The transferring of auto-genous stem cells by syringe, are simple. The other preference is the capacity of these cells in stimulation of pulp retreatment. Although, this procedure has some unfavorable results, such as the less viability of the cells and the migration of the cells to another sites throughout the body. To improve the chance for success and the usage of the maximal capacity of these stem cells in pulp renewal, 3 parameters including cells, growth factors, and platform have to be investigated [5].

The pulp cells should be cultured on membrane filters to turn 2 dimensional pellet culture system into 3 dimensional cells in post-natal stem cell treatment. The easiness of the growth of these cells on filters in the laboratory for cytotoxicity evaluation is a major benefit of this transfer process. But the difficulty of the generated pulp sheets implantation is the need for

Table 2. The effects of SHEDs therapy in comparison with the control group

Criteria	SHED group	Control group	Methods	*P* value
Serum Blood Urea Nitrogen (mg/ml) on day 2	17	27	Biochemistry Test	<0.05
Serum Creatinine (mg/dl) on day 2	1	1.7	Biochemistry Test	<0.05
Infiltration of macrophages (Count/HPF) in mice kidneys on day 2	20	50	F4/80 and Ly-6B Immunohistochemistry Assay	<0.05
Infiltration of PMNs (Count/HPF) in mice kidneys on day 2	20	50	F4/80 and Ly-6B Immunohistochemistry Assay	<0.05
Inflammatory cytokines (MIP-2) (pg/mg) in mice kidneys on day 2	27	68	Sandwich Enzyme-Linked Immunosorbent Assay	<0.05
Inflammatory cytokines (IL-1β) (pg/mg) in mice kidneys on day 2	8	20	Sandwich Enzyme-Linked Immunosorbent Assay	<0.05
Inflammatory cytokines (MCP-1) (pg/mg) in mice kidneys on day 2	80	225	Sandwich Enzyme-Linked Immunosorbent Assay	<0.05

specialized process for appropriate attachment to the canal system. As coronal canal stacked by scaffold that able to provide cell division, just the head of the canal will reach this cell structure because of the cells have not angiogenesis [8].

A scaffold have to consist of many growth factors including fibroblast and vascular endothelial growth factors, and also Bone Morphogenic Protein (BMP) that are needed for proliferation and differentiation of the stem cells. Besides, for scaffold implantation and transfer, it needs nutrients to amplify cell life and antibiotics to kill the bacteria in root canal. The scaffold substances might be natural or artificial, temporary or perpetual. The artificial substances including poly-lactic acid, poly-glycolic acid, and poly-caprolactone degrade throughout the body and could utilize for tissue engineering targets. The limitations of this process are related to porosity and pore size problems [9].

By 3-dimensional printing, just the cells remain that generate tissue and simulate the native teeth pulp tissue constructions. The principal of this method is the trend of pulp tissue when place it in the arranged and formed canal system in the head and coronal symmetry [10].

Gene therapy is a novel method that inoculates coding genes that could later express the purpose protein. Rutherford transferred the ferret pulps contain cDNA into the mouse BMP-7. Any reparation was done, but it was proposed that more investigations are needed for better pulp gene treatment. Despite, the use of viral delivery system in many tissues, there are crucial health risks such as mutagenesis, carcinogenesis, and immune system responses to virus and its proteins [10].

In another study, stem cells derived from apical papilla and dental pulp that could generate cells like odontoblast and produce dentine-like tissue on the present dentinal wall by cell regenerating methods. Also, pulp-like tissue could be produced renewal tissue in an emptied canal system in animal model [11].

The effects of SHEDs on bone regeneration

By the progress in the stem cell biology, dental stem cells will fortunately be capable to repair cleft palate, rescue damaged tooth and jaw bone, refine periodontal disorders, and also have major influence on regeneration of the whole tooth construction. Although, more studies are needed to provide a harmony between the osteogenesis and osteoclast genesis procedures. Also, the researches could perform in monkeys because their alveolar bone environments are more resemble to human [12].

The effects of SHEDs on kidney injury treatment

SHED therapy is useful for the ischemic kidney damage. *In vitro* studies showed that SHED significantly could reduce MCP-1 secretion in tubular epithelial cells caused by H2O2. Also, *in vivo* assays demonstrated the effects of SHED therapy in comparison with the control group (**Table 2**). So, SHEDs could utilize for acute kidney injury [13].

The effects of SHEDs on wound healing

Wound healing could improve with basic fibroblast growth factor (b-FGF) in addition to human deciduous teeth dental pulp cells (hDPCs). The immune-histologic experiments showed that human type I collagen, surrounded PKH26-positive cells at day 14 in nude mice *in vivo*. Also, the collagen fibril zones significantly enhanced at days 7 and 14 in wound induced by hDPC/b-FGF in comparison with the normal one. Also, SHEDs enhance HGF expression,

although it might be down regulated with antibodies, but it could improve wound in the scratch experiment [14].

Therapeutic application of SHEDs on type 2 diabetes patients

MSCs are able to treat diabetes, while the beneficial effects are not clear. In particular, the medical MSC treatment are unclear. In a follow-up study, twenty-four type 2 diabetes mellitus (T2DM) patients treated with insulin were isolated for receiving 3 systemic injections of SHED from 42 days to 12 months. Glycosylated serum albumin and hemoglobin level reduced significantly after SHED administration with total effective rate at 86.36% and 68.18%, respectively in the last of treatment and control duration. Three patients desisted of insulin injection after SHED administration. More researches revealed there was a low reply to SHED administration in hypercholesterolemia and low C-peptide. Also, unstable fever in 11.11% of patients, fatigue in 4.17%, and rash in 1.39% after SHED administration were seen. As, serum lipid level and baseline islet activity are major factors for treatment by MSC administration in T2DM patients, it was concluded that SHED administration is an assured and efficient treatment for islet activity and glucose metabolism recovery in T2DM patients [15].

Therapeutic effects of SHEDs on liver impairment

Liver transplantation is an end treatment for incurable liver involvement. Stem cells are important as a suitable cell sources for liver renewal. The therapeutic effects of SHED on hepatogenic were investigated in carbon tetrachloride (CCl4)-induced liver fibrosis model mouse (CCl4-ILFMM). The SHED administrated into CCl4-ILFMM were delivered to liver receivers to express human leukocyte antigen-ABC (HLA-ABC), human hepatocyte specific antigen, and hepatocyte paraffin 1, and also human albumin. SHED administration significantly improved liver disorders and caused anti-fibrotic and anti-inflammatory influences on the liver receivers. HLA-ABC cells derived from SHED and classified from the elementary liver receiver cells with CCl4 defect did not mix with the host mice liver cells. Classified HLA cells expressed human hepatocyte-specific genes such as albumin, cytochrome P450 1A1, fumarylacetoacetase, tyrosine aminotransferase, uridine 5'-diphospho-glucuronosyltransferase, transferrin and transthyretin, and also secreted human albumin, urea and blood urea nitrogen. Besides, HLA-ABC cells derived from SHED were administrated to CCl4-treated mouse, again. The donor cells inserted to secondary liver receivers, and expressed hepatocyte paraffin 1 and human albumin, and also HLA-ABC. The secondary administration improved a liver impairment in secondary liver receivers. Thereby, SHED could promote hepatic disorders and directly transform to hepatocyte without cell fusion in CCl4-treated mice, and suitable for liver renewal [16].

SHEDs have few oncogenesis, proliferative, multi-potency, and immune-suppressive ability. They have an anti-fibrotic influence on liver fibrosis *in vivo*. SHED administration and the bio three dimensional printers that could provide scaffold-free three dimension images of the liver and diaphragm, are a novel treatment in regenerative medicine for uncontrolled pediatric surgery including biliary atresia and diaphragmatic hernia [2].

Therapeutic effects of SHEDs on nerve impairment

SHEDs and their medium could be influence on neuron disorders via several mechanisms, such as cell replacement, paracrine effects, angiogenesis, synaptogenesis, immunomodulation, and apoptosis inhibition. SHED-exos is as an appropriate regenerative agent in neuron dysfunctions. Many common therapeutic applications of SHEDs were observed but their focus on neuro-protection is rather than neuro-regeneration [17].

SHEDs have a great immune-modulatory and neuroprotective potential. An experiment showed that SHED transplantation regulate peripheral c-Jun in the trigeminal ganglia (TG) in a mouse model of trigeminal neuralgia, and it had analgesic effects. In this study, chronic constriction damage to the infra-orbital nerve (CCI-ION) was induced. The mechanical threshold was evaluated by von Frey filaments, and the mRNA levels of c-Jun in the ipsilateral TG were tested. The phosphorylation of c-Jun in the ipsilateral TG was tracked using immunohistochemistry and western blotting. PKH26-labelled SHEDs were expanded to any parts of

TG, lung, liver and spleen. Intravenous SHED administration significantly enhanced the mechanical threshold in CCI-ION mice and down-regulated the c-Jun mRNA in the TG injury. SHED administration obstacle the activation of c-Jun in the TG. So, systemic SHED administration down-regulated the c-Jun in the TG, returned trigeminal neuralgia and removed pain. The phosphorylation of c-Jun lead to hyper-algesia and allodynia improvement, so SHED transplantation might improve trigeminal neuralgia [18].

Mechanical allodynia is a painful sensation make happened with innocuous stimuli like light touch. Although, inflammatory hyperalgesia play a maintenance role, but allodynia has no biological effect. SHED could reduce mechanical allodynia *in vivo* by the siglec-9/MCP-1-mediated tissue-improving mechanism. The influences of SHEDs on mechanical allodynia were evaluated in animal model. Systemic transplantation of SHED and conditioned medium from SHED (SHED-CM) significantly inverse the mechanical allodynia caused with spinal nerve transection at day 6. SHED or SHED-CM significantly decreased the activated transcription factor 3-positive neurons and macrophages in the ipsilateral side of the dorsal root ganglion at day 20. SHED or SHED-CM down-regulated the activation of microglia and astrocytes in the ipsilateral side of the dorsal spinal cord. Systemic administration of ectodomain of sialic acid-binding Ig-like lectin-9 and monocyte chemoattractant protein-1 have not any influence on the mechanical allodynia, but systemic transplantation of SHED-CM with 30-50 kDa proteins inverse the pain. So, the 30-50 kDa molecular weight proteins released from SHED could maintain and recover dorsal spinal cord neurons injury and also promote mechanical allodynia [19].

Trigeminal neuralgia is an immedicable advanced neuron illness. SHEDs have neuroprotective and immunomodulatory effects to attenuate trigeminal neuralgia. The analgesic effects of SHEDs in chronic constriction damage to the infraorbital nerve (CCI-ION) had investigated in rats. The intravenous or topical administration of SHEDs reduced the reactions of mice to mechanical stimulation after neuron damage for eight weeks. PKH26-labeled SHEDs spread to the ipsilateral trigeminal ganglions 1 to 2 days after topical administration. SHED administration at the injection area decreased inflammatory cell penetration and pro-inflammatory cytokine amounts in the damaged nerve and suppressed CCI-ION- of transient receptor potential vanilloid type 1 level in the trigeminal nerve and ganglion in the early phase. So, SHED could treat the trigeminal neuralgia and another chronic neuropathic symptom [20].

The effects of SHEDs on systemic lupus erythematosus

The MSC characterizations of SHED have compared with BMMSCs. *In vitro* stem cell tests, like flow cytometry, inductive differentiation, telomerase activity, and western blot to access differentiated SHED and also *in vivo* investigations to find tissue renewal of SHEDs have performed. Besides, intravenous SHED administration have done to recover systemic lupus erythematosus (SLE)-like MRL/lpr mouse. The outcomes showed that SHEDs are able to differentiate into osteogenic, odontogenic, adipogenic, and also neural cells. They could express mesenchymal surface molecules such as STRO-1, CD146, SSEA4, CD73, CD105, and CD166, and also activate multiple signaling pathways, like TGFβ, ERK, Akt, Wnt, and PDGF. As, BMMSCs have an immunomodulatory activity, they could treat immune illness. But, the immunomodulatory properties of SHED compared with BMMSCs showed significant influences on T helper 17 cells *in vitro*. Besides, SHED administration could reverse SLE-associated defects in MRL/lpr mouse. Cellular characterizations revealed that SHED administration increase the ratio of regulatory T cells to T helper 17 cells. So, SHEDs are an available and possible MSC origin to recover immune illness like SLE [21].

The effects of SHEDs on brain injury

Traumatic brain injury (TBI) is a main problem all over the world. For this reason, BV-2 microglia cells with SHEDs were cultured by a transwell assay. The amounts of neuro-inflammatory agents and nitrite were examined using enzyme-linked immunosorbent assay (ELISA) and Griess test. Then, SHED-Exos were cultured by activated BV-2. ELISA, Griess assay, flow cytometry, immunofluorescence, and qRT-PCR were done for inflammatory agents. At last,

SHEDs and SHED-Exos were administrated by local injection into TBI animal model. The lesion volume and neuro-inflammation were measured by histopathology and immune-fluorescence. SHED-Exos could decrease neuroinflammation with replacing microglia polarization. The transplantation of SHED-Exos significantly promoted animal motor functional improvement and decreased cortical lesion in comparison with the normal one at 14 day. SHED-Exos contributed to practical improvement after damage with changing microglia M1/M2 polarization in animal model. So, the SHED-Exos could decrease the neuroinflammation. The beneficial effects of odontogenic stem cells, and SHED-Exos on TBI or other neurological diseases must be explored. SHEDs based therapies emerge as a potential therapy option for neurodegenerative disorders because their homing, engraft, differentiate and generate factors for CNS improvement [22].

The beneficial effects of SHED were mentioned as follows

SHED provides a storage of cells as a donor for life, before any injury make happens. SHED could use for any age and its collection and isolation is simple and safe. Not only for the donor, but also, it can use for close relatives of donors. It is not extensive and its price is less than 1/3 of cord blood preservation. Embryonic stem cells and SHEDs considered without ethical concerns.

By fantastic progress in the prevention, detection and therapeutic effects on clinical diseases, stem cell study is being track in the hope of receiving main clinical advances. By tissues generated from stem cells, researches are attempting to develop therapeutic applications to rebuilding and replacing injured cells and give hope to patients involving with various illness. Nowadays, several methods have been introduced for the culture of stem cells in vitro, which will support unexpected chances of human embryology. Besides, a set of standard surgery process and a safe measurement methods are needed to determine the possibility of the medical usage of SHEDs.

The limitations of SHED were mentioned as follows

Although, SHEDs have a chemical potential to find injury tissue, but if a physical occlusion such as a clogged artery had existed, these stem cells could not reach to the target cells. So, if the cause of the occlusion is not removed, there will be weak, slow, or no tissue regeneration. There are still some limitations for SHEDs including unknown immune system reaction, the possibility of stem cell migration and tumor generation, immune rejection after SHED transplantations, hemorrhage among neurosurgery and also postoperative infection. In addition, the effectiveness of permanent preservation of SHED and SHED-exos, the expansion of a vigorous GMP-grade construction method, regulation of the source of transplantation, and assessment of the effectiveness and security in humans are the other limitations of SHED transplantation [23, 24].

Author's views

The tendency to use SHEDs has been considered in recent years due to the capacity of these cells to develop into adipocyte, neural cells and osteogenic cells. The effects of SHED and the progress in the use of these cells in medical engineering and cell and tissue regeneration are so remarkable. SHED therapy is promising in particular for treatment of the autoimmune and degenerative diseases. Although the culture and maintaining of these cells might be difficult, but they could be carefully thawed when needed to preserve the viability of the cells. Despite these limitations, therapeutic application of SHEDs should be considered especially for regenerative medicine that repair dysfunctional or injured tissues. In conclusion, future researches could remove the limitations of SHED application to use them in various medical fields.

Conclusion

SHEDs with high proliferation rate could differentiate into a wide variety of cells. By the appearance of stem cell banking, SHEDs could use in different aspects such as tissue engineering and medicine. These outcomes contribute to preclinical documents that approve the use of SHED in the treatment. SHEDs administration as a perfect cell source is a promising novel therapy for regenerative medicine especially neurodegenerative defects. Also, the applications of SHEDs have been investigated in pulp implantation, postnatal stem cell therapy, three-dimensional printing, and gene therapy. Well proliferation property,

low invasive procurement, neuronal differentiation and neuro-trophic ability, with unremarkable ethical aspects are the profits of SHEDs than other MSCs. The treatment ability of SHED is related to the paracrine activity of extracellular released factors, specially the secretome, like exosomes that are essential part of SHEDs. Despite these potentials, there are still some limitations for SHED, including the effectiveness of permanent preservation of SHED and SHED-exos, the expansion of a vigorous GMP-grade construction method, regulation of the source of transplantation, and assessment of the effectiveness and security in humans. Also, more experiments are required to determine if stem cells derived from a tissue can contact with other tissues.

Acknowledgements

The authors would like to thank the Research Council of Hamadan University of Medical Sciences, Hamadan, Iran. The study was funded by Vice-chancellor for Research and Technology, Hamadan University of Medical Sciences, Hamadan, Iran.

The present study was approved by the Ethics Committee of Hamadan University of Medical Sciences, Hamadan, Iran.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Farideh Kamarehei, Department of Microbiology, Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran. E-mail: kamarehee@yahoo.com

References

[1] Shi X, Mao J and Liu Y. Pulp stem cells derived from human permanent and deciduous teeth: biological characteristics and therapeutic applications. Stem Cells Transl Med 2020; 9: 445-464.

[2] Taguchi T, Yanagi Y, Yoshimaru K, Zhang XY, Matsuura T, Nakayama K, Kobayashi E, Yamaza H, Nonaka K, Ohga S and Yamaza T. Regenerative medicine using stem cells from human exfoliated deciduous teeth (SHED): a promising new treatment in pediatric surgery. Surg Today 2019; 49: 316-322.

[3] Luo P, Jiang C, Ji P, Wang M and Xu J. Exosomes of stem cells from human exfoliated deciduous teeth as an anti-inflammatory agent in temporomandibular joint chondrocytes via miR-100-5p/mTOR. Stem Cell Res Ther 2019; 10: 216.

[4] Nakamura S, Yamada Y, Katagiri W, Sugito T, Ito K and Ueda M. Stem cell proliferation pathways comparison between human exfoliated deciduous teeth and dental pulp stem cells by gene expression profile from promising dental pulp. J Endod 2009; 35: 1536-1542.

[5] Wang X, Sha XJ, Li GH, Yang FS, Ji K, Wen LY, Liu SY, Chen L, Ding Y and Xuan K. Comparative characterization of stem cells from human exfoliated deciduous teeth and dental pulp stem cells. Arch Oral Biol 2012; 57: 1231-1240.

[6] Almeida-Junior LA, Marques NCT, Prado MTO, Oliveira TM and Sakai VT. Effect of single and multiple doses of low-level laser therapy on viability and proliferation of stem cells from human exfoliated deciduous teeth (SHED). Lasers Med Sci 2019; 34: 1917-1924.

[7] Zhang X, Lei T, Chen P, Wang L, Wang J, Wang D, Guo W, Zhou Y, Li Q and Du H. Stem cells from human exfoliated deciduous teeth promote hair regeneration in mouse. Cell Transplant 2021; 30: 9636897211042927.

[8] Murray PE, Garcia-Godoy F and Hargreaves KM. Regenerative endodontics: a review of current status and a call for action. J Endod 2007; 33: 377-390.

[9] Janicki P and Schmidmaier G. What should be the characteristics of the ideal bone graft substitute? Combining scaffolds with growth factors and/or stem cells. Injury 2011; 42 Suppl 2: S77-S81.

[10] Rai S, Kaur M and Kaur S. Applications of stem cells in interdisciplinary dentistry and beyond: an overview. Ann Med Health Sci Res 2013; 3: 245-254.

[11] Bansal R and Jain A. Current overview on dental stem cells applications in regenerative dentistry. J Nat Sci Biol Med 2015; 6: 29-34.

[12] Rutherford RB. BMP-7 gene transfer to inflamed ferret dental pulps. Eur J Oral Sci 2001; 109: 422-424.

[13] Huang GT, Yamaza T, Shea LD, Djouad F, Kuhn NZ, Tuan RS and Shi S. Stem/progenitor cell-mediated de novo regeneration of dental pulp with newly deposited continuous layer of dentin in an in vivo model. Tissue Eng Part A 2010; 16: 605-615.

[14] Jindal L, Bhat N, Vyas D, Thakur K and Neha MS. Stem cells from human exfoliated deciduous teeth (SHED) - turning useless into miracle: a review article. Acta Sci Dent Sci 2019; 3: 49-54.

[15] Hattori Y, Kim H, Tsuboi N, Yamamoto A, Akiyama S, Shi Y, Katsuno T, Kosugi T, Ueda M, Matsuo and Maruyama S. Therapeutic poten-

tial of stem cells from human exfoliated deciduous teeth in models of acute kidney injury. PLoS One 2015; 10: e0140121.
[16] Nishino Y, Ebisawa K, Yamada Y, Okabe K, Kamei Y and Ueda M. Human deciduous teeth dental pulp cells with basic fibroblast growth factor enhance wound healing of skin defect. J Craniofac Surg 2011; 22: 438-442.
[17] Li W, Jiao X, Song J, Sui B, Guo Z, Zhao Y, Li J, Shi S and Huang Q. Therapeutic potential of stem cells from human exfoliated deciduous teeth infusion into patients with type 2 diabetes depends on basal lipid levels and islet function. Stem Cells Transl Med 2021; 10: 956-967.
[18] Yamaza T, Alatas FS, Yuniartha R, Yamaza H, Fujiyoshi JK, Yanagi Y, Yoshimaru K, Hayashida M, Matsuura T, Aijima R, Ihara K, Ohga S, Shi S, Nonaka K and Taguchi T. In vivo hepatogenic capacity and therapeutic potential of stem cells from human exfoliated deciduous teeth in liver fibrosis in mice. Stem Cell Res Ther 2015; 6: 171.
[19] Anoop M and Datta I. Stem cells derived from human exfoliated deciduous teeth (SHED) in neuronal disorders: a review. Curr Stem Cell Res Ther 2021; 16: 535-550.
[20] Bai X, Xiao K, Yang Z, Zhang Z, Li J, Yan Z, Cao K, Zhang W and Zhang X. Stem cells from human exfoliated deciduous teeth relieve pain via downregulation of c-Jun in a rat model of trigeminal neuralgia. J Oral Rehabil 2022; 49: 219-227.
[21] Hayashi Y, Kato H, Nonaka K and Nakanishi H. Stem cells from human exfoliated deciduous teeth attenuate mechanical allodynia in mice through distinct from the siglec-9/MCP-1-mediated tissue-repairing mechanism. Sci Rep 2021; 11: 20053.
[22] Bai X, Zhang X, Wang C, Liu Y, Liu X, Fan Y and Zhang X. Stem cells from human exfoliated deciduous teeth attenuate trigeminal neuralgia in rats. Stem Cells Int 2021; 2021: 8819884.
[23] Yamaza T, Kentaro A, Chen C, Liu Y, Shi Y, Gronthos S, Wang S and Shi S. Immunomodulatory properties of stem cells from human exfoliated deciduous teeth. Stem Cell Res Ther 2010; 1: 5.
[24] Li Y, Yang YY, Ren JL, Xu F, Chen FM and Li A. Exosomes secreted by stem cells from human exfoliated deciduous teeth contribute to functional recovery after traumatic brain injury by shifting microglia M1/M2 polarization in rats. Stem Cell Res Ther 2017; 8: 198.