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REVIEW

Exfoliated Deciduous Teeth Pulp Stem Cells: Data on Experimental and Clinical Potential

Mukaddes Esrefoglu[1], MD

1 Department of Histology and Embryology, Medical Faculty, Bezmialem Vakif University, Fatih, Istanbul, Turkey.

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Correspondence to: Mukaddes Esrefoglu, Professor, Bezmialem Vakif University, Medical Faculty, Adnan Menderes Bulvari, Vatan caddesi, 34093, Fatih, Istanbul, Turkey.
Email: mesrefoglu@bezmialem.edu.tr
Telephone: +905323465239
ORCID: 0000-003-3380-1480

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ABSTRACT

The stem cells from human exfoliated deciduous teeth (SHED) are multipotent adult mesenchymal stem cells playing essential roles in tissue regeneration and tissue repair. This type of stem cells are able to differentiate into various cell types. Their regenerative ability can be applied in dentistry as well as in various fields of regenerative medicine. The results obtained from experimental trials are generally promising. However clinical trials are still missing because of various challanges. Herein, I focus on the data obtained from fundamental and clinical trials assessing the benefits of SHED on regeneration of tooth decays, wound healing, craniofascial abnormalities, and treatment of various neurological, cardiovascular, digestive and muscular diseases.

Key words: Exfoliated teeth; Pulp; Stem cells; Treatment

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INTRODUCTION

The dental pulp stem cells are ectodermal-derived stem cells, originating from migrating neural crest cells and possess mesenchymal stem cell properties[1]. Human exfoliated deciduous teeth have been considered to be a promising source for regenerative therapy because they contain unique postnatal stem cells from human exfoliated deciduous teeth (SHED) with self-renewal capacity, multipotency and immunomodulatory function[2]. Cryopreservation of dental pulp tissues of deciduous teeth provide a suitable and desirable approach for stem cell-based tissue engineering in regenerative medicine.

Currently, several dental progenitor/stem cell types have been demonstrated. These are dental pulp stem cells (DPSCs) from permanenth teeth, stem cells from human exfoliated deciduous teeth, dental pulp pluripotent-like stem cells, stem cells from apical papilla, progenitor and stem cells from the periodontal ligament, and dental follicle precursor cells[3,4]. Dental pulp stem cells were first isolated from human permanent third molars in 2000 by Gronthos *et al*[5]. In 2003, Miura *et al*[6] successfully isolated SHED and identified that they had the general characteristics of DPSCs. SHED are distinct from DPSCs with respect to their higher proliferation rate, increased cell-population doublings, sphere-like cell-cluster formation, osteo-inductive capacity *in vivo*. After *in vivo* transplantation, SHED were found to be able to induce bone formation, generate dentin, and survive in mouse brain along with expression of neural markers. The results of Nakamura *et al*[7] have indicated that SHED possess higher proliferation ability than DPSCs. Significantly higher expressions of FGF-2, TGF-b2, Col I, and Col III have been detected in SHED compared with DPSCs. Higher expressions for genes that participate in pathways related to cell proliferation and extracellular matrix have also been found in SHED rather than DPSCs. Wang *et al*[8] have shown that SHED have higher capability of mineralization than the DPSCs. Additionally, the expression levels of Col I and proliferating cell nuclear antigen (PCNA) in SHED sheets were significantly

Table 1 The results of the fundamental and clinical researches about the benefits of SHED are summarized.

Disease	Research	Shed	Animal
Tooth decay	Differentiation capacity in in vitro/in vivo researches	Odontoblast and endothelial- like cells, pulp-like structure, pulp dentin	Mouse
	Clinical	ABSENT	
Neurological diseases	Differentiation capacity in in vitro/in vivo researches	Neuron (mature, dopaminergic), dopaminergic neuron-like cell, astrocyte, oligodendrocyte	Mouse, rat
	Experimental		
	Benefits	Anti-apoptosis of neurons and glia cells, preservation of neurofilaments and myelin sheat, neuro-protection, neuro-regeneration, restoration of motor deficits, improvement of cognitive functions	
	Experimental diseases	Spinal cord injury, Parkinson's disease	
	Clinical	ABSENT	
Cardiovascular diseases	Differentiation capacity in in vitro/in vivo researches	Myocyte	Mouse
	Experimental		
	Benefits	Anti-apoptosis, anti-inflammation	
	Experimental diseases	Ischemia-reperfusion injury	
	Clinical	ABSENT	
Digestive diseases	Differentiation capacity in in vitro/in vivo researches	Endoderm, functional hepatocytes	Mouse, rat
	Benefits	Hepatocyte protection, proliferation and differentiation of the progenitor cells, improvement of liver functions, anti-inflammation, antifibrosis, angiogenesis, macrophage differentiation, improvement of glucose intolerance, restoration of normoglycemia, immune regulation	
	Experimental diseases	Liver failure, cirrhosis, diabetes	
	Clinical	ABSENT	
Craniofacial abnormalities	Differentiation capacity in in vitro/in vivo researches	Osteoblast	Mouse, rat, dog, puppy, rabbit
	Experimental	Osteo-induction, bone formation, bone regeneration	
	Clinical	ABSENT	
Muscular diseases	Differentiation capacity in in vitro/in vivo researches	Myocyte, myogenic cell line	
	Experimental	ABSENT	
	Clinical	ABSENT	
Wound healing	Differentiation capacity in in vitro/in vivo researches	Adipocyte	Mouse
	Experimental	Production of factors related with tissue regeneration and wound healing, reduction of wrinkles, enhancement of dermal thickness	
	Clinical	ABSENT	

higher than those in DPSCs sheets. In spite of some differences, both DPSCs and SHED have been shown to possess ability to further differentiate along odontogenic, chondogenic, osteogenic, myogenic, neuorogenic and adipogenic pathways *in vivo*[5,6,9-12].

I focus on the results of the fundamental and clinical researches related with the benefit of SHED. The results related with the benefits of SHED obtained from experimental and clinical studies are summarized in Table 1.

EXPERIMENTAL AND CLINICAL RESEARCHES RELATED WITH SHED

Regeneration of tooth decays

Experimental researches: SHED have not been reported to produce mature enamel, some data on these stem cells to produce crown-like structure, dentin and pulp have been accumulated[5,6,9]. Huang *et al*[13] have reported that stem/progenitor cells including DPSCs and SHED are capable of produce dentin-pulp-like complex when transplanted into mice. Cordeiro *et al*[14] have demonstrated that SHED/scaffold recombinations prepared within human tooth slices also have the potential to form dental pulp-like structures. SHED were able to differentiate into odontoblast-like cells and also endothelial-like cells *in vivo*. SHED are not only capable of generating bone and dentin but also transforming into other mesenchymal and non-mesenchymal stem cell *in vitro*, such as adipocytes and neural cell[6]. Dentin formation was detected *in vivo* when SHED recombined with HA-TCP scaffolds[8].

Clinical researches: No human trial has been reported in terms of SHED transplantation into human dental tissues so far.

Neurological Diseases

Experimental researches: Most SHED express neural stem/progenitor cell markers including early neuronal and oligodendrocyte markers[15], cranial neural stem cell markers, and neural crest-related markers[9]. The transformation of SHED into neuronal cells, some of the glia cells or neural-crest derived cells is not unexpected at all. SHED express several neurotropic factors that promote neurite extension[15,16]. Yamagata *et al*[16], in a mouse hypoxic ischemia model, found that intracerebral transplantation of SHED and the administration of serum-free conditioned media derived from SHED produce anti-inflammatory conditions and promote functional recovery. Thus, tooth-derived stem cells have strong

immunoregulatory properties that promote tissue regeneration in the injured central nervous system. Recently, Gervois *et al*[15] have demonstrated that human DPSCs are capable of neuronal commitment following neurosphere formation, characterized by distinct morphological and electrophysiological properties of functional neuronal cells. SHED have been shown to suppress apoptosis in neurons and oligodendrocytes, resulting in the remarkable preservation of neurofilaments and myelin sheaths in the region surrounding the epicenter of the lesion when grafted into hemisected spinal cord[17,18]. In another study, the undifferentiated or neural phenotype-induced SHED were transplanted into a contused rat spinal cord 7 days after injury. Both cell types primarily differentiated into MAP2+ mature neurons and GFAP+ astrocytes and, to a lesser extent, into MBP− and NG2-expressing oligodendrocytes[19]. The undifferentiated SHED were transplanted into a fully transected rat spinal cord immediately after surgery. More than 30% of the engrafted SHED survived as a cell mass in the injured spinal cord 8 weeks after transplantation, and more than 90% of the engrafted SHED differentiated toward mature oligodendrocytes, expressing APC and MBP[20]. As a result of mentioned and various other animal studies, it is now clear that engrafted SHED provide a number of distinct therapeutic benefits for treating spinal cord injury. These cells suppress the early inflammatory response, inhibit apoptosis of neurons, regenerate the transected axon through the direct inhibition of multiple growth inhibitor signals, and replace the damaged spinal cord by differentiation into oligodendrocytes, neurons and astrocytes[21].

SHED have been shown to be able to differentiate into dopaminergic neural cells under the regulated experimental cell differentiation conditions. Zhang *et al*[22] were able to differentiate the SHED to neurons and dopamine neurons. They transplanted the neural-primed SHED to the striatum of the rats with 6-hydroxydopamine-induced Parkinson's disease. They detected that the neurons derived from grafted SHED have the same membrane potential profile as dopamine neurons, indicating these cells are dopamine neuron-like cells. Compatibly, significant restorations of motor deficits were observed. Similarly Fujii *et al*[23] reported SHED to have high plasticity for differentiating into dopaminergic neuron-like cells. They transplanted these cells into striatum of the rats with Parkinson's disease and 6 weeks later they detected that the therapy restored the striatal innervation of throsine hydroxylase-positive fibers and promoted neurological recovery. Similar beneficial effects of SHED on a few cellular and animal models of Alzheimer's disease have been reported. Mita *et al*[24] performed an animal study on mice. They administered serum-free conditioned medium derived from human SHED into nasal cavity and detected that the therapy resulted in substantially improved cognitive function of the mice with Alzheimer's disease. Neuroregenerative mechanisms included neuro-protection, axonal elongation, neuro-transmission, the suppression of inflammation, and microglial regulation.

Clinical researches: No human trial has been reported in terms of SHED transplantation into human body for detecting their benefits on neurodegeneration.

Cardiovascular Diseases

Experimental researches: A few studies have reported the beneficial effects of SHED on cardiovascular diseases in rodents. Yamaguchi *et al*[25] investigated the impact of SHED-conditioned medium on myocardial injury in a mouse model of ischemia-reperfusion (I/R). Administration of the medium reduced myocardial infarct size as well as decreased apoptosis and inflammatory cytokine levels, such as TNF-α, IL-6, and IL-β, in the myocardium following I/R. Recently, Petchdee *et al*[26] have reported the results of multiple intravenous injections of puppy deciduous teeth stem cells to the dogs with degenerative valvular heart disease which are the largest animals used in DPSCs therapies on that topic. Post stem cell injection showed measurable improvement in left ventricular ejection fraction.

Clinical researches: No human trial has been reported in terms of SHED transplantation into human body for detecting their benefits on cardiovascular diseases.

Digestive Diseases

Experimental researches: Previous experimental studies related with the benefit of SHED on digestive system focus on liver and pancreas. SHED are known to differentiate into hepatocytes. Yamaza *et al*[27] have reported that trans-spleen administration of SHED into CCl_4-induced cirrhotic mice significantly improves liver function, inflammation, and fibrosis. SHED may exert their effects either by repopulation of cells in injured liver or by paracrine mechanisms due to their immune-regulatory functions Ishkitiev *et al*[28] have detected that transplantation of human hepatocytes differentiated from SHED into the spleen of rats with acute liver injury or secondary biliary cirrhosis improves hepatic functions via transdifferentiation and repopulation of the cells. The study of Matsushita *et al*[29] even showed that a single intravenous administration of SHED or of SHED-derived serum-free conditioned medium into the d-galactosamine-induced rat model of acute liver failure markedly improved the condition of the injured liver and the animals' survival rate. SHED-derived serum-free conditioned medium has been shown to possess multiple regenerative roles in anti-apoptosis/hepatocyte protection, angiogenesis, macrophage differentiation and the proliferation/differentiation of liver progenitors.

In recent years experimental stem cell trials also focused on the treatment of diabetes. Izumoto-Akita T *et al*[30] showed that various factors secreted from SHED were effective to improve glucose intolerance in streptozotocin-induced diabetic mice. Kanafi *et al*[31] packed islet-like cell clusters obtained from SHED in immuno-isolatory biocompatible macro-capsules and transplanted into streptozotocin-induced diabetic mice. SHED were superior to DPSCs. Mice transplanted with macro-capsules containing islet-like clusters were restored to normoglycemia within 3-4 weeks, which persisted for 60 days.

Clinical researches: No human trial has been reported in terms of SHED transplantation or SHED-derived islet cell cluster transplantation into human body for detecting their benefits on digestive diseases.

Muscular Diseases

Experimental researches: SHED have been shown to possess ability to further differentiate along myogenic pathways[32]. However no experimental study has been performed on therapatic effecs of SHED on muscular diseases so far.

Clinical researches: Unfortunately, to date no human trial has been reported in terms of SHED transplantation into human body for detecting their benefits on muscular diseases.

Craniofacial Abnormalities

Experimental researches: SHED have been shown to be able to differentiate into osteoblasts and osteocytes[33]. SHED possess osteo-inductive capacity. Following transplantation into immunodeficient mice, SHED clones seemed to induce bone formation by the

organization of an osteo-inductive matrix, responsible for the recruitment of murine osteogenic cells[6]. Yamada *et al*[34] have shown that DPSCs and SHED of dog and puppy when implanted with platelet-rich plasma are able to structure well-formed neovascularized mature bone tissue, and enhance the osseo-integration.

In recent years studies related with the benefit of SHED application oral or craniofacial regeneration have been slightly accumulated. Nakajima *et al*[35] transplanted human DPSCs and SHED with a polylactic-coglycolic acid barrier membrane as a scaffold to immunodeficient mice for bone regeneration in an artificial bone defect of 4 mm in diamater in the calvaria. Although degree of bone regeneration with SHED relative to the bone defect was almost equivalent to that with DPSCs 12 weeks after transplantation, SHED produced larger osteoid tissue and widely distributed collagen fibers compared to DPSCs. Alkaisi *et al*[36] transplanted six million human SHED into the distracted area during the osteotomy in rabbits in order to assess the benefit of these stem cells during the mandibular distraction osteogenesis. The percentage of newly formed bone after 2, 4, and 6 weeks was significantly enhanced. So SHED might be the one of the best candidate as a cell source for the reconstruction of the damaged bones. DPSC-seeded scaffolds were also found to be beneficial in bone healing in a rat critical-size calvarial defect model. Bone mineral density and bone micro-architectural parameters were significantly increased when DPSC-seeded scaffolds were used[37]. Zhang *et al*[38] used human DPSCs seeded tyrosine-derived polycarbonate scaffolds for regeneration of a 5 mm rat mandibular ramus critical bone defect. They reported that the scaffolds containing DPSCs supported the rapid regeneration of osteo-dentin-like mineralized jaw tissue. In the same year, Jahanbin *et al*[39] reported the results related with their success of a maxillary alveolar defect repair in rats using osteoblast-differentiated human DPSCs.

Clinical researches: Unfortunately, to date no human trial has been reported in terms of SHED transplantation into human body for detecting their benefits on restoration of craniofascial defects.

Wound Healing

Experimental researches: Previously, Nakamura *et al*[7] have reported that SHED express several growth factors such as FGF, TGF-beta2, connective tissue growth factor, nerve growth factor, and bone morphogenetic protein. FGF-2 has been reported as a cytokine that acts to promote the proliferation of numerous kinds of cells and to control the extracellular matrix generation during tissue generation and wound healing. There are a few animal studies on the benefit of DPSCs and SHED on wound helaing. Nishino *et al*[4] isolated human DPSCs from human deciduous teeth and used those cells in a nude mouse full-thickness skin defect model for evaluating the course of wound healing. They observed that DPSCs together with FGF accelerated wound healing. Ueda *et al*[41] injected SHED subcutenously into the restricted area of the hairless mice irradiated dorsally with ultraviolet in order to genereate wrinkles. SHED-injected group appeared to have fewer wrinkles than the nontreated group. Additionally, the dermal thickness was significant increased in SHED-injected group and a marked increase in collagen bundles was also observed.

Clinical reseraches: Unfortunately, to date ho human trial has been reported in terms of SHED transplantation into human body for detecting their benefits on wound healing.

CONCLUSION

SHED should be considered as an excellent stem cell group in terms of being easily obtainable and possessing high differentiation capability. However, despite the success obtained from animal trials, clinical trials are still missing. It is obvious that before the clinical application of SHED, the experimental studies need to resolve various issues. Many factors of the microenvironment effects the integration of the donor cells into the host tissues. Thus the interaction between transplanted stem cells and local cells of microenvironment needs to be analyzed in detail.

I suggest that researchers need some time for performing clinical trials with SHED as well as many other stem cell types. By the way, preservation and deposition namely banking of individual dental stem cells would be appropriate.

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