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Data on Experimental and Clinical Potential of Dental Pulp Stem Cells

Mukaddes Esrefoglu*

Bezmialem Vakif University, Medical Faculty, Department of Histology and Embryology, Turkey

***Corresponding author:** Mukaddes Esrefoglu, Bezmialem Vakif University, Medical Faculty, Adnan Menderes Bulvari, Vatan caddesi, 34093, Fatih, Istanbul, Turkey

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ABSTRACT

Dental pulp stem cells (DPSCs) of the permanent teeth are multipotent adult mesenchymal stem cells playing essential roles in cellular regeneration, tissue repair and healing. Dental pulp stem cells are able to differentiate into various cell types. Their excellent regenerative ability can be applied in dentistry as well as in various fields of regenerative medicine. However, despite the success obtained from animal trials, clinical trials are still missing because of various challenges. Herein, I focus on the data obtained from fundamental and clinical trials assessing the benefits of DPSCs on regeneration of tooth decays, wound healing, craniofascial abnormalities, and treatment of various neurological, cardiovascular, digestive and muscular diseases.

Keywords: Pulp Stem Cells; Potency; Treatment

Introduction

Several types of stem cells have been described in the multicellular organisms in terms of mainly differentiation capacity. These are totipotent stem cells, pluripotent stem cells, multipotent stem cells (adult stem cells), and unipotent stem cells. The dental pulp stem cells (DPSc) are ectodermal-derived adult multipotent stem cells, originating from migrating neural crest cells and possess mesenchymal stem cell properties [1]. Their high plasticity and multipotential capacity to differentiate into a large array of tissues can be explained by its neural crest origin [2]. During last decade, human DPSCs have received extensive attention in the field of tissue engineering and regenerative medicine due to their accessibility and ability to differentiate in several cell phenotypes [1]. In the near future the multipotent stem cells of the permanent or deciduous teeth might be the main cell source for the stem cell banking. In this review, I focus on the results of the fundamental and clinical research related with the benefit of DPSCs. The results related with the benefits of DPSCs obtained from experimental and clinical studies are summarized in Table 1.

Table 1: The results of the fundamental and clinical research about the benefits of DPSCs are summarized.

Disease	Research	Potency	Animal
Tooth decay	Differentiation capacity *in in vitro/in vivo* research	Odontoblast-like cell, odontoblast, osteo/odontoblastic lineage, predendin-dentin-pulp-crown-bone- like tissues, pulp, dentin, periodontal bone	Mouse, swine
	Clinical	Absent	

Neurological diseases	Differentiation capacity in *in vitro/in vivo* researches	Neuron (functional, cholinergic, dopaminergic), GFAP and S-100 + glia cells	Mouse, rat, dog
	Experimental		
	Benefits	Motor nerve regeneration	
	Experimental diseases	Spinal cord injury, Alzheimer's disease	
	Clinical	Absent	
Cardiovascular diseases	Differentiation capacity in *in vitro/in vivo* research	Myocyte	Rat, dog
	Experimental		
	Benefits	Angiogenesis, reduction of infarct size, improvement of left ventricular function	
	Experimental diseases	Acute myocardial infarction, degenerative valvular heart disease	
	Clinical	Absent	
Digestive diseases	Differentiation capacity in *in vitro/in vivo* research	Endoderm, functional hepatocytes, insulin-producing pancreatic cell, pancreatic islets	Rat
	Experimental		
	Benefits	Repair of the liver, improvement of liver functions	
	Experimental diseases	Liver failure, cirrhosis, diabetes	
	Clinical	Absent	
Muscular diseases	Differentiation capacity in *in vitro/in vivo* research	Myocyte, myogenic cell line	Mouse, dog
	Experimental	Angiogenesis, reduction of fibrosis, improvement of muscle dystrophy	
	Clinical	Absent	
Craniofacial abnormalities	Differentiation capacity in *in vitro/in vivo* research	Osteoblast, osteo-dentin like mineralized tissue, bone-like tissue, periodontal bone	
	Experimental	Bone formation, bone regeneration, bone healing	Mouse, rat, dog, puppy
	Clinical	Repair of periodontal defect	From rat to human
Wound healing	Differentiation capacity in *in vitro/in vivo* research	Corneal epithelial cell, adipocyte	Mouse
	Experimental	Acceleration of wound healing	
	Clinical	Absent	

Location and Isolation of DPSCs

The pulp is composed of the loose connective tissue that occupies the pulp cavity which is the most central region of the tooth. The connective tissue of the pulp is devoid of elastic fibers but is rich in vessels, nerve fibers and various types of cells including fibroblasts, telocytes, mast cells, macrophages, and leukocytes. Nowadays it has been clear that the connective tissue of the pulp of the permanent teeth and deciduous teeth hosts some multipotent stem cells called 'dental pulp stem cells. The dental pulp consists of four layers which are the odontoblastic zone, cell free zone, cell rich zone, and central zone. The cell-rich zone is the area that is richly populated with stem/progenitor cells beside the other cell types and serves as a reservoir for the replacement of destroyed odontoblasts [3]. Dental pulp stem cells are generally localized in the perivascular region of the pulp tissue. Their location associate with the expression of some vascular antigens suggest that these stem cells may be of a vascular origin [4]. Recently, several studies suggested that dental pulp stem cells might be derived from neural crest [1-3,3,5]. These cells express several neural crest-related markers including S-100, nestin, CD57, CD271, glial fibrillary acidic protein and share many similarities with cranial neural crest stem cells on the aspects of immunophenotypes and other biological behaviors [4]. Currently, several dental progenitor/stem cell types have been demonstrated. These are dental pulp stem cells from permanenth teeth (DPSCs), stem cells from human exfoliated deciduous teeth (SHED), dental pulp pluripotent-like stem cells, stem cells from apical papilla, progenitor and stem cells from the periodontal ligament, and dental follicle precursor cells. There has

been an intense investigation on the characteristics of these cells and their potentialities [6,7].

Even though there is no specific biomarker available for the identification of DPSCs, these cells express several markers including the mesenchymal and bone-marrow stem cell markers, neural cell markers, neural stem/progenitor cell markers and embryonic stem cell markers [4,8-10]. Negative markers include CD14, CD34, CD45, HLA-DR [9]. It is important to remember that DPSCs do not necessarily express all of these markers; each DPSCs may express some of these markers at different levels. DPSCs isolated by their high proliferative potential tend to include a large population cell expressing CD44, CD90, and CD166 [8]. DPSCs were first isolated from human permanent third molars in 2000 by Gronthos, et al. [11]. In 2000, they mixed approximately 5.0 X 10^6 of DPSCs with 40 mg of HA/TCP ceramic powder and transplanted subcutaneously into the dorsal surface of 10-week-old immunocompromised beige mice. They reported that DPSCs are clonogenic and highly proliferative cells which are capable of generating a dentin-like structure lined with human odontoblast-like cells that surrounded by a pulp-like interstitial tissue. Govindasamy, et al. [12] reported that stem cells from the third molar were shown to have a lower population doubling time, higher colonogenic activity and an improved growth curve compared with those from the deciduous incisor. That data indicates that stem cells from the human third molar are appropriate candidates for experimental, pre-clinical and even clinical research. It is now well known that DPSCs possess ability to further differentiate along odontogenic, chondrogenic, osteogenic, myogenic, neuorogenic and adipogenic pathways *in vivo* [3,11,13-15].

Experimental and Clinical Research Related with DPSCs

Regeneration of Tooth Decays

Experimental Research: Tooth decays cannot be spontaneously regenerated after eruption because the ameloblasts which are responsible for production of the enamel disappear during the eruption. Although DPSCs has not been reported to produce mature enamel but crown-like structure, dentin and pulp [3,11,15,16]. Some studies have shown that these stem cells can also bring about the formation of bone-like tissues [3]. Numerous experimental approaches have demonstrated that isolated DPSCs can be directed in transplants to differentiate into cells forming predentin-like pattern area. The stem cell transplantation therapy should be a splendid therapy used in regenerative medicine. DPSCs have been shown to differentiate *in vitro* toward osteo/odontogenic phenotypes (verified by the deposition of mineralized matrix and positive staining for dentin sialophosphoproteins) [15]. Gronthos, et al. [11] observed a dentin-pulp-like structure, similar to the one observed in human teeth, 6 weeks after the transplantation of DPSCs along with HA/TCP powder into immunocompromised mice. Collagenous matrix was deposited perpendicular to the odontoblast-like layer and the odontoblast-like cells extended cytoplasmic processes into the dentinal matrix. When Takeda, et al. [17] cultured human DPSCs in a medium promoting differentiation toward the cells of the osteo/odontoblastic lineages; the cells produced calcified matrix and dentin-like matrix on scaffolds *in vivo*. However, during long-term passage, these cells underwent a change in morphology and lost their differentiation ability due to the changes in the expression of several genes, such as WNT16 or due to the failure of routine culture medium to simulate the in-situ niches of these stem cells. The observations of Arthur, et al. [13] suggest that following dentin matrix damage, EphB/ephrin-B molecules are important for perivascular DPSC migration toward the dentin surfaces and differentiation into functional odontoblasts. When DPSCs are transplanted alone or in combination with bone morphogenic protein-2, these stem cells can significantly promote the repair and reconstruction of dentin-pulp-like complex [16]. Prescott, et al. [18] placed the material containing DPSCs, a collagen scaffold, and dentin matrix protein-1 into the simulated perforation sites in dentin slices and transplanted it subcutanously into the nude mice. Six weeks later, organization of newly derived pulp tissue was seen by light microscopy. Huang, et al. [19] have reported that stem/progenitor cells including DPSCs are capable of produce dentin-pulp-like complex when transplanted into mice. Recently, Hu, et al. [20] have reported the results of cell injection or cell sheet transplantation of human DPSCs into swines which are the largest animals used in dental stem cell therapies. Both human DPSC injection and cell sheet transplantation significantly regenerated periodontal bone in swine.

Clinical Research: No human trial has been reported in terms of DPSCs transplantation into human dental tissues so far. Future strategies will no doubt concentrate on making a bio-tooth by detecting the differentiation mechanisms of the dental stem cells, optimizing the bio-scaffolds, and exploring the microenvironment necessary for the cellular adaptation and differentiation. The stem cell-based approaches to tooth reconstruction will provide an unpredictable opportunity to recover tooth loss and other dental diseases [3].

Neurological Diseases

Experimental Research: DPSCs might express neural stem/progenitor cell markers including early neuronal and oligodendrocyte markers [21], cranial neural stem cell markers, and neural crest-related markers [3]. The transformation of DPSCs into neuronal cells, some of the glia cells or neural-crest derived cells is not unexpected at all. Moreover, DPSCs express several neurotropic factors that promote neurite extension [21,22]. Recently, Gervois, et al. [23] have demonstrated that human DPSCs are capable of neuronal commitment following neurosphere formation, characterized by

distinct morphological and electrophysiological properties of functional neuronal cells. The results of Jang, et al. [24] demonstrated that stem cells from cryopreserved dental pulp could successfully differentiate into cholinergic neurons *in vitro* and enhance motor nerve regeneration when transplanted into rats. Ullah, et al. [25] have shown that human DPSCs and differentiated neuronal cells from DPSCs increase specific markers for angiogenesis, axonal fiber, and myelin sheath when transplanted into the sciatic nerve resection site of the rats. At 12th weeks after cell transplantation, both groups showed notably increased behavioral activities and higher muscle contraction forces compared with those in the non-cell transplanted control group. When DPSCs were transplanted into compressed mouse spinal cords on day 7 or day 28 after injury, the engrafted DPSCs differentiated into glia cells expressing S-100 and GFAP [21]. As a result of mentioned and various other animal studies, it is now clear that engrafted DPSCs provides 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 [26].

Human DPSCs have been shown to be able to differentiate into dopaminergic neural cells under the regulated experimental cell differentiation conditions [27]. Similar beneficial effects of DPSCs on a few cellular and animal models of Alzheimer's disease have been reported [28,29]. Wang, et al. [28] co-cultured human DPSCs with human neuroblastoma cell line damaged by okadaic acid and observed re-elongation of retracted dendrites. Additionally, they observed the morphology of restored neurons, with elongated dendrites, densely arranged microfilaments, and thickened microtubular fibrils. Recently, Feitosa, et al. [20] have reported the results of cell injections of human immature DPSCs into the spinal cords of three dogs with chronic spinal cord injury which are the largest animals used in DPSCs therapies on that topic. There was significant improvement in terms of the limb functions evaluated by Olby scale, though it was not supported by the imaging data provided by MRI.

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

Cardiovascular Diseases

Experimental Research: A few studies have reported the beneficial effects of DPSCs on cardiovascular diseases in rodents. Gandia, et al. [31] have found DPSCs beneficial by improving left ventricular function, inducing angiogenesis and reducing infarct size in rats with experimental acute myocardial infarction. However, they obtained no histological sign of differentiation of DPSCs into endothelial cells, smooth muscle cells or cardiac muscle cells in the infarct area.

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

Digestive Diseases

Experimental Research: Previous experimental studies related with the benefit of DPSCs on digestive system focus on liver and pancreas. DPSCs are known to differentiate into hepatocytes [32]. DPSC-derived hepatocytes possessing detoxification and glycogen storage capacities indicate that they share multiple functions with real hepatocytes [33]. Cao, et al. [34] transplanted hepatocyte growth factor (HGF) over-expressing DPSCs into the rats with liver cirrhosis intravenously. The HGF over-expressing DPSCs showed increased survival and hepatogenic differentiation in host liver tissue at 6 weeks after injection. They also exhibited a significantly greater repair potential than DPSCs expressing HGF at physiological levels. Additionally in recent years pancreatic islets were generated from DPSCs in a 3D culture system [35].

Clinical Research: No human trial has been reported in terms of DPSCs transplantation into human body for detecting their benefits on digestive diseases.

Muscular Diseases

Experimental Research: DPSCs have been shown to possess ability to further differentiate along myogenic pathways [3]. Recently Pisciotta, et al. [36] injected human DPSCs which were differentiated toward myogenic cell line into the dystrophic gastrocnemius muscles of mdx/SCID mice. Within 1-4 weeks, they detected that the therapy promoted angiogenesis and reduced fibrosis through a paracrine effect and eventually led to an improvement of the histopathology of the dystrophic muscle. Similarly, Martínez-Sarrà, et al. [37] assessed the effects of human dental pulp pluripotent stem cells on muscle regeneration in two genetic mouse models of muscular dystrophy. In dystrophic mice, dental stem cells engrafted in the skeletal muscle of both dystrophic murine models and showed integration in muscular fibres and vessels. Stem cell therapy resulted in reduced fibrosis and collagen content, larger number of types II fast-glycolytic fibres and infiltration of higher numbers of proangiogenic CD206+ macrophages. The largest animals exposed to the DPSC treatment are the golden retriever dogs suffering from muscular dystrophy. Kerkis, et al. [38] transplanted DPSCs into 4 littermate dogs aged 28 to 40 days by either arterial or muscular injections. Human DPSC presented significant engraftment in the muscles, although human dystrophin expression was modest and limited to several muscle fibers. Better clinical condition was also observed in the dog which received monthly arterial injections and was still clinically stable at 25 months of age.

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

Craniofacial Abnormalities

Experimental Research: DPSCs have been shown to be able to differentiate into osteoblasts. DPSCs express bone-related markers, such as bone sialoprotein, alkaline phosphatase, osteocalcin, osteonectin, and collagen type I and type III [39]. Odontoblast differentiation, assessed by the expression of dentin sialophosphoprotein and enamelysin/matrix metalloproteinase, was induced in the presence of bone morphogenetic protein-2 in the culture of DPSCs in 3-dimensional cell pellets. Moreover, these pellets stimulated reparative dentin formation in an amputated pulp model in the dog [16]. Yamada, et al. [40] have shown that DPSCs 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 DPSCs application oral or craniofacial regeneration have been slightly accumulated. Nakajima, et al. [41] transplanted human DPSCs 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 diameter in the calvaria. They detected bone regeneration within 12 weeks after transplantation.

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 [42]. Zhang, et al. [43] 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. [44] reported the results related with their success of a maxillary alveolar defect repair in rats using osteoblast differentiated human DPSCs.

Clinical Research: Li, et al. [45] harvested DPSCs from inflammatory pulp tissues of two patients suffering from peridontal intrabone defects. They engrafted DPSCs loaded onto the scaffold material β-tricalcium phosphate into the periodontal defect area in the root furcation. After 1, 3, and 9 months, the outcome was evaluated by clinical assessment and radiological study. DPSCs were able to engraft and had an effect of regeneration of new bones to repair periodontal defects 9 months after surgical reconstruction.

Wound Healing

Experimental Research: Nishino, et al. [46] 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.

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

Conclusion

DPSCs should be considered as an excellent stem cell group in terms of being easily obtainable and possessing high differentiation capability. Their excellent regenerative ability can be applied in dentistry as well as in various fields of regenerative medicine. However, despite the success obtained from animal trials, clinical trials are still missing because of various challanges. It is obvious that before the clinical application of DPSCs the experimental studies need to resolve various issues. It is now well-known that transplantation of the stem cells into any environment does not necesserily imply that these cells are able to survive and to function properly. Many factors of the microenvironment effect the integration of the donor cells into the host tissues. Thus, the interaction between transplanted stem cells and local cells or microenvironment needs to be analyzed in detail. I suggest that researchers need some time for performing clinical trials with DPSCs 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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