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Human dental pulp stem cells differentiation: A review

Elham Mohammadi Golrang [1], Fatemeh Dibaji [2], Naghmeh Bahrami [3*], Atena Mohammadi Golrang [4]

1. School of Dentistry, Tehran University of Medical Sciences, International Campus, Tehran, Iran.

2. Department of Endodontics, School of Dentistry, Tehran University of Medical Sciences, International Campus, Tehran, Iran.

3. Craniomaxillofacial Research Center, Department of Oral and Maxillofacial Surgery, School of Dentistry, Tehran University of Medical Sciences, Tehran, Iran.

4. Department of Kinesiology and Physical Education, Mc Gill University, Montreal, Quebec, Canada.

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**Corresponding author:*
Naghme Bahrami

Department of Oral and Maxillofacial Surgery, School of Dentistry, Tehran University of Medical Sciences, North Amirabad St, Tehran, Iran.

Tel: +98-21-84902473
Fax: +98-21-84902473
Email: naghmehbahrami@Gmail.com

ABSTRACT

The advent of regenerative medicine has brought us the opportunity to regenerate, modify and restore human organs function. Stem cells, a key resource in regenerative medicine, are defined as clonogenic, self-renewing, progenitor cells that can generate into one or more specialized cell types. Human dental pulp stem cells (HDPSCs) are ectodermal-derived stem cells, originating from migrating neural crest cells and are capable of providing enough cells for potential cell-based therapies. During last decade, HDPSCs 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. In this review, we have described the potential of HDPSCs to differentiate into odontoblasts, osteoblasts, hepatocytes, neuroblasts and angioblasts in response to different bioactive factors. Therefore, the culture and selective differentiation of HDPSCs should provide further understanding of dental pulp progenitors and their potential use for new therapeutic approaches in regenerative medicine.

Keywords: Human dental pulp stem cells (HDPSCs), Differentiation, Bioactive factors, Inductive factors.

Introduction

Adult stem cells are able to replace cells after disease. Throughout the last years, researches have highlighted that stem cells are capable to differentiate into more cell types than formerly believed [1]. This phenomenon is probably because of their transdifferentiation potential and plasticity. It is well known that stem cells in adult may be able to populate other tissues and possibly differentiate into other cell types after their exposure to a new environment [2].

Human dental pulp stem cells (hDPSCs) can be found within the "cell rich zone" of dental pulp particularly in the perivascular and perineurosheath regions. Their embryonic origin, from neural crests, clarifies their multipotency [3]. They are also considered as an interesting and potentially important source of autologous stem cells that are ready for use in therapeutic purposes, such as the repair and regeneration of various tissues. It has been reported that these cells can be easily cryopreserved and stored for long periods of time and still retain their multipotency and differentiation capacity [4,5]. They also can be more easily sourced as they can be obtained from teeth impacted third molars or from sound teeth that are considered to be extracted due to orthodontic or periodontal reasons.

This review recognize the available information on the effect of different inducing factors as a regulator of hDPSCs differentiation, including self-renewal capability and

multi-lineage differentiation.

Dental Stem Cells

Teeth develop due to interactions between the dental epithelium and the underlying ectomesenchymal cells, forms the enamel organ, the papilla and the dental follicle [6-9]. MSCs give rise to other components of the tooth, such as dentin, enamel, pulp, periodontal ligament, and the cementum [10,11].

Human dental stem cells that have been isolated and characterized, depending on their harvest sites, are:

1. Human dental papilla cell line: DP-805 [12].

2. Human dental pulp stem cells: HDPSCs [4, 13-15].

3. Stem cells from human exfoliated deciduous teeth: SHEDs [16,17].

4. Stem cells from apical papilla: SCAPs [18-20].

5. Periodontal ligament stem cells: PDLSCs [21-23].

6. Dental follicle stem cells: DFSCs [24,25].

HDPSCs aremostly interesting because teeth, regardless of their small size, are a source of abundant cells for therapeutic procedures, and their harvesting can be linked to routine tooth extraction, which does not place an additional burden on the patient [26]. These stem cells have a high level of clonogenicity and can differentiate into a variety of cell times, such as odontoblasts, adipocytes, osteoblasts, neurons, chondrocytes, and myoblast cells [27-29].

Human Dental Stem Cells Identification

The mesenchymal and tissue stem cell committee of the international society for cellular therapy (ISCT) proposed a set of standards to define human MSCs for both laboratory-based scientific investigations and preclinical studies [30,31].

They proposed three criteria to define MSCs:

1. Plastic adherence is a well-described property of MSC and unique subsets of MSCs.

2. Surface antigen has been used for identification of a cell population. It has been shown that more than 95% of MSCs expressed CD105, CD73 and CD90, while less than 2% of MSCs expressed hematopoietic Ag. Thus, ISCT proposed that MSCs must express CD105, CD73 and CD90, and lack in expressing the hematopoietic Ag. Some of the examples of hematopoietic Ag are CD45, CD34, CD14 or CD11b, CD79 or CD19 and HLA-DR.

3. Multipotent stem cells have the ability differentiate into all cell types within one particular lineage and self-renewing. Stem cells are categorized by their potential to differentiate into other types of cells which are totipotent, pluripotent, multipotent and unipotent [32,33].

Furthermore four commonly used stem cell identification techniques from a population of mixed cells are:

1. Staining the cells with specific antibody markers and using a flow cytometer, in a process called fluorescent antibody cell sorting (FACS).

2. Immunomagnetic bead selection.

3. Immunohistochemical staining.

4. Physiological and histological criteria, including phenotype, proliferation, chemotaxis, mineralizing activity and differentiation [34].

Osteogenic Differentiation of HDPSCs

Modulation of the osteogenic potential in human mesenchymal stem cells has become an important topic in orthopedics field [35]. Various studies have shown the potential of dental stem cells differentiation to osteoblast. Kadkhoda et al. evaluate the osteoblast differentiation of periodontal ligament-derived stem cells for bone regeneration in rabbit calvaria and indicated that PDLSCs can be a good source for bone regeneration [36].

Human dental pulp is now considered as a remarkable reservoir of stem cells highly amenable for regenerative medicine for both oral and non-oral diseases. Maioli el at. investigated the response of hDPSCs to melatonin, a mixture of hyaluronic, butyric, and retinoic acids (HA + BU + RA), or a combination of the two mentioned conditioned media. This invitro resultsillustrated that osteogenic differentiation enhanced synergistically when hDPSCs are culturedin a conditioned medium containing both melatonin and HA + BU + RA [37].

Additionally, Mangano et al. challenged bone formation on different titanium surface textures with either human osteoblasts or stem cells from human dental pulps to understand their osteointegration. Cells cultured on the titanium surfaces underwent protein secretion and gene expression examination. Results

showed hDPSCs were capable to quickly differentiate into osteoblasts and endotheliocytes and, then, able to produce bone tissue along the implant surfaces [38]. Bakopoulou et al showed hDPSCs induced by media containing dexamethasone, KH_2PO_4 and β-glycerophosphate can undergo osteo/odontogenic differentiation [18]. An invitro study done by Taohong et al. demonstrated that insulin-like growth factor 1 (IGF-1) can promote the proliferation and osteo/odontogenic differentiation of HDPSCs by activating MAPK pathways [39]. These evidences prove that different types of dental stem cells including dental pulp stem cell, can be used in tissue regeneration protocols as an accessible stem cell source for osteogenic differentiation and biomineralization that could be further applied for stem cell-based bone regeneration and osteointegration.

Odontogenic Differentiation of HDPSCs

Human dental pulp stem cells have a potential for pluripotency and can differentiate into odontoblast-like cells, which synthe size and secrete the collagenous and non-collagenous proteins for instance alkaline phosphatase (ALP), OPN and DSPP to form the reparative dentin after tooth injury [40, 41]. Qin Liu et al. investigate the effect of melatonin on the proliferation and differentiation of the HDPCs. They showed that melatonin-treated HDPCs exhibited an increase of ALP activity, expression of DSPP, mRNA levels of ALP and DSPP, and mineralization nodules formation. Their findings revealed that melatonin at physiological concentrations can prevent proliferation and promote the differentiation of HDPCs [42]. Huixia et al. investigated the inductive effects of fibroblast growth factor 2 (FGF2) and transforming growth factor beta 1 (TGFβ$_1$)on the odontoblastic differentiation of human dental pulp stem cells and they concluded that., together, FGF2 acted primarily on the cell proliferation, while TGFβ$_1$ and FGF2 + TGFβ$_1$ mainly stimulated the odontoblastic differentiation of hDPSCs [43]. In another study, simvastatin at 1 μmol/L promoted mineralized tissue formation and noted as ideal active ingredient to accelerate the odontogenic differentiation of hDPSCs. These pieces of evidence highlight the role that hDPSCs have in the mechanism of regulating odontoblasts to achieve dentine regeneration.

Hepatogenic Differentiation of HDPSCs

Different studies have shown that the application of human dental pulp stem cells improves structural and functional recovery of number of injured organs as they have the ability to differentiate into neurogenic, osteogenic/odontogenic, adipogenic, myogenic, and chondrogenic lineages [44].

For the first time in 2014, Young-Ah Cho el al. have partially examined the therapeutic effects of a combination of melatonin and hDPSC transplantation on carbon tetrachloride (CCl4)-induced liver fibrosis in mice. They demonstrated that the combination of melatonin and HDPSC significantly suppressed liver fibrosis and restored ALT, AST, and ammonia levels. They showed that melatonin promotes hepatic differentiation of hDPSCs by modulating the BMP, p38, ERK, and NF-jB pathway [45]. Thus combined treatment of hDPSCs and melatonin could be a feasible method for the treatment of liver cirrhosis.

In the study of Ishkitiev et al. the hepatic differentiation of HDPSCs was also verified after cells exposure to hydrogen sulfide (H_2S) at physiological concentrations [46]. Consistent with these findings, Okada et al. determine the effects of H2S on hepatic differentiation between human bone marrow stem cells and stem cells from human primary tooth pulp. They concluded that H2S increased the level of hepatic differentiation in both cells and the level of hepatic differentiation in human primary tooth pulp compared with human bone marrow stem cells was the same or higher [47].

Neurogenic differentiation of HDPSCs

Adult human dental stem cells are putatively neural crest (NC) cell derived [48] and thus may have neurogenic potential that relates to the generation of neurons and their connections and Schwann cells. Dental stem cells express a variety of neural cell markers like nestin, βIII tubullin, glutamine acid decorboxylase (GAD), neuronal nuclei (Neu N), glial fibrillary acidic protein (GFAP), neurofilament M (NFM), Neuron Specific Enolase (NSE) and 2'3'-cycle nucleotide-3' -phosphodiesterase (CNP ase) when induced with neurogenic medium [49]. Bahrami et al. demonstrated that dental follicle stem cells and PDL stem cells that have been cultured in standard neural inductive medium containing retinoic acid, exhibit neurogenic differentiating potential [29]. Furthermore, Bayat et al. in agreement with previous finding, examine the differentiation ability of wisdom tooth follicle stem cells into nerve and bone tissue. They isolate the stem cells of 3 impacted 3rd molars, then cultured in standard medium for neural differentiation and bone differentiation. After twenty-one days the differentiation of the stem cells were examined and compared. Results showed neurogenic and osteogenic differentiation potential in derived stem cell from tooth follicle cells [9]. Gangliosides also play a role in the neuronal differenti-

ation process of HDPSCs. In a study when ganglioside biosynthesis was inhibited in HDPSCs by knockdown of UDP-glucose ceramide glucosyltransferase, differentiation into neural cells was prevented [49]. It is shown that simultaneous protein kinase C and cyclic adenosine monophosphate activation induces neuronaldifferentiation of human dental pulp stem cells [50]. Basic fibroblast growth factor also has the same effect on and involves in the mechanisms controlling HDPSCs neurogenic differentiation [51]. Other findings suggest that in response to the neuronal inductive stimuli such as dopaminergic and motor neuronal inductive media, a greater proportion of HDPSCs acquire a phenotype resembling mature neurons [52]. Taken together, these data suggest that dental pulp stem cells could provide a novel alternative cell population, when cultured in neuronal inductive stimuli, for neural tissue engineering and neural damages repair.

Angiogenic differentiation of HDPSCs

Angiogenesis is the formation of capillaries from prior blood vessels which is an important process in tissue engineering. If blood supply cannot be established quickly, there will be inadequate oxygen and nutrient transport and necrosis of the implanted tissue will happen. Although HDPSCs show self-renewal and multilineage differentiation capacity, but only little is known about the angiogenic abilities and mechanisms of the HDPSCs. Bronckaers et al. studied the angiogenic profile of both cell lysates and conditioned medium of HDPSC. Numerous pro-and anti-angiogenic factors such as vascular endothelial growth factor (VEGF), monocyte chemotactic protein-1 (MCP-1), plasminogen activator inhibitor-1 (PAI-1) and endostatin were found both at the mRNA and protein level. HDPSCs were able to significantly induce blood vessel formation and induce angiogenesis [53]. Additionally HDPSCs improve left ventricular function, induce angiogenesis, and reduce infarct size in rats with acute myocardial infarction [54]. These data suggest HDPSCs can show a great clinical potential, not only for tissue engineering but also for the treatment of chronic wounds, stroke and myocardial infarctions.

Conclusion

Dental mesenchymal stem cells are defined as non-hematopoietic stromal cells with the ability to transdifferentiate into various lineages and serve to develop, repair and regenerate the mesenchymal tissues. There are several types of dental MSCs depending on the tissue origin, such as HDPSCs, DFSCs and SHEDs [42,55], which have difference in membrane biomarkers and the ability to differentiate, repair and regenerate. However, it is not yet clear which type of stem cell sources are most potent and best for targeted therapy, understanding the gene expression profile, identifying specific growth factors and their mechanisms [56] will definitely help developing our understanding of molecular triggering and is fundamental to the development of successful cell-based therapies [57]. Latest studies show HDPSC to have self-renewal and multilineage differentiation capacity. Since these cells can be easily isolated, cultured and cryopreserved, they represent an attractive stem cell source for tissue engineering. Stem cells derived from human dental pulp form a suitable source for tissue engineering and cell-mediated therapy, although additional analyses should be considered.

Conflict of Interest

There is no conflict of interest to declare.

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