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INVITED REVIEW

Dental Tissue-Derived Stem Cells as a Candidate for Neural Regeneration

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ABSTRACT

In recent years, stem cell therapy tried to improve the life of patients that suffer from neurodegenerative disease, like Alzheimer's disease. Although teeth are non-essential for life, but the dental tissues are an important source of mesenchymal stem cells that are suitable for neural regeneration. The studies showed that dental stem cells (DSCs) have the potential to differentiate into several cell types that among the most important is neural progenitor. In this review article, discusses the types of dental stem cells and then focused on application of dental stem cells on neural regeneration.

Key Words: Stem Cells, Cell therapy, Dental Stem Cells, Dental Pulp Stem Cells, Neuron

Introduction:

In science, stem cell is an undifferentiated cell that has the potential for self-renewal and the ability of differentiating into more than one cell phenotype [1]. Several stem cell populations isolated from different parts of the mature and immature tooth. These dental stem cells, including 6 types: DPSCs (Dental Pulp Stem Cells), SHEDs (Stem cells from Human Exfoliated Deciduous

List of abbreviation: DPSCs (Dental Pulp Stem Cells), SHEDs (Stem cells from Human Exfoliated Deciduous teeth), DFPCs (Dental Follicle Precursor Cells), SCAPs (Stem Cells from the Apical Papilla), PDLSCs (Periodontal Ligament Stem Cells), GMSCs (Gingival Mesenchymal Stem Cells), SCs (Stem Cells), BMSCs (Bone Marrow Stem Cells), ASCs (Adult Stem Cells), GFAP (Glial Fibrillary Acid Protein), IGF-2 (insulin- like growth factor-2), EMSCs (ectomesenchymal stem cells), PNS (peripheral nerve system), NSCs (neural stem cells), BMPs (bone morphogenetic proteins) and FGFs (fibroblast growth factors)

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teeth), DFPCs (Dental Follicle Precursor Cells), SCAPs (Stem Cells from the Apical Papilla), PDLSCs (Periodontal Ligament Stem Cells) and GMSCs (Gingival Mesenchymal Stem Cells). Dental stem cells have multi-differentiation potential into cell lineages, including osteogenic, adipogenic, and neurogenic. Therefore, these cells are suitable for cell therapy. Researchers showed that NSCs renewed a damage nervous system. DPSCs and SHEDs were able to differentiate into neurons, in rat and human. Furthermore, studies showed that transplantation of DPCs and SHEDs into caused to express neuronal markers in brain [2, 3]. This review article discusses the types of dental stem cells, and then focused on application of dental stem cells in neural regeneration.

1. Origin of the dental stem cells

The tooth development formed during the sixth week of development, and then neural crest cells migrated into head and neck mesenchyme and also the ectoderm conversion to the dental laminae. The forming of tooth composed of epithelial and mesenchymal interactions, these interactions formed separate tooth germs [4-7]. The tooth germ is organized into three parts, namely enamel organ, dental papilla and dental follicle. The dental papilla develops into odontoblasts, which are dentin-forming cells [8, 9]. Mesenchymal cells within the dental papilla develop into tooth pulp. The dental follicle gives rise to three essential nature: cementoblasts, osteoblasts, and fibroblasts. Cementoblasts formed the cementum covering the root of a tooth [10]. Osteoblasts give rise to the alveolar bone and fibroblasts develop the PDL, which connect teeth to the alveolar bone through Sharpey's fibres that insert into the cementum [11].

The studies showed that development of mice teeth associated with gene expression such as Barx1, Lhx8, Msx1 and Msx2, also some secretory molecules such as BMPs and FGFs [12]. Bernick and Nedelman showed that during the aging process appeared a decrease in the size of the pulp cavity and deposition of calcium in the root and crown of the dental Pulp [13], it could indicate that dental pulp stem cells efficiency associated with age of subjects.

2. Types of dental stem cells

2.1 Dental pulp stem cells

Gronthos and co-workers in 2000 were the first persons that identification of stem cells from adult human dental pulp [14]. Dental pulp has a population of stem cells, which is often called odontoblast cells Because these cells synthesis and secretion of dentin matrix [15]. The origin of odontoblast cells not clear, but one of the hypothesis showed that the origin of these cells were progenitor stem cells [16]. The studies showed that DPSCs have high efficacy in proliferation and frequency of colony-forming compared with BMMSCs [14]. Furthermore, researchers showed that DPSCs formed functional dental tissue in vivo transplantation of mice. In addition, DPSCs express neuronal precursors and glial cell markers such as Nestin and GFAP respectively; and have the ability of differentiation into neural-like cells [17]. Studies demonstrated mouse and human dental tissues preserved the odontogenic potential in during early tooth development [18, 19] **2.2 Stem cells from human exfoliated deciduous teeth**

These stem cells have high efficacy like stronger proliferation rate, cell-population doublings, and sphere-like cell-cluster formation [3]. SHED expressed cell markers such as STRO-1 and CD146, and embryonic stem cell surface antigens such as Oct4, Nanog, and SSEA-3/4 [20].

Studies demonstrated that SHED have a high capacity for induction of bone formation in vivo [3, 21, 22]. Also, SHED have a neural crest-cell origin of the dental pulp and expressed neuronal and glial cell markers [23]. Neural crest cells have the ability of giving rise to a variety of cell types such as neural cells, pigment cells, smooth muscle, craniofacial cartilage, and bone [24].

2.3 Periodontal ligament stem cells

The PDL is a fibrous connective tissue that fixed a tooth to the alveolar bone [25]. Human PDLSCs located in periodontal ligament from third molar teeth.

Seo and coworker [26] showed that PDLSCs have potential to differentiate along cementoblast-like cells and adipocytes. Studies showed that isolated hPDLSCs displayed fibroblasts and spiky morphology; also an expression of mesenchymal stem cell markers such as CD146/MUC18 and STRO-1 [26]. In addition, PDLSCs have a potential to secretion of interleukin-6 (IL-6) so suppress the proliferation, differentiation and immune reaction of B cells [27, 28]. Furthermore, a tendon-specific transcription marker called scleraxis expressed higher levels in PDLSCs than in DPSCs or BMSCs. Therefore, PDLSCs are a unique population of adult MSCs [22].

2.4 Root apical papilla stem cells

Located at the apex that known as (SCAP). During root development, there is an "apical cell-rich zone lying" between the apical papilla and the pulp. Abe and co-worker in 2007 isolated and characterized of Human SCAP [29]. SCAP has a higher proliferative potential, then this population suitable for cell therapy; also SCAP could differentiate into odontoblasts and adipocytes [30, 31]. Furthermore, SCAP has significantly greater potential in comparison with DPSCs such as doubling population numbers, capacity of tissue regeneration, bromodeoxyuridine uptake rate, number of STRO-1 positive cells, express a higher level of survivin (anti-apoptotic protein) and positive hTERT (human telomerase reverse transcriptase that maintains the telomere length) activity [31].

Studies showed that SCAP have a positive staining for several neural markers by immunocytochemical staining such as Nestin, tubulin III, NeuN (neuronal nuclear antigen), glutamic acid decarboxylase, CNPase (glial marker) [32]. Therefore SCAP are a suitable source for neural researches and therapy of neurodegenerative diseases.

2.5 Dental follicle precursor cells

The DF is a loose ectomesenchyme that originated from connective tissue and isolated from human third molars [25]. For the first time Morsczeck and co-worker in 2005 showed the existence of progenitor cells of DF in wisdom teeth [34]. In addition Handa and co-workers in 2002 showed the presence of DF in bovine [33]. In general, DF had a high ability to differentiated into multi-linage like chondrogenic, osteogenic and adipogenic and neurogenic [35, 36], although there is conflict idea about the differentiation potential of DFSCs into chondrogenic [36].

The dental follicle expressed some cell markers such as Nestin, STRO-1, Notch1 [34] and IGF-2 [37]. Although the DF expressed MSC markers like CD29, CD44, and CD 105 [35]. In comparison with BM cells, DFPCs expressed higher levels of IGF-2.

Studies showed that the addition of TLR3 and TLR4 agonists to DFPCs caused to secretion of TGFB and IL-6 [38, 39]. Morsczeck and co-worker in 2010 demonstrated that SHED and DFCs have different neural differentiation potentials and cell marker expression patterns under the same cell culture conditions [39].

2.6 Gingival stem cells

Gingiva connected to the alveolar bone of tooth sockets. The fibroblasts of gingival contribute to the wound healing process by secreting extracellular matrix proteins and growth factor [40-42]. Zhang and co-worker are the first persons that isolated a progenitor stem cells within gingival tissues [42]. The neural crest origin of gingiva make it suitable for neural regeneration. The study showed colony forming efficiency among three MSCs types as follows: DSCs > GMSCs > PDLSCs [43].

GMSCs could differentiate into osteoblasts, adipocytes, chondrocytes, and neural cells; also they express some markers such as Oct-4, SSEA-4 and STRO-1 [44-48].

3. Dental stem cells in neural regeneration

Studies showed that NSCs isolated from dental tissue were a good choice for neural regeneration [49-53]. Studies demonstrated that transplantation of dental EMSCs have potential to adopting a neural phenotype and make renewal neurogenesis in experimental animals [54, 55, 3]. In CNS and PNS injury animal models transplanted of NCSC-derived dental tissue make trouble in regeneration and recovery [50, 51, 56-60].

Studies showed that transplanted of DPSCs into striatum from the right dorsolateral caused to induce a significant promotion of neurological dysfunction in animal models [61].

Researchers showed that transplantation of SHED spheres improved the behavioral disorders in a Parkinson rat model [62]. Studies showed that injection of DPSCs into the cerebro-spinal fluid caused to integrate into the brain and induced neuronal properties in cortical lesion models [63]. Studies showed that HDPCs caused to expressed of trophic factor, the existence of axons or oligodendrocytes in spinal cord injury models [64].

Studies showed that differentiation of MSCs to neural cell-linage essentially require to Nestin expression [65]. Martens and co-workers showed that human DPSCs have ability of differentiation to Schwann-like cells. In addition, hDPSCs expressed Schwann cell markers. These findings, make hDPSCs suitable for cell therapy in PNS injury [66]. Many factors play role in neuronal differentiation such as expression of Nestin [67], tubulin3 (Tub3) [68], and MAP2 [69]. The existence of Nestin displayed the ability of differentiating into neurons [67, 71]. Also, studies demonstrated that Nestin expressed by other cell types such as myofibroblasts, and pancreatic fibroblasts [72], pericytes [73], hair follicle stem cells [74] and endothelial cells [75]. Nestin is a neuronal marker in the brains of rat and human [76]; and play an important role in neuronal differentiation of vertebrate cells [68, 70]. In addition, these neuronal markers (Nestin and Tub3) were used to examine neuronal differentiation in the hippocampus [54].

This evidence opens new doors on the treatment of human neural disorders, like brain, and neurodegenerative diseases.

Conclusion:

Many characteristics of dental stem cells, including: neural crest origin, expression of neural markers such as Nestin, Map2 and Tub3 make dental stem cells as a candidate for neural regeneration. Because of dental stem cells have a common origin with the nervous system, dental stem cells may be ideal for cell therapy in conditions such as stroke, Alzheimer disease, spinal cord trauma, and other neurodegenerative diseases.

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