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Review article

Dental stem cells: Emerging Future

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ABSTRACT

Stem cells are clonogenic cells that are capable of self-renewal and multi-lineage differentiation. Dental stem cells are the highly proliferative cells that have the potential to differentiate into numerous cell types such as odontoblasts, osteoblasts, chondrocytes and adipocytes. The natural and non-invasive sources of dental stem cells are the teeth. Dental pulp is the most common source of postnatal stem cells. Due to its multipotency, proliferative activity and accessibility, these are mesenchymal cells used for tissue regeneration. These are obtained from human permanent and primary teeth, human wisdom teeth, human exfoliated deciduous teeth, apical papilla, periodontal ligament, supernumerary teeth and dental follicle. Through this article, we attempt to review the different types of dental stem cells reported in literature.

KEY WORDS: Dental pulp cells, Apical papilla, Progenitor cells, Dental follicle.

INTRODUCTION

Stem cells are cells that have the ability to continuously self-replicate (i.e., produce daughter cells having the same characteristics as themselves), generate daughter cells with different and more restricted properties, and re-populate a host in vivo [1]. Adult stem cells are undifferentiated cells found among differentiated cells in a tissue or organ that can renew itself.

Dental stem cells are considered as a new source of adult stem cells that could be used for regenerative medicine. Dental stem cells could be removed from an individual's primary or permanent teeth, expanded, and put back into the same individual when repair becomes necessary [2]. Generally, dental stem cells were first isolated by Gronthos and co-workers from the dental pulp and exfoliated deciduous teeth [2, 3]. Dental stem cells can also be extracted from the apical papilla of shed primary teeth (SCAP) [4]. Dental papilla stem cells (DPSCs) exhibit a multipotent character since they are capable of differentiating into various cell types, such as chondrocytes, adipocytes, osteoblasts, myocytes, neuronal cells, and cardiomyocytes [5, 6]. Adult dental papilla stem cells can divide only a finite number of times (according to the age of the individual), and they may accumulate genetic changes over time [7].

Dental pulp cells can be reprogrammed into induced-pluripotent stem cells at a higher rate compared with other cell types of human origin tried so far [8]. Animal studies have shown potential of DPSCs for repair and regeneration of various tissues, such as bone, heart, muscles, and teeth [9-14]. DPSCs play major role in bone and cartilage tissue engineering, especially when they can be used as autologous transplants. Recently, the first clinical trial of DPSC application in patients for bone reconstruction was successfully carried out by Papaccio and co-workers [15]. Karaoz et al in 2009 demonstrated that dental pulp cells have a mesenchymal character based on their ability to differentiate into many cell types [16]. According to the literature, there are several types of stem/progenitor cells existed in dental tissue.

Dental Pulp Stem Cells (DPSCs)

The presences of stem cells in dental pulp tissue primarily have been reported by Yamamura in 1985 [17-19]. Later on, Caplan et al [20] have demonstrated that these cells presented osteogenic and chondrogenic potential in vitro, and could also differentiate into dentin, in vivo. In 2000, Gronthos et al [21] have isolated dental pulp stem cells from adult human dental pulp, which had the ability to regenerate a dentin-pulp-like complex. Interestingly, some recent works have found the presence of stem cells in inflamed pulp with capacity to form mineralized matrix both in vitro and in vivo. These findings make dental pulp as an interesting tissue source of putative stem cells, even in diseased form [22]. DPSCs were similar to mesenchymal stem cells in some ways that they are of fibroblastic morphology with selective adherence to solid surfaces, having good proliferative potential and capacity to differentiate in vitro, and the ability to repair tissues in vivo. DPSCs could differentiate into osteoblasts, chondrocytes & adipocytes, and also myocytes, neurons and hepatocytes lineages in vitro [18]. DPSCs were characterized by their negative expression of hematopoietic antigens (e.g., CD45, CD34, CD14), and positive expression of stromal-associated markers (e.g., CD90, CD29, CD73, CD105, CD44).

They also express multipotent marker (STRO-1) and extracellular matrix proteins, such as collagen, vimentin, laminin, and fibronectin [23-25]. The pluripotent stem cell markers, such as Oct4, Nanog, Sox2, Klf4, SSEA4 & c-Myc have been reported to express on DPSCs [26-28]. Recently, it was demonstrated that core transcription factor of the reprogramming Oct4, Nanog, Klf4 and c-Myc become significantly down-regulated following the DPSC differentiation [18]. Apart from stemness markers, DPSCs were also shown to express bone markers, such as bone sialoprotein, osteocalcin, alkaline phosphates (ALP), and type I collagen. This indicates their differentiation commitment into bone tissue [29]. On the other hand, the expression of dentin sialophosphoprotein (an odontoblast specific protein precursor) was not present in the cultures of hDPSCs implied that these cells represent an undifferentiated pre-odontogenic phenotype [30]. From immunological perspective, it has been reported that DPSCs displayed more immnosuppressive activities than the BM-MSCs [31].

Based on some investigations, there was a sub-type of DPSCs referred to as "immature dental pulp stems cells" (IDPSCs), which have promising potential in future stem cell researches. IDPSCs were firstly, isolated from pulp tissue of the human exfoliated deciduous as well as permanent teeth [32]. These cells express both embryonic and MSC markers. It has been indicated that transferring of human IDPSCs (hDPSCs) into mouse blastocysts resulted in formation of human/mouse chimera which was able to retain proliferation and differentiation capacity [33]. Furthermore, hIDPSCs possess the capacity to rapidly reprogrammed into induced pleuripotent stem cells (iPSc) which were able to produce primary hIDPSC-iPSC colonies even under feeder-free conditions [34].

Dental Stem cells from Human Exfoliated Deciduous teeth (SHED)

Miura et al in 2003 have reported to isolate a stem cell population from the living pulp remnants of exfoliated deciduous teeth. These authors have termed the cells as stem cells from human exfoliated deciduous teeth (SHED) [35]. These cells which were believed to be of the neural crest origin were heterogeneous fibroblast-like population possessing an extensive proliferating capacity than either DPSCs or BM-MSCs [36]. In terms of surface epitopes, it has been found that they express markers of MSCs (STRO-1, CD146, SSEA4, CD90, CD73, CD 105, CD106 and CD 166) and lack of hematopoietic/endothelial markers (CD34, CD31).

Under an appropriate culture conditions, SHED were able to differentiate into the variety of cell types, including neural cells, angiogenic endothelial cells, adipocytes, osteoblasts, and odontoblasts. [37-39] In vivo transplantation of SHED have been reported to result in formation of bone and dentin like-tissue [40-43]. There were some studies suggested that SHED was different from IDPSCs in terms of expression of stem cell markers [32, 33]. Moreover, some research works have been reported that SHED would possess immunomodulatory function as seen in BM-MSCs [42].

Periodontal Ligament Stem Cells (PDLSC)

Periodontal ligament stem cells (PDLSCs) have first been introduced by Seo et al [44]. Like MSCs, PDLSCs have been reported to form adherent clonogenic population of fibroblast-like cells in the culture. They express both early MSC markers such as, STRO-1 and CD146, and other MSC and pluripotent markers, such as CD44, CD90, CD105, CD73, CD26, CD10, CD29 and CD166; meanwhile, they have no expression for CD40, CD80, and CD86 [44-46]. Some investigations have revealed that PDLSCs may be positive for embryonic stem cell markers, as well, including SSEA1, SSEA3, SSEA4, TRA-1-60, TRA-1-81, Oct4, Nanog, Sox2 and Rex1, and ALP [47]. Based on some research works, SSEA4-positive PDLSCs displayed the potential to generate adipocytes, osteoblasts, chondrocytes (from mesodermal layer), neurons (from ectodermal layer), and hepatocytes (from endodermal lineage) in vitro [44, 47, 48].

Furthermore, it has been shown that transplantation of PDLSCs into immunocompromised rodents resulted in the generation of cementum/PDL-like structure and contributes to periodontal tissue repair [44]. PDLSCs show immunomodulatory activity by up-regulation of soluble immunosuppressive factors (TGF-β1, hepatocyte growth factor (HGF) and indoleamine 2, 3-dioxygenase (IDO) in the presence of activated peripheral blood mononuclear cells (PBMNCs). Similar to the DPSCs, PDLSCs are positive for HLA-ABC (MHC class I antigen) while negative for HLA-DR (MHC class II antigen) [45].

Dental Follicle Progenitor Cells (DFPCs)

In 2005 & 2007, Morsczeck et al [46] and Kemoun et al [47] respectively have identified unique undifferentiated lineage

committed cells possessing mesenchymal progenitor features in the human dental follicle. The cells were referred to as "dental follicle precursor cells" (DFPCs) [48, 49]. Characteristically, DFPCs, similar to the bone marrow stem cells, are adherent and colony-forming cells. These cells have been reported to express Notch-1, CD13, CD44, CD73, CD105, and STRO-1[48, 50].Human DFPCs has been believed to consist of precursor cells for cementoblasts, periodontal ligament cells, and osteoblasts. Under appropriate in vitro conditions, they were capable of differentiating into osteoblasts, cementoblasts, chondrocytes and adipocytes. Interestingly, although both DFPCs and SHED were of the neural crest origin, their neural differentiation potentials were different under the same culture conditions. It has been reported that SHED possess good differentiation potential than DFPCs in terms of the expression of Pax6 which is a marker of retinal stem cells [41].

Stem Cells from the Apical Papilla (SCAP)

Stem cells from dental apical papilla (SCAP) were first identified and characterized by Sonoyama et al. in human permanent immature teeth [51]. These authors described the cells as adherent clonogenic cells with mesenchymal stem cell features, which are expressed STRO-1, CD24, CD29, CD73, CD90, CD105, CD106, CD146, CD166, and ALP, and not expressing CD34; CD45; CD18; and CD150. Among these markers, CD24 would be of a specific marker for SCAP since it's not found in the other dental stem cells. Excitingly, some authors have reported that SCAP display higher telomerase expression than both DPSCs and BMMSCs [54]. Furthermore, SCAP has been shown to positively stain with several neural markers implying their possible origin from the neural crest [52].

In terms of differentiation, SCAP were capable of generating osteoblasts, odontoblasts and adipocytes in vitro. An in vivo study has demonstrated that these cells form hard tissue when being loaded onto hydroxyapatite (HA) and implanted subcutaneously in immunocompromised rats [51-53]. Moreover, SCAP have been reported to possess a significantly higher mineralization potential as well as proliferation rate than DPSCs. This finding might be of some importance for their use in dental and/or bone tissue engineering and regeneration [54]. About the possibility of immunogenicity of SCAPs, an independent study have reported that swine SCAPs are non-immunogenic and suppressed T cells proliferation in vitro [55].

Stem Cells derived from Gingiva (GSCs)

The isolation of a stem cell population from gingiva was firstly reported by Zhang et al in 2009. These authors derived the cells from the spinous layer of human gingiva and referred to them as gingival stem cells (GSCs). In terms of markers, it has been shown that GSCs were negative for CD45/CD34, but positive for CD29, CD44, CD73, CD90, CD105, CD146, STRO-1 and SSEA4 [56].

CONCLUSION

Dental stem cells have shown great implications in regenerative medicine for the treatment of various human diseases including dental related problems such as continued root formation, pulp healing and regeneration, implantation and transplantation, pulp/dentin tissue engineering and regeneration, bioroot engineering, reconstruction of periodontium, and in cancer management research. The characterization of these cells, and purpose of their potentialities in terms of regenerative specificity, may results in new clinical treatment modalities.

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