



Dental stem cells and their application in Dentistry: a literature review

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• Conflicts of interest: none declared.

ABSTRACT

Objective: the aim of this study was to conduct a literature review of the types of stem cells of dental origin and their applications in Dentistry. **Material and Methods:** for this, we selected scientific articles published between 2000 and 2016 through the databases PUBMED and LILACS. **Results:** there are five main sources of stem cells of dental origin: stem cells from dental pulp of permanent teeth and deciduous teeth, apical papilla, periodontal ligament and dental follicle. These cells have been studied for the treatment of periodontitis, bone repair, regeneration of the pulp after necrosis as well as the development of new teeth. **Conclusion:** stem cells from dental origin are an interesting alternative for research and application in regenerative therapies in Dentistry.

Keywords: Stem cells; Tissue engineering; Dentistry.

Introduction

Stem cells (SCs) are undifferentiated cells with self-renewal ability and capacity to differentiate into specialized cell types.^{1,2} Regarding the origin, they can be classified as embryonic stem cells (ESCs) and adult stem cells (ASCs).³ Embryonic stem cells (ESCs) are derived from the inner cell mass of the blastocyst and form all cell types, derived from the three germ layers, and are therefore pluripotent.^{3,4} The zygote and cells derived from the first two cellular divisions constitute the most primitive cells (totipotent cells) that are capable of forming the embryo and the embryonic annexes (e.g. placenta, amniotic membranes etc).

ASCs are present in a number of postnatal tissues and are responsible for normal tissue renewal as well as for regeneration and healing after injuries. Due to the ability to self-renew and to differentiate into cells that are found throughout the body, there is a great interest in using stem cells for the regeneration of injured tissues as well as to develop tissue-engineered implants and bio-hybrid organs, in order to restore tissue function. The use of ASCs in regenerative medicine and tissue engineering research has important advantages in comparison with ESCs, since there are no ethical complications and the process of differentiation of these cells is better controlled.⁵

Mesenchymal stem cells (MSCs) are ASCs, and were first described in 1966 by Friedenstein *et al.*⁶ Since then, clinical and biological interest in MSCs have increased and the Mesenchymal Stem Cells Committee of the International Society for Cellular Therapy proposed a minimum criteria for the identification of these cells: adherence to plastic culture surfaces, potential of osteogenic, adipogenic and chondrogenic differentiation *in vitro* as well as expression of surface antigens CD73, CD90 and CD105 and lack of expression of hematopoietic and endothelial markers CD14 or CD11b, CD34, CD45, CD79a- α or CD19 and human leukocyte antigen-DR (HLA-DR).⁷

MSCs can be isolated from different locations, such as bone marrow, umbilical cord, placenta, adipose and dental tissues.^{8,9} Because dental stem cells (DSCs) are easy to obtain and present a great potential of differentiation, there has been a growing interest in their use in regenerative medicine for treatment of various human diseases.¹⁰

In human postnatal dental tissues, five main sources of DSCs have been identified: dental pulp stem cells (DPSCs),¹¹ stem cells from human exfoliated deciduous teeth (SHEDs),¹² periodontal ligament stem cells (PDLSCs),¹³ dental follicle stem cells (DFSCs)¹⁴ and stem cells from apical papilla (SCAPs).¹⁵ Regardless the tooth tissue of origin, DSCs can be isolated either disaggregating the tissue enzymatically and/or mechanically, or also by explant. After enzymatic and/or mechanical dissociation, cells are placed in culture medium for growing on plastic flasks or dishes. In explant method, the dental tissue is placed on a plastic surface and the cells migrate out from the tissue fragment adhering to culture flasks or dishes (Figure 1).

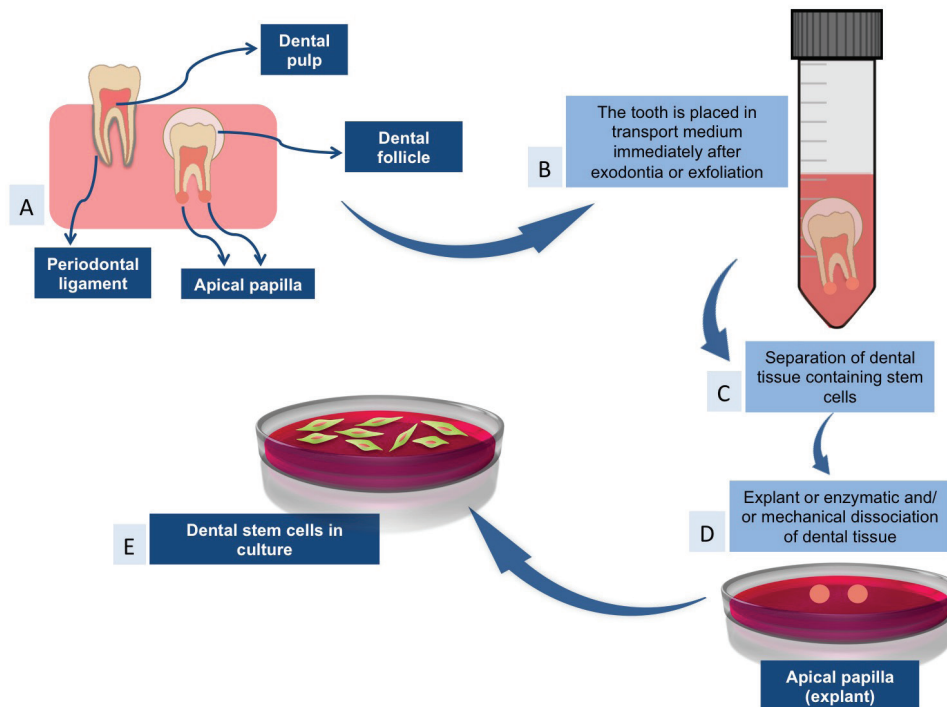


Figure 1. Sources of dental stem cells and their isolation. A: Main sources of dental stem cells. B: After tooth extraction or exfoliation, the tooth is immediately taken to the cell culture lab in a transport medium. To obtain dental pulp stem cells from tooth with fully formed roots, the tooth cleavage to allow contact between culture medium and pulp tissue is required. C: As these cells have distinct characteristics and a single tooth can have more than one tooth tissue to obtain stem cells, these tissues are separated in the cell culture lab in a sterile environment. D: From the dental tissue, stem cells can be isolated by enzymatic or mechanical dissociation and also by explant. E: Dental stem cells in culture. These cells are adherent to plastic surface and exhibit morphology similar to fibroblasts

Specific properties, such as proliferative and differentiation potential, are slightly different among DSCs. Thus, the aim of this study was to conduct a literature review of DSCs and their applications in Dentistry.

Material and Methods

Scientific papers published between 2000 and 2016 were selected through PUBMED (Public Medicine) and LILACS (Latin American and Caribbean Health Sciences) databases. The key words used were: “dental stem cells”; “stem cells” AND “application” AND “dentistry”; “dental stem cells” AND “tissue engineering”. Full texts of the articles written in Portuguese and English were included. Papers that did not directly address the subject were excluded.

Results

• Dental Pulp Stem Cells

DPSCs were first isolated from human third molars by Gronthos *et al.*¹¹ These cells express surface markers similar to those of MSCs, such as CD73, CD90, CD105 and are negative for CD14, CD34 and CD45.

In the pulp chamber, DPSCs are inactive, becoming active after injury. When dentin injury occurs, these cells migrate to the damaged region, proliferate and are able to differentiate towards osteoblast-like cells to form reparative dentin.¹⁶ *In vitro*, these cells have the capacity to differentiate into osteoblasts, adipocytes, chondroblasts, odontoblasts, muscle cells, neural cells, endothelial cells, hepatocytes, and melanocytes.¹⁷⁻²³

• Stem Cells from Human Exfoliated Deciduous Teeth

SHEDs were first obtained by Miura *et al.*¹² and are able to differentiate into adipocytes, chondroblasts, osteoblasts, odontoblasts, and muscle cells *in vitro*.^{1,24,25} In addition, they can also differentiate towards neural cell lines.^{1,24,25} *In vivo*, SHEDs do not differentiate directly into osteogenic cells but induce bone formation as well as assist in the process of angiogenesis.^{1,12}

In comparison with DPSCs, SHEDs have higher cell proliferation rate, shorter population doubling time and increased clonogenic potential.^{25,26} Regarding the expression of surface markers, these two cell types are similar, being positive for mesenchymal markers and negative for hematopoietic markers.^{1,24}

• Periodontal Ligament Stem Cells

The periodontal ligament is a connective tissue composed by, among other cell types, PDLSCs, which were first isolated by Seo *et al.*,¹³ from extracted human third molars.

PDLSCs exhibit self-renewal capacity and express cell surface markers similar to bone marrow-derived MSCs. They are able to differentiate towards osteoblasts, odontoblasts, adipocytes, neural cells, cementoblasts, and chondroblasts *in vitro*.^{1,13,20,27,28}

• Stem Cells from Apical Papilla

SCAPs were initially isolated from third molars and incisors of swine by Sonoyama *et al.*²⁹ and obtained from humans in 2008¹⁵. SCAPs express STRO1, CD24, CD29, CD73, CD90, CD105, CD106, CD146, CD166, alkaline phosphatase (ALP) and do not express hematopoietic and endothelial markers (CD14, CD34 e CD45). Among these markers, CD24 would be specific of SCAPs, since it was not found in other DSCs.^{15,30} In addition, these cells also express neural markers.³⁰

SCAPs differentiate towards osteoblasts, adipocytes, and odontoblasts *in vitro*, but chondrogenic differentiation potential has not been demonstrated.^{15,30} When associated with a hydroxyapatite scaffold and implanted in immunocompromised rats, formation of mineralized tissue (bone and dentin-like) was found.³¹ Moreover, these cells have significantly higher proliferation and mineralization potential in comparison with DPSCs.³²

• Dental Follicle Stem Cells

Dental follicle is a loose connective tissue that surrounds the crown of non-erupted teeth.¹⁴ It originates the root cementum, periodontal ligament and alveolar bone during rhizogenesis, and coordinates the tooth eruption process.³³

DFSCs were first obtained from human third molars by Yao *et al.*,¹⁴ who demonstrated the property of self-renewal, clonogenic potential and osteogenic differentiation. DFSC express mesenchymal surface markers and are negative for hematopoietic markers.¹ These cells differentiate towards cementoblasts, adipocytes and cells of neural lineage *in vitro*.³³⁻³⁵ Few studies were able to perform chondrogenic differentiation.^{36,37} These studies suggest that DFSCs show variation in the ability to differentiate depending on the dental development stage. DFSCs also present heterogeneity in cellular proliferation rate.³⁸

Discussion

DSCs are highly proliferative and multipotent cells, and can differentiate into many cell types. Therefore there is a growing interest in a better understanding of their potential and clinical applications. Moreover, the use of these cells in Medicine and Dentistry has been proposed because of their easy obtainment, being isolated from permanent teeth indicated for extraction or naturally exfoliated deciduous teeth. For these reasons, DSCs banks have been created around the world.³⁹ In Brazil, The National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária – ANVISA*) authorizes the storage of SCs originated from umbilical cord blood and placenta, as well as SHEDs in private establishments with proper operating license, according to the Resolution of Board Directors (*Resolução da Diretoria Colegiada – RDC*) 56, from 12/16/2010 and RDC 9, from 03/14/2011. Currently, private cell banks provide SCs collection and storage service, without promising treatment for any disease.

DSCs have been studied for the regeneration of various tissues and organs, such as bones, vascular system, liver, pancreas, and cornea.^{1,37} Furthermore, these cells have also been studied for the treatment of neurodegenerative diseases.^{1,37} In the field of Dentistry, DSCs have been studied for the treatment of periodontitis, repair of maxillofacial bone problems, pulp regeneration after necrosis, as well as the development of new teeth.

• Use of the Dental Stem Cells for the Treatment of Periodontitis

Periodontitis is an inflammatory disease that causes injuries in the cementum, periodontal ligament and alveolar bone. Currently, there is no periodontal treatment that regenerates the modified region and the lost periodontal tissue into a normal and functional structure. As PDLSCs can differentiate into osteoblasts and cementoblasts, and induce tissue formation around the surface of dental implants, *in vivo* studies transplanted these cells associated with scaffolds in immunocompromised animal models and had showed regeneration of periodontal tissue.^{40,41} In humans, repair of structures affected by periodontal disease is possible.^{42,43} Feng *et al.*⁴² obtained significant improvement in the injured area after the use of PDLSCs, but only three patients were treated. In recent study, Chen *et al.*⁴³ performed autologous transplant of PDLSCs and DPSCs in 30 patients and showed that the use of these cells in areas of periodontal disease is safe and the does not produce significant adverse effects. Thus, the use of DPSCs for the regeneration of bone loss from periodontal disease may be clinically relevant. Therefore, the use of different populations of DSCs in the treatment of periodontal disease can be an interesting approach.⁴

• Use of the Dental Stem Cells for Bone Regeneration

DPSCs have been studied not only for bone loss caused by periodontal disease, as already mentioned, but also for reconstruction of maxillofacial bones. D'Aquino *et al.*⁴⁴ transplanted autologous DPSCs associated with a collagen scaffold to repair defects in alveolar bone secondary to extraction of impacted third molars in seven patients and, after three months,

there were bone regeneration areas. Three years after the transplant, Giuliani *et al.*⁴⁵ showed that the transplanted area was made of uniformly vascularized compact bone, with bone matrix histologically different from the normal alveolar bone. Despite the histological difference, there was no difference in dental function and chewing.⁴⁵ The authors suggest that the process of differentiation of CTPS can be more affected by the site of origin than by the signals sent by cells near the treated area.

• Use of the Dental Stem Cells for Pulp Regeneration

Dental pulp plays multiple roles in tooth homeostasis and maintenance of pulp tissue is important to its longevity.⁴⁶ After endodontic treatment, the dental pulp is replaced with inorganic material, leaving the tooth devitalized and more likely to fracture. Thus, studies have been conducted seeking an effective strategy for pulp regeneration after endodontic treatment.⁴⁷ Currently, two strategies have been investigated: DPSCs autologous transplantation associated with scaffolds and pulp canal revascularization, which attract MSCs to the site of injury. However, histological analysis after the root canal and pulp chamber revascularization shows that there is no tissue formation similar to pulp.⁴⁷ The majority of the cases present non-pulp-like tissues, comprising cementum, periodontal and bone-like-tissues.⁴⁷ In a study in an animal model (dogs), pulp-like tissue with nerves and vasculature was regenerated in the tooth root after transplantation of a subset of DPSCs (CD105+) with stromal cell-derived factor-1 (SDF-1).⁴⁶

• Use of the Dental Stem Cells for Formation of New Teeth

The development of a tooth is determined by several growth factors and complex interactions that result in tooth germ cell changes, leading to cell differentiation.^{1,4} Efforts have been employed to develop new teeth from DSCs. After subcutaneous transplantation of DPSCs and SHEDs in the dorsal surface of immunocompromised mice and rabbits, specialized dentin was produced and comprised of odontoblast-like cells surrounding an interstitial tissue similar to dental pulp.^{11,12,48} Seo *et al.*¹³ showed the ability of PDLSCs to form cementum *in vivo* after transplantation in the dorsum of immunocompromised mice. SCAPs actively participate in rhizogenesis and together with the PDLSCs can form root and periodontal ligament.¹ Sonoyama *et al.*²⁹ associated SCAPs and PDLSCs in a scaffold and showed the formation of structure similar to a tooth crown, capable of withstanding the impact resulting from mastication. Ikeda *et al.*⁴⁹ had extracted the first molar from mice with five weeks of age and, after three weeks, transplanted the tooth germ stem cells in the alveolar bone located in the previously extracted tooth area. The resulting bioengineered product was a functional tooth with normal structure, with adequate response to pain and mechanical stress.⁴⁹

Conclusion

Currently, the use of DSCs has been only applied in scientific research, but it is believed that, in a near future, this practice becomes a reality, which will represent a great advance in Dentistry.⁵⁰ More studies on the DSCs differentiation mechanisms and applications are needed to use these cells in routine dental practice. The creation of public DSCs banks for research is an important step for this.

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