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# Mesenchymal stem cells in periodontics: new perspectives

*Células mesenquimais indiferenciadas em periodontia: novas perspectivas*

Bruna Rabelo AMORIM<sup>1</sup>  
Enilson Antonio SALLUM<sup>2</sup>  
Marcio Zaffalon CASATI<sup>2</sup>  
Karina Gonzales Silverio RUIZ<sup>2</sup>  
Renato Correa Viana CASARIN<sup>2</sup>  
Kamila Rosamilia KANTOVITZ<sup>3</sup>  
Francisco Humberto NOCITI JUNIOR<sup>3</sup>

## ABSTRACT

*Tissue engineering is a contemporary field of science, which aims to create conditions based on principles of cell and molecular biology, bioengineering and biomaterials to regenerate tissues. Mesenchymal stem cells present high proliferation rates and are able to differentiate into multilineages under certain conditions, suggesting that they have great potential to act in regeneration field. Tooth derived stem cells are a suitable alternative source of mesenchymal cells once they are easily accessible and have poor morbidity to the donor. Studies showed that they have been isolated and characterized from diverse tissues such as dental pulp, exfoliated deciduous teeth, periodontal ligament, gingiva, dental follicle and apical papilla. However studies show that there is heterogeneity among these populations and there is no standard method to select the most appropriate tooth derived stem cells for regenerative procedures. The aim of this review is to present the current perspective of the multiple types of tooth-derived stem cells and to discuss the basis for their use in periodontal tissue engineering.*

*Indexing terms: Periodontics. Stem cells. Tissue engineering.*

## RESUMO

A engenharia de tecidos é um campo contemporâneo da ciência, que visa criar condições baseadas em princípios de biologia celular e molecular, bioengenharia e biomateriais para regenerar tecidos. As células tronco mesenquimais apresentam altas taxas de proliferação e são capazes de se diferenciar, sob certas condições, em multi-linhagens, sugerindo que elas têm grande potencial para atuar no campo da regeneração. As células tronco derivadas de tecidos dentais são uma fonte alternativa adequada de células mesenquimais uma vez que são de fácil acesso e têm baixa morbidade para o doador. Estudos demonstraram que elas já foram isoladas e caracterizadas a partir de diversos tecidos tais como polpa dentária, dentes decíduos esfoliados, ligamento periodontal, gengiva, foliculo dental e papila apical. Entretanto, os estudos demonstram que há heterogeneidade entre essas populações e não existe um método padrão para selecionar as células-tronco dentais mais apropriadas para procedimentos regenerativos. O objetivo desta revisão é apresentar o conhecimento atual dos vários tipos de células-tronco derivadas de dentes e discutir as novas perspectivas para seu uso na engenharia de tecidos periodontais.

**Termos de indexação:** Periodontia. Células-tronco. Engenharia tecidual.

## INTRODUCTION

Tissue engineering is an emerging field, which aims to guide formation, repair, and vascularization of organs by using biological and physical principals. The basic components for tissue engineering involve the interaction of three factors: scaffolds, signaling molecules, and cells. This interactive triad targets the production of functional and biocompatible conditions for tissue regeneration<sup>1</sup>. Stem cells (SCs) are an increasing subject once they are a way to regenerate injured tissues and should improve the treatment of some illness that so far has no resolution such as diabetes and Parkinson's disease. They can be obtained

from earliest stages of development to adult stage<sup>2-3</sup>. Embryonic SCs are a pluripotent cell type which can differentiate into all cells of the body but ethical issues like the using of human embryos for research purpose prevents further development in the field, thus Adult SCs are the cell choice for investigation. They have differentiation abilities but it is restricted to some cell types. Mesenchymal stem cells (MSCs) are included on this group<sup>4-5</sup>.

MSCs are widely studied within the medical field because of their therapeutic potential. They present high proliferation rates and can be induced to differentiate into multiple lineages<sup>2</sup>. These populations are very heterogeneous once there is no defined marker to identify mesenchymal stem cells<sup>6</sup>. International Society for cell

<sup>1</sup> Universidade de Brasília, Faculdade de Saúde, Laboratório de Histopatologia Bucal. Asa Norte, 70910900, Brasília, DF, Brasil. Correspondência para / Correspondence to: BR AMORIM. E-mail: <brunaamorim@unb.br>.

<sup>2</sup> Universidade Estadual de Campinas, Faculdade de Odontologia, Departamento de Prótese e Periodontia. Piracicaba, SP, Brasil.

<sup>3</sup> Faculdade São Leopoldo Mandic, Curso de Odontologia. Campinas, SP, Brasil.

therapy proposed a minimal criteria to define mesenchymal stem cells phenotype, which include be plastic adherent in standard cultures, expression of CD 105, CD 73 and CD 90 but not CD45, CD34, CD14 or CD11b, CD79a or CD19; major histocompatibility complex class II surface molecules and the potential to differentiate into osteoblasts, adipocytes and chondroblasts. Also they must present fibroblast-like spindle shape in culture<sup>7</sup>. Dental tissues are a good alternative source of MSCs, once they are easily accessible with insignificant or no morbidity of the donor site. Various types of tooth-derived stem cells (TDSCs) have been isolated from dental tissues, which include

dental pulp<sup>8-12</sup>, exfoliated deciduous teeth<sup>13-17</sup>, periodontal ligament, dental follicle<sup>18-20</sup>, apical papilla<sup>21-24</sup>, periodontal ligament of deciduous teeth<sup>14-15,25-27</sup> and gingival tissue stem cells<sup>28</sup>. This review article proposes to summarize the literature regarding the current knowledge about stem cells from dental tissue, and their potential in regenerative therapy.

## **TOOTH DERIVED STEM CELLS (TDSCS)**

Variable methodologies are used to isolate and characterize TDSCs. A summary is represented in Table 1.

**Table 1.** Characterization of tooth-derived stem cells.

<b>TDSCs</b>	<b>Location</b>	<b>Positive markers</b>	<b>Negative markers</b>	<b>Differentiation capacity</b>
DPSCs	Permanent tooth pulp	CD29, CD44, CD73, CD90, CD 105, CD146, STRO-1, Oct 3/4, Sox2, nanog	CD 14, CD 34, CD 54	Osteoblast, adipocyte, chondrocyte, hepatocyte, neuron, endothelial like cells, smooth muscles cells
SHED	Deciduous tooth pulp	CD 29, CD 105, CD 146, STRO-1	CD 31, CD 34	Osteoblast, odontoblast, adipocyte, neural cell
SCAP	Apical papilla	CD 24, CD 29, CD 31, CD 44, CD 73, CD 90, CD 105, CD 106, CD 146, CD 166, STRO1, Oct 3/4, Sox-2, nanog, survivin	CD 14, CD 18, CD 34, CD 45, CD 150	Osteoblast adipocyte chondrocyte, hepatocyte, neuron, odontoblasts
DFPCs	Dental follicle	CD 29, CD 44, CD, 73, CD 90, CD 105, nestin	CD 14, CD 31, CD 34, CD 45, CD 117	Osteoblast, adipocyte, chondrocyte, hepatocyte, neuron
PDLSCs	Permanent tooth periodontal ligament	CD 44, CD 90, CD 105, CD 166, CD 146, STRO-1, Oct 3/4, Sox2, nanog, nestin	CD 14, CD 34, CD45	Osteoblast/cementoblast, adipocyte, neuron, choncrocytes,endothelial like cells

DePDL	Deciduous tooth periodontal ligament	CD105, CD 166, STRO-Oct4	CD 34, CD 45	Osteoblast adipocyte, cementoblast, chondrocyte
GSCs	Gingival tissue	CD 90, CD 105, CD 73, CD 44, CD 13	CD34, CD 38, CD 45, CD 54	Osteoblast, chondrocyte, adipocyte

Note: CD: Cluster of differentiation; DePDL: Periodontal ligament of deciduous teeth stem cells; DFPCs: Dental follicle progenitor cells; DPSCs: Dental pulp stem cells; GSCs: Gingival stem cells; Oct: Octamer; PDLSCs: Periodontal ligament stem cells; SCAP: Stem cells from apical papilla; SHED: Stem cells from human exfoliated deciduous teeth; Sox2: SRY: box containing gene 2.

## Dental Pulp Stem Cells (DPSCs)

In 2000, Gronthos and collaborators were the pioneers on isolation and characterization of DPSC, the first TDSCs<sup>8</sup>. When compared with human bone marrows stem cells (BMSCs), DPSCs showed higher proliferation rate and greater capacity to form mineral nodules, so they are more appropriate for regeneration of mineralized tissues than BMSCs. They are able to differentiate into osteoblast, smooth muscle cells, adipocyte-like cells, neuron, dentin, dentin-pup-like complex and endothelial like cells<sup>8,29</sup>.

## Stem cells from human exfoliated deciduous teeth (SHED)

SHEDs are progenitor cells first isolated in 2003, from the remnant pulp of exfoliated deciduous teeth<sup>13</sup>. They showed a higher proliferative rate, when compared to BMSCs and DPSCs<sup>13,15</sup>, and a higher capability to differentiate in osteoblast and adipocyte-like cells when compared to DPSCs in vitro<sup>15</sup>. They also showed the capability do differentiate into odontoblast, neural cells<sup>15,30</sup>.

## Stem cells from apical papilla (SCAPs).

SCAPs are cells isolated from apical papilla located on the root apex of developing teeth<sup>31</sup>. It is distinct from the pulp tissue<sup>32</sup>. They presented a higher proliferation, migration and telomerase activity. They are able to differentiate into osteoblastic, odontoblastic, adipocyte-like and neuron-like cells under specific induction<sup>22</sup>. A cDNA microarray profiled comparative analysis between SCAP and DPSCs concluded that genes such as CD24 and survivin were highly expressed in SCAPs<sup>22</sup>.

## Dental follicle progenitor cells (DFPCs)

DFPCs are cells obtained from dental follicle which is a condensation of cells originated from the ectomesenchyma that surrounds the tooth germ in early stages of tooth formation. It contains a heterogenic cell population that forms the periodontium<sup>18,33</sup>. They can differentiate into osteoblast, adipocyte, chondrocyte and

neuronal cells, but they present differences on proliferation and mineralization patters which suggests that they could commit in distinct lineages<sup>33</sup>.

## Periodontal ligament stem cells (PDLSCs)

PDLSCs are a heterogeneous cell population with neural crest cell origin. They have higher proliferation rate but forms less mineralized nodules when compared to BMSCs. They present the ability to differentiate into osteoblasts, cementoblasts, adipocytes, chondrocytes and endothelial like cells. In vivo experiments confirmed the ability to form periodontal ligament and cementum-like tissue<sup>34</sup>.

## Deciduous periodontal ligament cells (DePDL)

Periodontal ligament cells also can be isolated from deciduous teeth. It showed higher proliferative rate than PDLSCs, and share the same ability of differentiate into osteoblasts, cementoblasts, adipocytes and chondrocytes, but with a higher potential to differentiate into adipocytes<sup>25</sup>.

## Gingival tissue Stem cells (GSCs)

GSCs are obtained from gingival connective tissue, so the sample must be deepithelialized, to leave only connective tissue. They are able to differentiate into osteogenic, chondrogenic and adipogenic lineages. It also present an immunomodulatory capacity<sup>28</sup>.

## Induced pluripotent stem cells (iPSCs)

iPS cells are derived from somatic cells via transduction and expression of selective transcription factors. They can differentiate into all derivatives of the 3 primary germ layers<sup>35</sup>. They can be obtained from stem cells of apical papilla, dental pulp, exfoliated deciduous teeth stem cells, gingival, periodontal ligament and buccal mucosa fibroblast. They have the ability to differentiate into mesenchymal stem cells, neural crest-like cells, ameloblast-like cells, odontoblast-like cells and osteoprogenitor like

cells. Although iPS cells are an option without any ethical concerns and it has a great potential towards regeneration of periodontal ligament, alveolar bone, cementum and dentin-pulp complex, issues like epigenetic memory, viral-transduction, tumorigenesis and teratoma formation has to be further investigated<sup>35</sup>.

## **REGENERATIVE APPLICATIONS OF TDSCS**

Basic components for tissue engineering includes scaffolds, signal molecules and cells. Scaffolds are tridimensional structures, which mimics the extracellular matrix and must have physical, chemical and biological characteristics to provide a microenvironment for cell signaling activation, and stimulation of cellular growth, differentiation, cell adhesion and migration. The cells provide synthesis of extracellular matrix and tissue regeneration. MSCs presents important characteristics such as high proliferation rates and ability to differentiate into multilineages, therefore they have a great potential into tissue engineering field.

Increasing amount of research presents TDSCs applicability in diverse conditions, including myocardial infarction<sup>36</sup>, ischemic disease<sup>37</sup>, neural regeneration<sup>38</sup>, inflammatory diseases<sup>39</sup>, diabetes<sup>40</sup>, muscular dystrophy<sup>41</sup>, bone and cartilage defects<sup>42</sup>, hair follicle loss<sup>43</sup>, skin injuries<sup>44</sup>, salivary gland defects<sup>45</sup>, corneal reproduction<sup>46</sup>, and the regeneration of dental tissues<sup>12,22,35,47-49</sup>.

Several studies demonstrated that TDSCs have successfully regenerated dental tissues such as dentin, pulp and periodontal ligament<sup>12,22,47-49</sup>. In vivo experiments demonstrated that human PDLSCs and SCAP were able to generate periodontal ligament in minipigs<sup>22</sup>. Also DPSCs promoted complete pulp regeneration in dogs<sup>12</sup>. Combination of iPS cells with silk scaffold and enamel

matrix promoted PDL regeneration in mouse periodontal fenestration defects<sup>35</sup>.

Although the literature confirms the potential of TDSCs in regeneration, there are some aspects that must be discussed. First, proliferation capacity, clonogenicity and differentiation ability are different from each type of TDSCs lineages suggesting that it has an association with the type of original tissue. Even in the same population there are heterogeneous cell subpopulation with different behavior<sup>50</sup>. Notwithstanding that International Society for cell therapy defined a minimal phenotype criteria for MSCs, specific surface markers associated with TDSCs commitment are not established.

## **CONCLUSION**

Interest in regeneration topic has increased inside scientific community. TDSCs are potential actors for regenerative procedures once they are an easy available source that presents almost no morbidity to the donor. Studies, which used TDSCs for regeneration, presented promising results. However, MSCs populations obtained from dental tissues are heterogeneous and, currently, there is no standard method to select the most appropriate TDSCs for regenerative procedures. Further studies must be designed to confirm TDSC-based therapies as safe, predictable and reproducible.

## **Collaborators**

BR AMORIM, EA SALLUM, MZ CASATI, KGS RUIZ, RCV CASARIN, KR KANTOVITZ and FH NOCITI JUNIOR participated in all stages of the preparation of the manuscript.

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