

## Tooth-derived stem cells: Update and perspectives

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### Abstract

Tissue engineering is an emerging field of science that focuses on creating suitable conditions for the regeneration of tissues. The basic components for tissue engineering involve an interactive triad of scaffolds, signaling molecules, and cells. In this context,

stem cells (SCs) present the characteristics of self-renewal and differentiation capacity, which make them promising candidates for tissue engineering. Although they present some common markers, such as cluster of differentiation (CD)105, CD146 and STRO-1, SCs derived from various tissues have different patterns in relation to proliferation, clonogenicity, and differentiation abilities *in vitro* and *in vivo*. Tooth-derived tissues have been proposed as an accessible source to obtain SCs with limited morbidity, and various tooth-derived SCs (TDSCs) have been isolated and characterized, such as dental pulp SCs, SCs from human exfoliated deciduous teeth, periodontal ligament SCs, dental follicle progenitor cells, SCs from apical papilla, and periodontal ligament of deciduous teeth SCs. However, heterogeneity among these populations has been observed, and the best method to select the most appropriate TDSCs for regeneration approaches has not yet been established. The objective of this review is to outline the current knowledge concerning the various types of TDSCs, and discuss the perspectives for their use in regenerative approaches.

**Key words:** Cell-based therapy; Mesenchymal stem cells; Dental stem cells; Differentiation; Tissue engineering

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**Core tip:** Stem cells (SCs) present the characteristics of self-renewal and differentiation capacity, which make them promising candidates for regenerative approaches. Although they present some common markers, SCs derived from various tissues have different patterns of proliferation, clonogenicity, and differentiation. Tooth-derived tissues are an accessible source of SCs with limited morbidity. However, heterogeneity within populations of tooth-derived SCs has been observed, and the best method to select the most appropriate SCs for regenerative approaches has not yet been established.

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## INTRODUCTION

Stem cells (SCs) are cells that present two distinctive characteristics: they are able to continuously self-renew, and they can be induced to differentiate into multiple specialized cell types<sup>[1]</sup>. SCs have therefore been a subject of interest to researchers and the general public, as a way to regenerate damaged tissues and improve the resolution of some illnesses, such as Parkinson's disease<sup>[2]</sup> and diabetes<sup>[3]</sup>, that current approaches in the medical field have not yet achieved. In this context, many studies have been conducted to identify and isolate SCs and to understand their biologic aspects.

SCs can be isolated in the earliest stages of embryogenesis (embryonic SCs)<sup>[4-9]</sup> or in various postnatal tissues (adult SCs)<sup>[2,10,11]</sup> (Table 1). Although embryonic SCs present interesting properties, such as the ability to differentiate into hundreds of other cell types, the bioethical aspects involved in the study of these cells, especially for human embryos, have hindered advances in this field and research has thus been focused on adult SCs<sup>[1,10-12]</sup>. Adult SCs can be obtained from adult specialized tissues, such as bone marrow<sup>[13-16]</sup>, skin<sup>[17,18]</sup> and fat<sup>[19-23]</sup>, where they likely act to renew cell populations and maintain tissue homeostasis, or help to repair the tissue in case of injury<sup>[18,24,25]</sup>. Even though adult SCs can be obtained from less ethically concerning sources, they have some limitations compared to embryonic SCs, such as more limited lifespan and differentiation potential<sup>[1,11,24,26]</sup>. In order to overcome these drawbacks, adult SCs can be reprogrammed by the insertion of SC-associated genes, forming induced pluripotent SCs (iPSCs)<sup>[3,27-31]</sup>.

Within the medical field, mesenchymal SCs (MSCs) have been widely studied to understand their role in skeletal tissue development, physiology and repair<sup>[14]</sup>, and because of their promising therapeutic potential<sup>[2]</sup>. MSCs are characterized by the capacity to differentiate into multiple types of skeletal tissues<sup>[14,32-36]</sup>. They were first described as adherent, clonogenic, self-renewing, fibroblast-like cells (colony-forming unit fibroblasts) obtained from bone marrow<sup>[35,37,38]</sup>. Subsequently, several studies were performed to identify other sources and to understand how these cells can give rise to distinct cell types, for the purpose of using these cells in regenerative procedures<sup>[39-43]</sup>.

In this context, dental tissues have also been investigated as niches of MSCs, and many tooth-derived SCs (TDSCs) have been identified and characterized, including dental pulp SCs (DPSCs)<sup>[44-48]</sup>, SCs from human exfoliated deciduous teeth (SHED)<sup>[49-53]</sup>,

periodontal ligament SCs (PDLSCs), dental follicle progenitor cells (DFPCs)<sup>[54-56]</sup>, SCs from apical papilla (SCAP)<sup>[19,56-59]</sup>, and periodontal ligament of deciduous teeth SCs (DePDL)<sup>[50,51,60-62]</sup> (Figure 1). Dental tissues are an accessible source of MSCs that can be obtained with limited morbidity and without additional risks to the donor, as extracted/exfoliated teeth represent a waste product of dental procedures<sup>[13,63-65]</sup>. However, the properties of these TDSCs and their feasibility for regenerating tissues still need to be investigated in greater detail. Thus, the aim of the present review is to describe the current knowledge concerning TDSCs, and to consider the perspectives for their use in regenerative approaches.

## ISOLATION, CHARACTERIZATION, AND DIFFERENTIATION POTENTIAL OF TDSCs

Because of the variety of methodologies used to isolate and characterize MSCs, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy proposed minimal criteria to define human bone marrow SCs (BMSCs) and other types of MSCs *in vitro*<sup>[32]</sup>. Briefly, MSCs must adhere to plastic under standard culture conditions, express cluster of differentiation (CD)105, CD73 and CD90, but not CD45, CD34, CD14, CD11b, CD79a, CD19, or human leukocyte antigen-DR surface molecules, and have the potential to differentiate along osteogenic, chondrogenic and adipogenic lineages<sup>[32]</sup>. Therefore, studies characterizing TDSCs usually evaluate these criteria, as well as clonogenicity (capacity to form adherent colonies derived from one single cell) and differentiation potency, in order to compare them to each other and to BMSCs<sup>[66,67]</sup> (Table 2).

### DPSCs

DPSCs were the first TDSCs isolated and characterized in 2000<sup>[44]</sup>. Obtained from permanent third molars, these cells were found to be more proliferative than BMSCs, and had the capacity to form mineral deposits *in vitro*, though in reduced amounts compared to BMSCs<sup>[44]</sup>. DPSCs also failed to form lipid-laden adipocytes *in vitro*, whereas BMSCs are capable of differentiating into adipocytes<sup>[44]</sup>. However, more recent studies demonstrate that DPSCs can differentiate into adipocyte cells when other supplements are added to the adipogenic induction medium<sup>[46,65]</sup>.

When transplanted *in vivo*, some DPSC clones differentiate into aligned odontoblast-like cells, with prolonged processes oriented into newly formed dentin-like structures<sup>[44,46]</sup>, whereas BMSCs form distinct lamellae of bone<sup>[44]</sup>. DPSCs can also form reparative dentin-like tissue on the surface of human dentin *in vivo*<sup>[68]</sup>.

### SHED

In 2003, progenitor cells were isolated from the remnant pulp of exfoliated deciduous teeth<sup>[49]</sup>. SHED

**Table 1** Classification of stem cells according to their plasticity<sup>[1,2,41,66]</sup>

Stem cell type	Description
Totipotent	Stem cells able to differentiate into cells of all three germ layers (ectoderm, mesoderm and endoderm) and extra-embryonic tissues ( <i>e.g.</i> , zygote)
Pluripotent	Stem cells able to differentiate into all cells of the body, but that cannot form extra-embryonic tissues ( <i>e.g.</i> , embryonic stem cells and induced pluripotent stem cells)
Multipotent	Stem cells that have differentiation abilities restricted to some cell types, usually from the germ layer they are derived from ( <i>e.g.</i> , mesenchymal stem cells)

**Table 2** Characterization of tooth-derived stem cells

TDSCs	Ref.	Location	Expression markers		Differentiation capacity	
			Positive	Negative	<i>In vitro</i>	<i>In vivo</i>
DPSCs	[13,44,46,51,65]	Permanent tooth pulp	CD29, CD44, CD73, CD90, CD105, CD146, STRO-1, Oct-3/4, Sox-2, nanog	CD14, CD34, CD45	Osteoblast, adipocyte, chondrocyte, hepatocyte, neuron	Dentin-like structures
SHED	[49,51,53,69,70]	Deciduous tooth pulp	CD29, CD105, CD146, STRO-1	CD31, CD34	Osteoblast, odontoblast, adipocyte, neural cell	Dentin formation, induce bone formation by murine host cells
SCAP	[13,56,57,65]	Apical papilla of developing tooth	CD24, CD29, CD31, CD44, CD73, CD90, CD105, CD106, CD146, CD166, STRO-1, Oct-3/4, Sox-2, nanog, survivin	CD14, CD18, CD34, CD45, CD150	Osteoblast, adipocyte, chondrocyte, hepatocyte, neuron	Dentin-like tissue
DFPCs	[13,54,56,65,72]	Dental follicle of developing tooth	CD29, CD44, CD73, CD90, CD105, nestin	CD14, CD31, CD34, CD45, CD117	Osteoblast, adipocyte, chondrocyte, hepatocyte, neuron	Bone/cementum-like tissue
PDLSCs	[13,57,60,73]	Permanent tooth periodontal ligament	CD44, CD90, CD105, CD166, CD146, STRO-1, Oct-3/4, Sox2, nanog, nestin	CD14, CD34, CD34, CD45	Osteoblast/ cementoblast, adipocyte, neuron	Periodontal ligament/ cementum-like tissue
DePDL	[60]	Deciduous tooth periodontal ligament	CD105, CD166, STRO-1, Oct-4	CD34, CD45	Osteoblast, adipocyte	

CD: Cluster of differentiation; DePDL: Periodontal ligament of deciduous teeth stem cells; DFPCs: Dental follicle progenitor cells; DPSCs: Dental pulp 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.

were found to be more proliferative than BMSCs and DPSCs<sup>[49,51]</sup>, and showed higher capability for osteogenic and adipogenic differentiation than DPSCs *in vitro*<sup>[51]</sup>. SHED can also differentiate into neural cells<sup>[69]</sup>. When 12 single-colony-derived SHED clones were transplanted into immunocompromised mice, only three clones demonstrated the potential to generate ectopic dentin-like tissue on the hydroxyapatite/tricalcium phosphate (HA/TCP) carrier equivalent to that generated by multiclonal-derived SHED<sup>[49]</sup>. When SHED were seeded into human tooth slices and transplanted into immunodeficient mice, they were also able to form a dentin-like structure<sup>[70]</sup>. Although some researchers claim that SHED have the ability to differentiate into osteoblasts *in vivo*<sup>[51]</sup>, Miura *et al.*<sup>[49]</sup> reported that, in fact, SHED act as an osteoinductive factor, inducing the host cells to form bone.

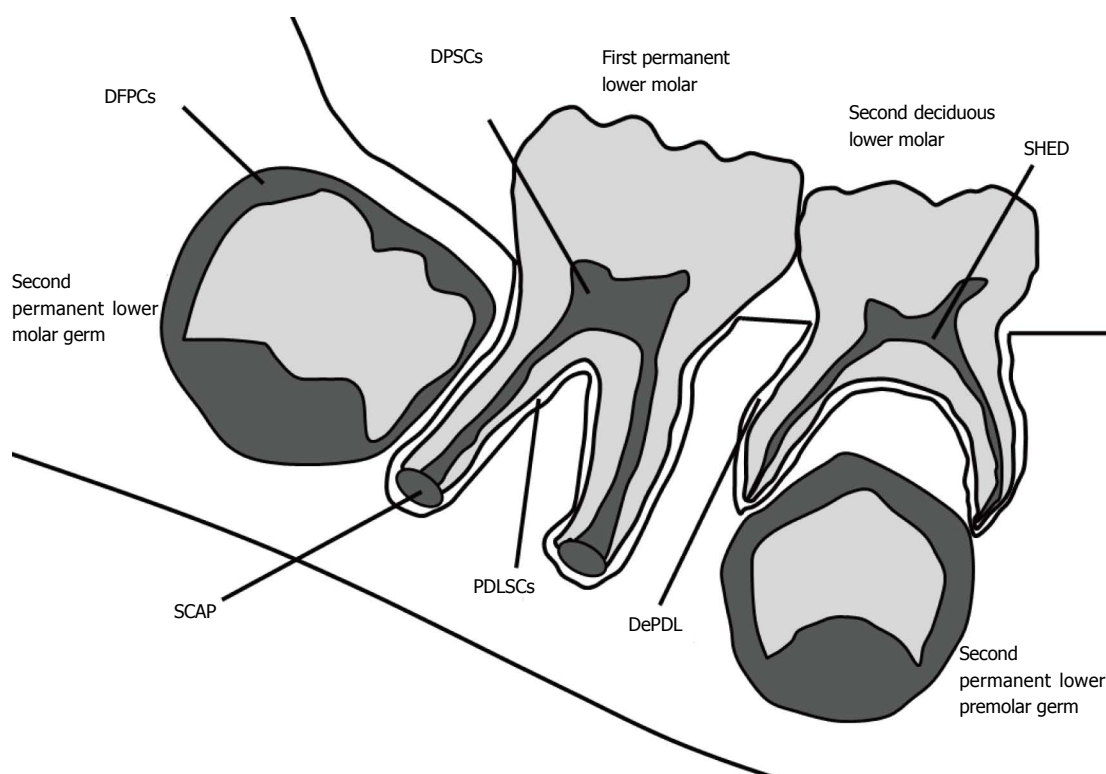
### SCAP

The apical papilla is the tissue located at the apex of the root of developing teeth<sup>[66]</sup>, and is distinct from the pulp<sup>[71]</sup>. As this tissue is associated with root formation, it potentially provides a source of MSCs for

this purpose. SCAP are the cells isolated from this tissue that present characteristics of MSCs, and can give rise to odontoblastic, osteoblastic and adipocyte-like cells when cultured under appropriate conditions<sup>[57]</sup>. SCAP also have the capability to form a dentin-like structure when transplanted into immunocompromised mice, using HA/TCP as a scaffold<sup>[57]</sup>. Sonoyama *et al.*<sup>[57]</sup> evaluated whether SCAP and DPSCs are the same or distinct MSC populations based on their cDNA microarray profile, and observed that many genes were differentially expressed by these MSC populations. In particular, CD24 and survivin were highly expressed in the SCAP population. Additionally, SCAP also showed other favorable characteristics, such as higher proliferative rate and telomerase activity, and improved migration capacity<sup>[57]</sup>.

### DFPCs

The dental follicle is a condensation of ectomesenchymal cells that surrounds the tooth germ in early stages of tooth formation and contains cells that form the three tissues that constitute the periodontium: periodontal ligament, cementum and alveolar bone<sup>[54,72]</sup>. When the



**Figure 1 Sources of tooth-derived stem cells.** DePDL: Periodontal ligament of deciduous teeth stem cells; DFPCs: Dental follicle progenitor cells; DPSCs: Dental pulp stem cells; PDLSCs: Periodontal ligament stem cells; SCAP: Stem cells from apical papilla; SHED: Stem cells from human exfoliated deciduous teeth.

heterogeneity of DPFCs was analyzed, it was observed that, although all cloned cell lines were positive for MSC-related surface markers (CD105, CD44, CD29) and negative for hematopoietic markers (CD34, CD117), they were different in terms of proliferation and mineralization patterns, indicating that they could be committed to distinct lineages<sup>[72]</sup>.

In order to avoid donor variability, TDSCs from follicle, pulp and papilla were isolated from a single donor tooth and the morphology, proliferation rate, expression of MSC-specific and pluripotency markers, and *in vitro* differentiation into osteoblasts, adipocytes, chondrocytes and hepatocyte-like cells were compared<sup>[65]</sup>. Adherent, fibroblast-like morphology was observed in all TDSCs cultured under the same standard conditions, and DFPCs were more proliferative than DPSCs and SCAP<sup>[65]</sup>. Although all three cell types were able to differentiate into the osteoblast lineage, DFPCs and DPSCs showed higher potentials than SCAP to form mineralized nodules *in vitro*<sup>[65]</sup>. Additionally, when cultivated under chondrogenic-inducing conditions, DFPCs expressed all three chondrogenic-specific markers (aggrecan, and type I and type III collagen), whereas DPSCs and SCAP only expressed aggrecan<sup>[65]</sup>.

### PDLSCs

The periodontal ligament harbors a heterogeneous cell population, with subsets of cells in various stages of commitment to fibroblastic and osteoblastic/cementoblastic lineages<sup>[34,73,74]</sup>. Within these subsets,

it was supposed that putative MSCs would be present in the periodontal ligament, which was confirmed in 2004<sup>[73]</sup>. PDLSCs show expression of STRO-1 and CD146, SC markers previously reported to be expressed in BMSCs and DPSCs, and also express scleraxis, a tendon-specific transcription factor<sup>[73]</sup>.

PDLSCs are more proliferative and clonogenic than BMSCs<sup>[34]</sup>. PDLSCs can also differentiate into adipocytes<sup>[34,73]</sup> and chondrocytes<sup>[34]</sup>, as well as osteoblasts/cementoblasts<sup>[34,60,73]</sup>. Although PDLSCs are able to form mineralized tissue *in vitro* when osteoblastic/cementoblastic differentiation is induced, they form fewer mineralized nodules than BMSCs<sup>[34,73]</sup>. Additionally, when transplanted into immunocompromised mice, some clones of PDLSCs have been shown to form periodontal ligament-like structures *in vivo*<sup>[73]</sup>.

### DePDL

As MSCs can be isolated from the pulp of deciduous teeth, it was thought that the periodontal ligament of deciduous teeth may also harbor MSCs<sup>[60]</sup>. In 2010, DePDL were isolated and compared with their permanent counterparts and found to be more proliferative than PDLSCs<sup>[60]</sup>. Moreover, it was observed that, although DePDL and PDLSCs have the ability to differentiate into both adipocyte-like and osteoblast-like cells *in vitro*, DePDL show a higher potential for adipogenic commitment, and PDLSCs have a higher potential for osteogenic commitment<sup>[60]</sup>.

### ***iPSCs from TDSCs***

Following reports of reprogramming of dermal fibroblasts to behave like embryonic SCs<sup>[27,28]</sup>, studies were conducted to evaluate if other cell types could also be reprogrammed, including TDSCs<sup>[29,30]</sup>. It was reported that human gingival and periodontal ligament fibroblasts<sup>[29]</sup>, SHED, SCAP and DPSCs<sup>[30]</sup> can be reprogrammed as iPSCs, with formation of teratomas after implantation in immunocompromised mice<sup>[29,30]</sup>.

## **PERSPECTIVES ON TDSCs IN REGENERATIVE APPROACHES**

Tissue engineering is an emerging field based on basic science and engineering technology, designed to create suitable conditions to regenerate damaged tissues<sup>[75-78]</sup>. The basic components for tissue engineering involve an interactive triad of scaffolds<sup>[79-81]</sup>, signaling molecules<sup>[82-84]</sup> and cells<sup>[24,33,41,85]</sup>, which play a fundamental role in the regeneration process<sup>[24,76,86,87]</sup>. Scaffolds serve as a three-dimensional template mimicking the extracellular matrix; signaling molecules enhance this cellular activity by stimulating cells to migrate, proliferate and differentiate; and cells provide the machinery synthesis of the extracellular matrix and tissue regeneration<sup>[24,75,76,88,89]</sup>. Due to their interesting properties, including self-renewal and differentiation abilities, MSCs are considered important for tissue maintenance and renewal, and, therefore, a promising candidate for tissue engineering<sup>[24,90-94]</sup>.

Some studies demonstrated that cell-based therapies are able to regenerate dental tissues<sup>[48,57,70,95-98]</sup>. In a study in dogs, complete pulp regeneration was achieved when CD105<sup>+</sup> DPSCs with stromal cell-derived factor-1 were transplanted into pulp, and this was not observed when total pulp cells or CD105<sup>+</sup> adipose-derived cells were used<sup>[48]</sup>. Supplementation of guided tissue regeneration with periodontal ligament cells for the treatment of class II and III furcation defects in dogs enhances periodontal regeneration<sup>[95,97]</sup>. Twelve weeks after PDLSCs with an HA/TCP scaffold were transplanted into periodontal defects in a minipig model, new bone, cementum and periodontal ligament formation was observed<sup>[98]</sup>. Sonoyama *et al.*<sup>[57]</sup> also explored the potential of human PDLSCs and SCAP to generate a root-periodontal ligament complex in minipigs. They were able to obtain engineered roots capable of supporting porcelain, though with lower compressive strength. Nakahara<sup>[96]</sup> reported the formation of root and periodontal ligament in a new culture system using one tooth crown collected from a neonatal mouse, which was referred to as a "test-tube dental implant". The author stated that cell therapy will be the next generation of dental medicine, but further information regarding human SCs is necessary for safe and reliable clinical applications<sup>[96]</sup>.

In regard to human clinical trials, autologous progenitor cells obtained from periodontal ligament have been used to treat intrabony defects<sup>[99]</sup>. These progenitor cells were of a later cell lineage with

decreased capacity for osteogenic and adipogenic differentiation compared to PDLSCs *in vitro*. Despite this, these progenitors were able to promote improvement in clinical and radiographic parameters. Another study reported the cultivation of periodontal ligament cells on titanium pins that were subsequently implanted in patients and in dogs<sup>[91]</sup>. Clinical evaluation of the implants placed in the patients showed satisfactory mechanical function, and radiographs revealed bone filling and formation of a lamina-dura around the implants. Additionally, histologic evaluation of the implants placed in dogs revealed a ligament-like formation. Although these studies are not directly related to MSCs, they indicate that cell therapy can be a feasible clinical approach in the near future.

Despite these promising studies in cell-based tissue engineering, it is important to highlight that the best method to select the most appropriate MSC type for regenerating dental tissues is not yet clear. Although BMSCs, DPSCs, SHED, SCAP, DFPCs, PDLSCs, and DePDL present a common marker profile, they differ in their clonogenicity, proliferative ability, and differentiation potential *in vitro* and *in vivo*, suggesting that these properties are related to the microenvironments of origin of each cell lineage<sup>[13,24,34,44,60,65,67,73]</sup>. Additionally, it has been noted that, even in the same population of MSCs, there are heterogeneous cell subpopulations with distinct differentiation potentials<sup>[100]</sup>. This heterogeneity in relation to the ability to differentiate *in vitro* and to form dental tissues *in vivo* has also been reported in some TDSCs lineages, including DPSCs<sup>[44,46,67]</sup>, SHED<sup>[49]</sup>, DFPCs<sup>[72]</sup>, and PDLSCs<sup>[34,73,74,101-104]</sup>. Therefore, it can be concluded that, although there are MSC-related surface markers, such as STRO-1, CD146 and CD105, specific surface markers associated with the hierarchical commitment to differentiation pathways of TDSCs are not yet well established. In this context, further advances in understanding the regulation of MSCs during differentiation and dental development are required in order to develop new approaches for dental tissue regeneration with predictable outcomes<sup>[19,26,67,89]</sup>.

## **CONCLUSION**

The interest in organ regeneration using SCs has increased in the last decade. In this context, TDSCs are promising candidates, as they are readily available, highly proliferative, and present multi-differentiation abilities. Research on cell therapy for regenerating dental tissues has already been done, and shows promising results. Nevertheless, further research is needed to better characterize TDSCs and to understand their differentiation pathways in order to develop the most appropriate approaches for SC-based tissue engineering-therapies in dental practice.

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