Stem Cell Biology and Regenerative Medicine

Barbara Zavan
Eriberto Bressan *Editors*

Dental Stem Cells: Regenerative Potential

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Contents

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Dental Stem Cells (DSCs): Classification and Properties

Chiara Gardin, Sara Ricci, and Letizia Ferroni

Embryonic Origin and Components of the Tooth

A tooth is a complex structure made up of two major parts: the crown and the root. The crown of the tooth is what is visible in the mouth, whereas the root is the portion normally not visible in the mouth because it is anchored within the bone. Embryologically, mammalian teeth develop from sequential and reciprocal interactions between oral epithelium and neural crest-derived mesenchyme [1]. Most of the dental tissues have a cranial neural crest origin, namely dentin, dental pulp, cementum, periodontal ligament, and alveolar bone. The outer mineralized layer of enamel covering the tooth crown is the only component of ectodermal origin (Fig. 1).

Dentin comprises the main portion of the tooth. It is a mineralized connective tissue secreted by the odontoblasts, which are specialized cells located at the periphery of the dental pulp. The thickness of dentinal layer increases with age due to the deposition of secondary and tertiary (reparative) dentin, reducing the volume of the pulp chamber and the root canals [2]. It has been shown that the presence of dentin is essential for the differentiation of inner dental epithelial cells into ameloblasts [3]. Ameloblasts start to produce and secrete specific enamel matrix proteins, and soon after tooth eruption in the oral cavity, they completely disappear. During that time, tooth root develops, accompanied by cementum deposition and periodontium formation [4]. The cementum is a mineralized tissue covering the root of the tooth and produced by the cementoblasts. The main role of cementum is to serve as a medium by which the periodontal ligament can attach to the tooth for stability. At

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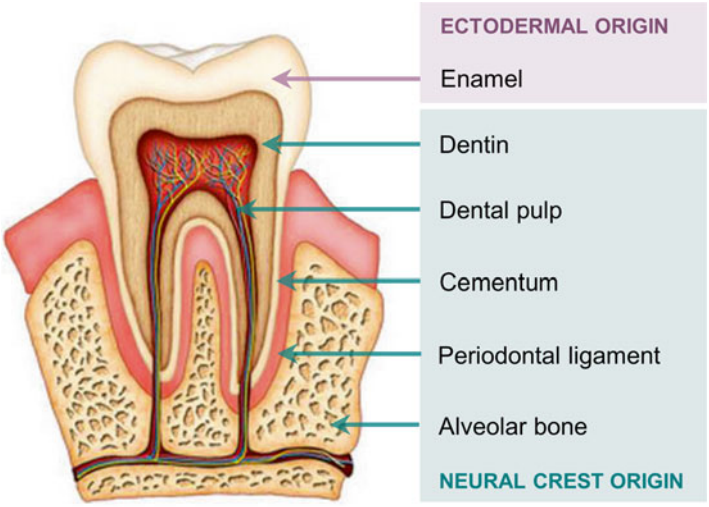

Fig. 1 Embryonic origin of the different tooth components. (Reproduced from www.bronxdental-spa.com/root-canal-bronx.htm)

the cementum-enamel junction, the cementum is acellular. This acellular type of cementum covers about two-third of the root; the apical portion of the root, that is more permeable, is covered by cellular cementum [5]. The periodontal ligament anchors the tooth to the alveolar bone, which is the bone in which teeth are encased. The outside wall of the alveolar bone is compact bone; the trabecular bone is inside and contains bone marrow. The number and the size of the trabeculae in this bone are determined by the function activity of the organ.

Dental pulp is the soft connective tissue of the tooth. It is located in its central cavity and is surrounded by the hard structures of enamel, dentin and cement. The dental pulp contains four layers. The external layer (*odontoblast layer*) is made up of odontoblasts producing dentin; the second layer (*cell-free zone*) is poor in cells and rich in collagen fibers; the third layer (*cell-rich zone*) contains fibroblasts and undifferentiated mesenchymal cells. From this layer, undifferentiated cells migrate to various districts where they can differentiate under different stimuli and make new differentiated cells and tissues. The innermost layer (*core of the pulp)* comprises blood vessels and nerves that enter the tooth mostly through the apical foramen. Other cells in the pulp include fibrocytes, macrophages, and lymphocytes [6].

Dental Stem Cells (DSCs)

Unlike other tissues such as bone, which have the ability to repair and remodel throughout life, human teeth have a very limited capacity to regenerate upon injury or disease [7]. Of all the dental components, the acellular enamel is incapable of

regenerating its original structure, whereas the remaining dental tissues possess that capacity in varying degrees, dependent on multiple factors [8]. Stem cells have been opening a promising future in regenerative medicine because of their two remarkable features known as self-renewal and multilineage differentiation. Stem cells reside in a dynamic and specialized microenvironment denoted to as niche, which is composed of heterogeneous cell types, extracellular matrix (ECM), and soluble factors [9]. The niche regulates stem cells behavior, by maintaining a balance between quiescence, self-renewal, and differentiation [10]. Based on their origin, stem cells can be generally classified in Embryonic Stem Cells (ESCs), which differentiate into all cell types found in the human body, and Adult Stem Cells (ASCs), whose differentiation potential is restricted to certain cell lineages. ASCs have been identified in almost every adult tissues from both epithelial and mesenchymal origin, including skin [11], bone marrow [12], adipose tissue [13], peripheral blood [14], cartilage [15], intestine [16], and periosteum [17]. For this reason, ASCs are also referred to as postnatal stem cells. ASCs are more applicable than ESCs in stem cell-mediated therapies and regenerative medicine because these cells lack ethical concerns. In addition, they have low immunogenicity and less tumorigenic potency than their embryonic counterparts, being promising candidates for regenerative therapies [18].

Several populations of ASCs have been identified also in various dental tissues, and they are collectively referred to as Dental Stem Cells (DSCs) [19]. DSCs are considered a promising source of ASCs since they are easily accessible by tooth extraction with a local anesthetic or when a primary tooth is replaced. More interestingly, DSCs can also be harvested from inflamed or diseased dental tissues, and their properties are similar to those of DSCs obtained from healthy tissues [20–22]. Therefore, it is believed that DSCs could retain, at least to some extent, the stem cell properties and tissue regeneration potential, making them an important tool for future developments in regenerative medicine. Another advantage of teeth as a source of stem cells is that, due to their ectomesenchymal origins, DSCs may display characteristics of both mesoderm and ectoderm [23]. This fact is very important because the association of mesenchymal (that will form odontoblasts, cementoblasts, osteoblasts, and fibroblasts) and epithelial (that will form ameloblasts) stem cells it is necessary for regenerating or building a new tooth.

Classification and Properties of DSCs

To date, seven different human dental stem/progenitor cells have been isolated and characterized: Dental Pulp Stem Cells (DPSCs) [7]; Stem cells from Human Exfoliated Deciduous teeth (SHED) [24]; Periodontal Ligament Stem Cells (PDLSCs) [25]; Dental Follicle Progenitor Cells (DFPCs) [26]; and Stem Cells from Apical Papilla (SCAP) [27]. DPSCs, SHED, and SCAP are generally referred to as dental pulp-related stem cells, PDLSCs and DFPCs as periodontium-related stem cells [28]. Other dental-related stem cells have been identified later. These are

Fig. 2 Timeline in the history of identification of the different DSCs

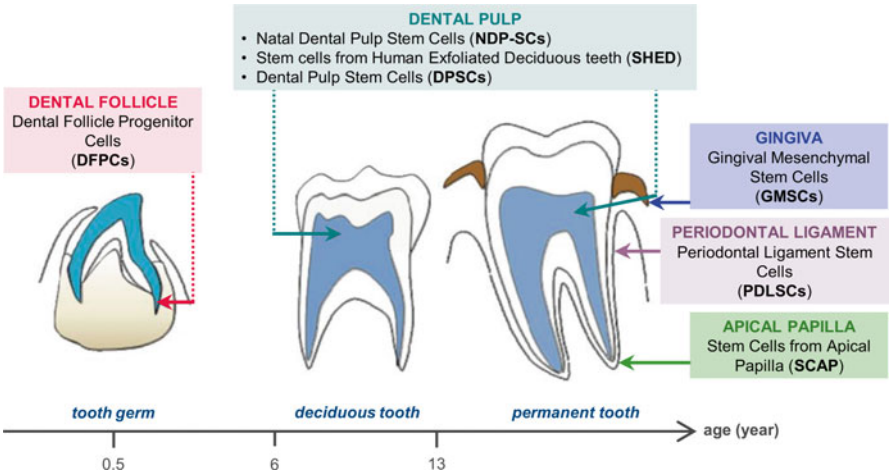

Fig. 3 Tooth developmental stages showing the anatomical localization of the different DSCs. (Reproduced from [31])

Gingival Mesenchymal Stem Cells (GMSCs) [29], and human Natal Dental Pulp Stem Cells (NDP-SCs) [30].

In this section, each type of DSCs will be described following the chronological order of their discovery (Fig. 2). Different biological aspects of DSCs will be discussed, starting from their first identification, the anatomical localization in the tooth (Fig. 3), the methods for their isolation, the peculiar expression of surface markers, and the differentiation potential in vitro and in vivo. The main biological properties of DSCs are summarized in Table 1.

Dental Pulp Stem Cells (DPSCs)

DPSCs Identification, Isolation, and Characterization

DPSCs from adult human dental pulp were first identified by Gronthos and colleagues in 2000 [7], even though the existence of stem cells in dental pulp has been reported by Yamamura in 1985 [58]. DPSCs were isolated on the basis of their high proliferation and frequency of colony formation that produced sporadic, but densely calcified nodules. The authors demonstrated that DPSCs could develop in vitro into odontoblasts, the cells that form the mineralized matrix of dentin. In addition, when

Table 1 Properties of DSCs

Type of DSCs	Location	Cell surface markers		Differentiation potential		References
		Positive	Negative	In vitro	In vivo	
DPSCs	Dental pulp of permanent tooth	CD9, CD10, CD13, CD29, CD44, CD59, CD73, CD90, CD105, CD106, CD146, CD166, STRO-1, Nanog, Oct-4, Sox-2	CD14, CD34, CD45, HLA-DR	Odontogenic Osteogenic Neurogenic Adipogenic Myogenic Chondrogenic	Dentin/pulp-like complex	[7, 23, 32–39]
SHED	Dental pulp of deciduous tooth	CD13, CD29, CD44, CD73, CD90, CD105, CD106, CD146, CD166, STRO-1, Nanog, Oct-4, SSEA-3, SSEA-4, TRA-1-60, TRA-1-81	CD14, CD34, CD45, HLA-DR	Odontogenic Osteogenic Neurogenic Adipogenic Myogenic Chondrogenic	Dentin formation New bone formation by recruiting host murine cells	[24, 40–43]

(continued)