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Dental Stem Cells: classification and applications

Células madre dentales: clasificación y aplicaciones

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Abstract:

In the last decades, the term stem cells has been one of the main topics to be discussed due to its scientific and medical importance, since its implementation in the field of medicine offers very promising alternatives in the treatment and above all solution of diseases such as diabetes, Alzheimer, Parkinson's disease, cancer, in treatments of traumatology and orthopedics, transplants, oral surgery, as well as the reconstruction of organs and tissues including those of dental origin, among others. Stem cells are undifferentiated cells characterized by their great capacity for self-renewal, clonality and differentiation; they are present in the embryonic and adult stages of life in human beings. At present, a large number of sources of mesenchymal stromal cells (MSC) in the oral cavity are classified into eight main populations, which are very easy to obtain for the dental team, including: dental pulp, exfoliated primary teeth, dental follicle, dental germ, apical papilla, periodontal ligament, gingiva, and periosteum. The objective of the following review is to show the panorama of the research from its origin, generalities, classification and application of this group of cells, since in spite of the advances in stem cell biology, some ethical controversies, as well as tumor formation and rejection limit their usefulness. That is why in this review it is carefully described the potential of dental stem cells to differentiate into osteoblasts, osteocytes, odontoblasts, chondrocytes, adipocytes and neural cell.

Keywords:

Stem cells, dental-derived mesenchymal stem cells, regenerative medicine

Resumen:

En las últimas décadas, el termino células madre ha sido uno de los temas principales a debatir por su importancia científica y médica, ya que su implementación en el campo de la medicina nos ofrece alternativas muy prometedoras en el tratamiento pero sobre todo solución de enfermedades como son la diabetes, Alzheimer, enfermedad de Parkinson, cáncer, en tratamientos de traumatología y ortopedia, trasplantes, cirugía oral, así como la reconstrucción de órganos y tejidos incluyendo los de origen dental, entre otras. Las células madre son células indiferenciadas que se caracterizan por su gran capacidad de autorrenovación, clonalidad y diferenciación, están presentes en las etapas de vida embrionaria y adulta en los seres humanos. En la actualidad se detallan una gran cantidad de fuentes de células estromales mesenquimales (MSC) en cavidad oral clasificadas en ocho poblaciones principales, de muy fácil obtención para el cuerpo odontológico, incluyendo: pulpa dental, dientes primarios exfoliados, folículo dental, gérmenes dentales, papila apical, ligamento periodontal, encía y periostio. El objetivo de la siguiente revisión es mostrar el panorama de la investigación desde su origen, generalidades, clasificación y aplicación de este grupo de células, ya que a pesar de los avances en la biología de las células madre, algunas controversias tanto éticas, así como la formación de tumores y el rechazo limitan su utilidad. Es por ello que en esta revisión se describen cuidadosamente el potencial de las células madre dentales para diferenciarse en osteoblastos, osteocitos, odontoblastos, condrocitos, adipocitos y células neuronales.

Palabras Clave:

Células madre, células madre mesenquimales de origen dental, medicina regenerativa

INTRODUCTION

Stem cells are undifferentiated cells characterized by their great capacity for self-renewal (ability to proliferate), clonality (ability to arise from a single cell) and differentiation (ability to differentiate into various cell types), and are present in embryonic and adult life stages. Because of their special and unique properties, stem cells are considered for their use in therapies for various diseases or in the treatment of missing tissues. They are divided into several categories according to the specific function they perform (Figure 1).[1–15]

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CLASSIFICATION OF STEM CELLS

There are different classifications of stem cells depending on their source of origin or their differentiation potential.

By their source of origin, they can be classified into embryonic stem cells, which have the capacity to form embryonic layers such as the endoderm, mesoderm and ectoderm; and adult stem cells, which are capable of producing at least one type of cell of a specific lineage.[15]

They can also be classified according to their differentiation potential (Figure 1):

- **Totipotent stem cells,** derived from the inner cell mass of the embryo, are considered the stem cells with the greatest potential since they possess the capacity to divide and differentiate into any of the cell types: embryonic tissue (endoderm, mesoderm or ectoderm) and extraembryonic (placenta, yolk sac and amnion) to give rise to new embryos.[2,8,10–12]

- **Pluripotent stem cells (PSCs),** are capable of differentiating into a wide variety of specialized cell types derived from one of the primary germ layers (ectoderm, mesoderm or endoderm), these in turn are divided into: embryonic stem cells (ESC) which are harvested from blastocysts at an early stage (approximately 4-14 days after conception) and induced pluripotent stem cells (iPSC), which are artificially derived from an adult cell.[2,9,13,14]

- **Multipotent stem cells,** they have a limited differentiation capacity, they can give rise to different cell types but within a specific lineage, an example is hematopoietic stem cells which can only develop into different types of blood cells.[2,15] In this category is the subgroup of adult stem cells, known as mesenchymal stromal cells (MSC), which is a group of cells considered ideal due to their high multipotent differentiation with therapeutic potential, (Figure 2) these are extracted from various tissues such as bone marrow, adipose tissue, cartilage, umbilical cord blood, salivary glands and various dental tissues.[9]

- **Unipotent stem cells** also called oligopotential, are defined as a group of cells with a very limited differentiation capacity, since they can only differentiate into a specific lineage. For example, type II pneumocytes in the normal lung behave in this way, giving rise to the generation of type I pneumocytes after apoptosis or injury of these cells.[15]

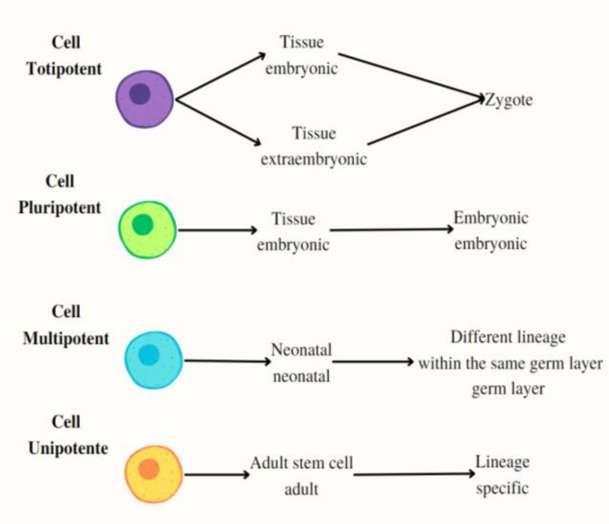

Figure 1. Classification of stem cells with respect to their differentiation potential.[2,8–15]

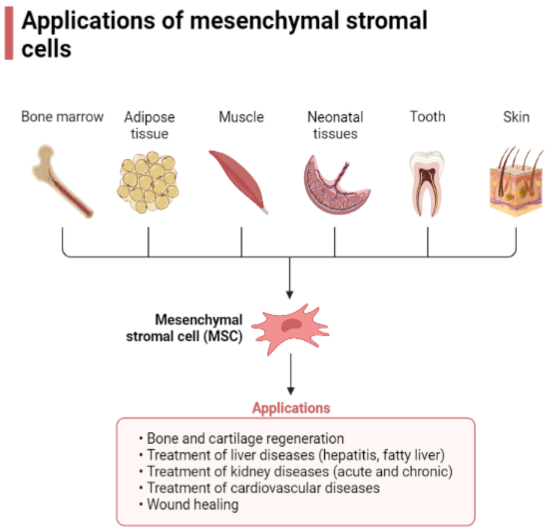

Figure 2. Mesenchymal stromal stem cell applications.[9]

DENTAL STEM CELLS

Dental stem cells possess a multi-differentiation potential with the ability to give rise to at least three Distinct cell lineages: osteo/odontogenic, neurogenic and adipogenic.[16]

Various texts have reported the existence of eight main populations of MSCs derived from dental origin, stem cells from:[9,17]

- Dental pulp **(DPSCs)**.
- Periodontal ligament **(PDLSCs)**.
- Human exfoliated deciduous tooth **(SHEDs)**.
- Mesenchymal derived from alveolar bone **(ABSMCs)**.
- Dental follicle progenitor **(DFPCs)**.
- Apical papilla **(SCAPs)**.

- Tooth germ progenitor **(TGPCs)**.
- Gingival mesenchyme **(GMSCs)**.

These eight populations are in turn classified according to their capacity to generate dentin-pulp complex or not, each with different characteristics (Table 1).[18]

Table 1. *Classification of dental cells depending on their capacity to generate or not dentin-pulp complex.[18]*

	Ability to generate dentin-pulp complex	**Cell**
Dental	They have this capacity	DPSCs SHEDs SCAPs TGPCs
Non dental	They are not capable of generating such a complex	PDLSCs ABSMCs, DFPCs GMSCs

DENTAL PULP STEM CELLS (DPSCS)

DPSCs were the first dental stem cells to be identified, can be easily collected from extracted permanent teeth (derived from retained third molars, indicated by orthodontic treatment or supernumerary teeth) or from exfoliated deciduous teeth, which are easier to obtain because they are less traumatic.[9, 19]

DPSCs have the ability to differentiate into cells very similar to mesenchymal stem cells present in bone marrow.[20,21] It is suggested that their use is focused on regeneration of dental pulp, bone, nerve tissue and cartilage.

Despite the different *in vivo* and *in vitro* studies that have been performed, most of the therapies have not been applied in human medicine since the paracrine effects of the bioactive factors secreted by these cells have not been understood to date.[22]

Application:

- **Dental:** in cases of periodontitis, for repair of damaged pulp tissue.[21]
- **Bone regeneration:** ectopic form in bone structures.[22]
- **Corneal reconstruction:** Regeneration of corneal epithelial cells.[23]
- **Neuronal regeneration:** The adult mammalian central nervous system lacks the regenerative power of damaged neuronal cells. Transplanted stem cell therapy showed encouraging effects by providing neuronal progenitors.[23]
- **Muscle regeneration:** ability to differentiate into cardiomyocytes cells.[24]

HUMAN EXFOLIATED DECEIVED TOOTH STEM CELLS (SHEDS)

SHEDs are located in the commonly called milk teeth or first dentition, they possess a highly proliferative cell population even much higher than DPSCs capable of differentiating and giving rise to a great variety of cell types, among which odontoblasts, neural cells and adipocytes stand out.[25,26] Shown to be a promising cell source for periodontal regeneration, SHEDs are isolated from the dental pulp of exfoliated primary teeth.[26]

Application:

- **Dental:** *In vitro* studies have shown to contribute to the regeneration of dentin and periodontal tissues (regeneration of the dentin-pulp complex).[26]
- **Bone regeneration:** there are reports of several studies in which regeneration of bone defects in rats was achieved.[27]
- **Neuronal regeneration:** In several studies in mice and rats, a significant improvement in various diseases such as Alzheimer's, traumatic cell injury, Parkinson's disease, etc., was observed.[19]
- **Renal regeneration:** Regeneration of renal tubular epithelial cells was achieved in acute kidney injury in mice.[19]
- **Hepatic regeneration:** In hepatic fibrosis, a direct transformation into hepatocytes was observed, recovering hepatic dysfunction with anti-inflammatory capacities in mice.[19]

STEM CELLS OF THE APICAL PAPILL (SCAPS)

SCAPs are found in the apical papilla of immature permanent teeth in which they have been shown to be a unique group of cells responsible for root development, they are considered newly isolated cells.[28–31]

Application:

- **Dental:** Regeneration capacity of the dentin-pulp complex, in bioroot engineering, which would replace the use of dental implants, however, its use still requires further research.[29]
- **Bone regeneration:** The proliferation of odontoblasts from these cells was obtained as a result of several studies, which gives a good outlook for the repair of bone defects.[32]
- **Neuronal repair and regeneration:** This type of cells demonstrated their potential to repair the severed spinal cord and promote functional recovery after injury.[32]
- **Angiogenesis:** A series of experiments demonstrated that SCAPs have the ability to promote angiogenesis.[33]

Table 2. *Biological* characteristics and multipotent capacity of dental stem cells.[9,19,22-23]

	DPSC	SHED	DFSC	SCAP	GMSC	PDLSC	TGPC	ABSMC
Location	Dental pulp	Tooth pulp of exfoliated deciduous tooth	Dental Follicle Tissue	Apical Papilla	Gingival Tissue	Periodontal Ligament	Tooth Germ of Third Molars	Gingival
Morphological Characteristics								
Form	Similar to Fibroblasts	Similar to Fibroblasts	Similar to Fibroblasts	Similar to Fibroblasts	Similar to Fibroblasts	Similar to Fibroblasts	Similar to Fibroblasts	Similar to Fibroblasts
Proliferation potential	+++	+++	+++	+++	+++	+++	+++	+++
Clonogenic potency	+++	+++	+++	+++	++	+++	+++	++
Immunoreactivity Biomarkers	CD9, CD10, CD13, CD14, CD19, CD24, CD29, CD31, CD34, CD44, CD45, CD59, CD73, CD90, CD105, CD106, CD117, CD133, CD146, CD166, CD271.	CD11b, CD13, CD14, CD19, CD29, CD34, CD43, CD44, CD45, CD56, CD73, CD90, CD105, CD146, CD166	CD9, CD10, CD13, CD29, CD31, CD34, CD44, CD45, CD53, CD59, CD73, CD90, CD105, CD106, CD133, CD166, CD271	CD13, CD14, CD18, CD24, CD29, CD34, CD44, CD45, CD51, CD56, CD61, CD73, CD90, CD105, CD106, CD117, CD146, CD150, CD166	CD14, CD29, CD34, CD44, CD45, CD73, CD90, CD105, CD106, CD117, CD146, CD166	CD9, CD10, CD13, CD14, CD29, CD31, CD34, CD44, CD45, CD59, CD73, CD90, CD105, CD106, CD146, CD166	CD14, CD29, CD34, CD44, CD45, CD73, CD90, CD105, CD106, CD133, CD166, STRO-1	CD11b, CD13, CD14, CD19, CD29, CD31, CD34, CD44, CD45, CD71, CD73, CD90, CD105, CD146, CD166, STRO-1
Multipotential								
Osteogenic-	+++	+++	+++	+++	+++	+++	+++	+++
Chondrogenic-	+++	+++	++	++	+++	++	++	+++
Neogenic	+++	+++	+++	+++	+++	+++	+++	+
Adipogenic	+++	++	++	++	++	++	++	++
Tissue repair, regeneration	Dental, bone, corneal, neuronal and muscle	Dental, bone, neuronal, renal, hepatic	Dental, neuronal	Dental, bone, neuronal, angiogenesis	Dental	Dental. Bone	Dental, muscle, neuronal, bone, hepatic	Dental, bone

+++ High ++Moderate +Low

*Dental pulp stem cells **(DPSC)**, human exfoliated deceived tooth stem cells **(SHED)**, dental follicle progenitor stem cells **(DFSC)**, stem cells of the apical papilla **(SCAP)**, gingival mesenchymal stem cells **(GMSC)**, periodontal ligament stem cells **(PDLSC)**, dental germ progenitor cells **(TGPC)**, alveolar bone derived mesenchymal stem cells **(ABSMC)**.*

PERIODONTAL LIGAMENT STEM CELLS (PDLSCS)

PDLSCs are located in the periodontal spaces, which gives them a proximity to the blood vessels that are responsible for innervating the dental organ, are populations of cells that when differentiated can give rise to periodontal tissues comprising cementoblasts (which form dental cementum) and osteoblasts (bone forming cells), these various tissues are responsible for supporting the tooth structure, are cells that interact directly with the niche of the periodontium.[16,31]

Application:

- **Dental:** Regeneration of the periodontal ligament closely related to periodontitis.[22,34]
- **Bone regeneration:** As already mentioned, they are precursor cells of osteogenic lineages.[16]
- They have also demonstrated potential for differentiation of adipogenic and chondrogenic cells.[19]

DENTAL FOLLICLE PROGENITOR STEM CELLS (DFSCS)

DFSCs are a group of dental mesenchymal stem cells found in the dental follicle, which surrounds the enamel organ and the dental germ papilla, these cells harbor high pluripotency. Due to this ability, they are considered very promising candidates in regenerative medicine. An advantage of this type of cells is that they are easily accessible because they are found in the impacted third molars.[35]

Application:

- **Dental:** These cells promote apical bone formation, craniofacial bone regeneration and periodontal tissue regeneration.[35]
- **Neuronal regeneration:** These cells are candidates for the treatment of spinal cord injury.[32]

ALVEOLAR BONE DERIVED MESENCHYMAL STEM CELLS (ABSMCS)

Cells with a multipotent capacity for differentiation into osteoblasts, chondroblasts and adipocytes. In addition, studies have shown that they are capable of inducing ectopic bone formation *in vivo*.[36]

Application:

- **Dental:** Regeneration of cranial bones such as the alveolar bone.
- They are considered viable candidates for immunomodulatory cell therapies, which would be intended to treat inflammatory conditions.[36]
- **Bone regeneration:** osteoblast differentiation capacity.[37]

DENTAL GERM PROGENITOR CELLS (TGPCS)

TGPCs are a relatively new population of stem cells that show a similar differentiation lineage to other DMSCs. In some studies, they have been isolated from dental germ of third molars in late bell stage.[37]

Application:

- **Dental:** For engineered regeneration of complete teeth.[38]
- **Hepatic:** In *in vivo* studies these cells can differentiate into cells with phenotypic, functional and morphological characteristics very similar to hepatocytes, which opens a panorama for their use in the treatment of liver diseases.[37]
- **Musccle:** Myogenic therapy.[39]

GINGIVAL MESENCHYMAL STEM CELLS (GMSCS)

GMSCs are cells obtained from gingival tissues (commonly called gingiva), being this a very easy access site, these cells have shown an excellent self-renewal capacity.[37]

Application:

- **Dental:** These cells promote the regeneration of the oral mucosa.
- **Bone regeneration:** Because of their multipotential in osteocytes.
- **Neural regeneration:** NC-derived GMSCs have a higher potential to differentiate into neural cells and chondrocytes than mesoderm-derived GMSCs.[40]

As already reviewed in detail, each dental cell lineage has a specific function and a distinct multipotential capacity as summarized in Table 2.

CONCLUSION

Stem cell research has boomed exponentially, although the same cannot be said of the application, since the therapeutic phase is at a slower stage. Current studies have confirmed that the use of stem cells of dental origin could be an ideal option for the regeneration of a large number of tissues, not only dental, but also bone, neuronal, muscular, etc., since they are relatively easy to obtain.

Although each experiment carried out with them and the results obtained are important, the obstacles that exist for their application, such as some ethical controversies, as well as the formation of tumors and rejection, limit their usefulness and experimentation in human beings, which motivates us to continue in the search for knowledge for their future application

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