International Arab Journal of Dentistry

Volume 9 | Issue 3 Article 4

7-30-2018

Stem cells in the oral cavity

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STEM CELLS IN THE ORAL CAVITY

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Abstract

Stem cells are unspecialized cells that are able to replicate repeatedly through cell division. Under certain conditions, they differentiate into cells with specialized functions providing an excellent tool for cell therapy especially in case of degenerative pathologies. There are two kinds of stem cells: Embryonic and adult. The embryonic stem cells, also called pluripotent, are capable of differentiating into all cell types of the body whereas the adult stem cells are less versatile and more difficult to identify, to isolate and to purify. Compared to the embryonic stem cells derived from placenta or umbilical cord, adult stem cells are considered to be the only hope for those people who haven't done cryopreservation or banking.
Throughout this paper, an overview of the location of stem cells in the oral cavity will be presented emphasizing especially on their therapeutic potentials.

Keywords: Stem cells - adult stem cells - dental pulp stem cells - apical stem cells - dental follicle precursor cells - bone jaw stem cells.

IAJD 2017;8(3):99-103.

LES CELLULES SOUCHES AU NIVEAU DE LA CAVITÉ BUCCALE

Résumé

Les cellules souches sont des cellules non spécialisées capables de se multiplier plusieurs fois par division cellulaire. Sous certaines conditions, ils se différencient en cellules fonctionnelles spécialisées fournissant un excellent outil de thérapie cellulaire, notamment en cas de pathologies dégénératives. Les cellules souches sont de deux types: embryonnaire et adulte. Les cellules souches embryonnaires, également appelées cellules pluripotentes, sont capables de se différencier en tout type de cellules de l'organisme. Les cellules souches adultes sont moins polyvalentes et plus difficiles à identifier, à isoler et à purifier. Comparées aux cellules souches embryonnaires dérivées du placenta ou du cordon ombilical, les cellules souches adultes sont considérées comme le seul espoir pour les personnes qui n'ont pas fait de la cryoconservation ou la mise en banque.
Dans cet article, un aperçu de l'emplacement des cellules souches dans la cavité buccale sera présenté avec un accent particulier sur leur potentiel thérapeutique.

Mots-clés: cellules souches - cellules souches adultes - cellules souches de la pulpe dentaire.

IAJD 2017;8(3):99-103.

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Introduction

Stem cell research provides an excellent advancement in tissue engineering. It represents a new and promising strategy for hard tissue repair and regeneration.

Stem cells are undifferentiated cells that possess the ability of self-renewal or differentiation into multiple cell types.

There are two major sources: embryonic stem cells from placenta or umbilical cord and adult stem cells.

Adult stem cells are the only hope for those who haven't done cryopreservation or banking and their major types are: hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs) and endothelial stem cells (ESCs).

Even though in 1985 Yamamura [1] was the first to report the presence of stem cells in dental pulp tissues (DPSCs), the major breakthrough was with Gronthos and his team who identified an isolated odontogenic progenitor population from adult dental pulp, which had the ability to regenerate a dentin-pulp-like complex [2, 3]. Nevertheless, teeth and attached gingival tissue can be an accessible source of dental mesenchymal stem cells. The oral cavity represents a new field of research with the possibility of finding a source of autologous or allogeneic mesenchymal stem cells that can be used in the treatment of many medical conditions.

Stem cell characteristics

Under the influence of appropriate conditions: surrounding tissues (niche) and specific signals, stem cells have the remarkable potential to proliferate for an extended period and to differentiate into many different specialized cell types. These "mother" cells have a high capacity for infrequent, asymmetric self renewal dividing into two [4]: a stem cell (for self-renewal) and a differentiated progenitor (potency) with a more specialized function to maintain tissue homeostasis in order to terminally differentiate into all kinds of post-mitotic cells, such as a muscle cell, red blood cell, or a brain cell [5].

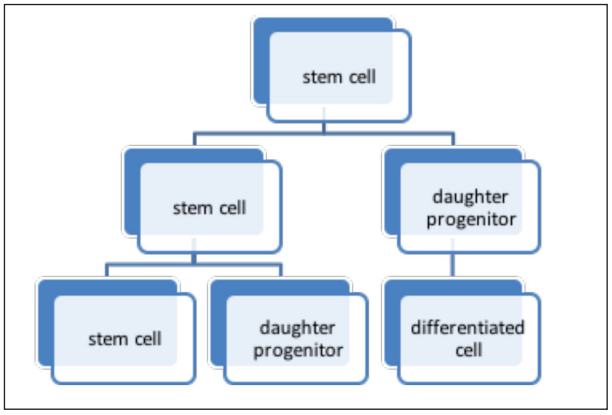

Fig. 1: Hierarchy of differentiation of stem cells.

Stem cells classification [6]

Stem cells are typically classified either by their potency:

Totipotent: cells extracted from at the morula stage.

Pluripotent: cells extracted from the inner cell mass at the blastocyte stage.

Multipotent: cells capable of differentiating into any type of organ.

Unipotent: cells capable of differentiating into a specific type of tissue.

or by their origin:

Embryonic stem cells: Embryonic stem cells (ESCs) derive from the inner cell mass (ICM) of the blastocyst from embryos. They are pluripotent because they have an unlimited capacity for self-renewal and the potential to differentiate into cells of all three germ layers dividing into any cell type [7]. Ethical, legal, and medical (tissue-rejection) issues render these cell types unsuitable for clinical development [8].

Adult stem cells: Found in differentiated tissues like bone marrow, peripheral blood, umbilical cord, connective tissue, dental pulp, placenta and amniotic membrane. These cells are multipotent because they have a limited self-renewal capacity to differentiate only into cell types to re-establish tissues from which they are derived. Also known as somatic or postnatal stem cells, they maintain a differentiation potential throughout the organism's life such as dental stem cells [2, 9].

Stem cells properties

The criteria for selection of stem cells in any medical regeneration are based on two properties:

Stemness: the possibility of a stem cell to differentiate rapidly into the type of cells required [6].

Plasticity: the possibility of a cell to change and differentiate into another type of cell in order to generate a new line [6].

Dental Stem Cells

Tooth development

Teeth are ectodermal organs similar to hair, scales, nails, feathers, and mammary glands. They all develop in a similar fashion but deviates during later stages and give rise to different structures (Fig. 2). They progress during the 6th week of embryonic life through a combination of ectoderm and mesenchyme with a continuous and dynamic reciprocal signaling interaction between them which guides the morphogenesis of organs [9].

The development of teeth comprises several stages [9], that includes the formation of an epithelial placode (epithelial thickening), the cap stage where the cervical loop is formed with more extensive growth and

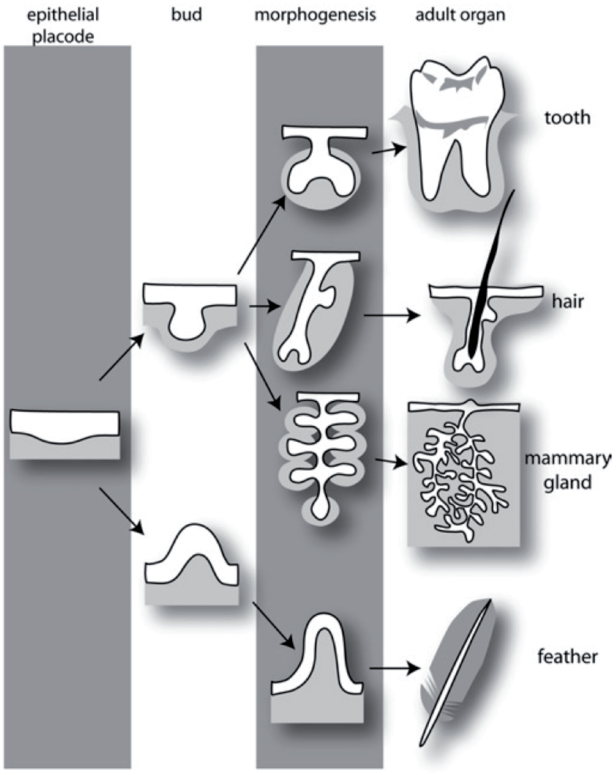

Fig. 2: The development of all ectodermal organs at early stages [11].

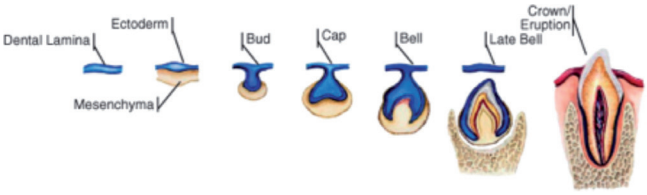

Fig. 3: Developmental stages of the tooth [11].

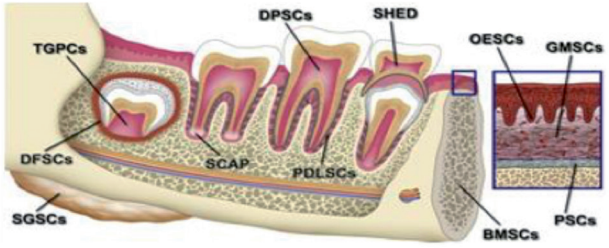

Fig. 4 : Dental stem cell varieties.
DPSCs: dental pulp SC ; SHED: SC from human exfoliated deciduous teeth; PDLSCs: periodontal ligament SC; DFSCs: dental follicle SC; TGPCs: tooth germ progenitor cells; SCAP:SC the apical papilla; OESCs: oral epithelial progenitor SC ; GMSCs: gingiva-derived MSCs; PSCs: periosteum-derived SC,SGSCs: salivary gland SC [22].

folding of the dental epithelium, and the bud stage where the epithelium of the placode invaginates into the mesenchyme and forms an epithelial bud surrounded by condensed dental mesenchyme.

These cell to-cell and cell-to-extracellular matrix (ECM) interactions involve both ectodermal and mesenchymal stem cells using a series of signaling factors -polypeptides known as growth factors- such as Fgf 8/ Lhx 6-7 / Bmp 4-2 / Shh/ Wnt/ Notch (Fig. 3) [10].

Types of dental and oral stem cells

Dental stem cells

Dental stem cells (DSC) are mesenchymal stem cells (MSC) known to be multipotent with immunomodelatory properties. They can be induced into myocytes, osteoblasts, adipocytes, chondrocytes, and neural tissues [12]. Furthermore, DSC hold the status of more immature, youthful form of MSC compared to umbilical cord- and Wharton's Jelly-derived stem cells.

Extraction protocol of dental stem cells

Freshly extracted teeth are immediately placed in sterile 10 ml tubes filled with 3 ml culture medium Dulbecco's modified Eagle medium DNEM-F12 (SIGMA, USA) culture media supplemented with 20% fetal bovine serum (FBS) (Sigma Aldrich, St Louis, USA) / antifungal (Gentamycin) for antifungal control of the culture until they reach the laboratory and kept at 4°C for less than 12 hours. Medium are pre-warmed to 37°C prior use to imitate body temperature [13].

Samples are processed in a tissue culture laboratory within routinely sterilized class II tissue culture hoods, handled by wearing personal protective equipment.

The soft tissue surrounding the tooth is cleared away using a scalpel. Later, the tooth is submerged briefly in iode povidone solution for 10 seconds for sterilization.

To extract the pulp, the coronal portion of the tooth is cut using a sterilized mounted cutting disc on a motorized hand piece. A groove is prepared laterally along the tooth crown and root at the cementum-enamel junction so the tooth can be easily split using a chisel and hammer. Cooling of the tooth due to heat generation is insured with PBS [14].

The fragilized tooth is then separated into two parts, coronal and apical, to uncover the pulp. Whether it is a PDL or mucosa or pulp, tissue is fragmented and minced by using sterilized scalpels in small pieces inside of Petri boxes with 4 ml of culture media under sterilized tissue culture hoods with laminar flow and in aseptic conditions and then incubated at 35°C in 5% CO2 [2].

Dental pulp stem cells

Dental pulp stem cells (DPSC) are another alternative noninvasive source to be used for future regenerative therapies, comparable in its therapeutic potentials to bone marrow mesenchymal stem cells [15]. They can be differentiated by modulation with growth factors, transcriptional factors, extracellular matrix proteins and receptor molecules into different cell types including odontoblasts, osteoblasts, chondrocytes, cardiomyocytes, neuron cells, adipocytes, corneal epithelial cells, melanoma cells and insulin secreting beta cells [16]. Theses DPSCs have a high proliferative capacity and immediately differentiate into odontoblasts, osteoblasts, chondrocytes, neuron like cells, cardiomyocytes, adipocytes, insulin secreting beta cells to produce dentin, bone, and cartilage tissues respectively [17]. They show promise for use in regenerative dental therapies [18].

Human exfoliated deciduous teeth stem cells

Stem cells can be isolated from the pulp of human exfoliated deciduous teeth (SHEDs). These cells induce bone formation and differentiate into other non-dental mesenchymal cells in vitro with higher proliferation rates. They secrete neurotrophic factor for repair therefore can be useful for the treatment of neurodegenerative diseases [19].

Apical papilla stem cells

Stem cells from apical papilla (SCAPs) are cells found at the tooth root apex. They have higher proliferation rates and are capable of differentiating into odontoblasts and produce dentin in vivo [19].

Human gingiva and oral mucosa cavity stem cells

The gingiva and oral mucosa share histological and biological functions similarities to skin, specifically, oral defense and resistance to shear stress or friction [20].

Human periodontal ligament stem cells

Periodontal ligament stem cells (PDLSCs) can differentiate into cementoblast-like cells. They have also the capacity to form connective tissue rich in collagen I fibers.

Dental follicule precursor cells

Dental follicle precursor cells (DFPCs) are derived from dental follicle tissue which is a loose connective tissue surrounding the developing tooth. These cells have the ability to produce bone and cementum. Therefore they are used in periodontal and bone regeneration therapies. Third molar teeth derived cells differentiate into odontoblasts. They also exhibit a better plasticity than other dental stem cells, with more advantages as a stem cell resource for regenerative therapies [21].

Oral mesenchymal stem cells

These include jaw bone marrow mesenchymal stem cell and salivary gland stem cells.

The jaw bone marrow mesenchymal stem cells (JBMMSC) are non-dental-derived stem cells related to the development of teeth and jaws. They express both odontogenic and osteogenic-related protein, and the latter showed stronger positive expression [23].

The salivary gland stem cells are also a source for adult stem cells.

Application of dental pulp stem cells in regenerative medicine

Dental stem cells are being used for regenerative therapies in:

- Bone related diseases, oro-maxillo-facial bone repair and orthopedic surgeries because they can differentiate into multiple cell types including osteoblasts and chondrocytes.

- Nerve defects in cases of neuronal disorders and accidental brain injuries [23].

- Cardiac repair (infracted myocardium) for having the ability to secrete proangiogenic factor, the property of vasculogenesis and the capability to stimulate angiogenesis.

- Corneal stromal regeneration [2].

Even though they are multipotent and highly proliferative, postnatal stem cells constructs intended for tissue engineering are influenced by the initial cell seeding density. The optimal number of cells to be loaded onto scaffolds is critical for promoting extracellular matrix synthesis. Cell seeding density and media supplements may have a synergistic effect on proliferation and differentiation.

Future prospects

There are worldwide donor tissue shortages, and many allogeneic grafts are eventually rejected. Autologous stem cells present a prospect for personalized regenerative therapy and an alternative to cadaveric tissue grafts. Even though mesenchymal stem cells derived from bone marrow are the only known cell type to differentiate into bone, dental stem cells have raised a great deal of interest in a wide range of therapeutic applications.

Future studies should concentrate on elucidating their potentials and their application in many regenerative therapies. It is necessary to identify and classify this potential source of stem cells as efficient, safe and profitable before its adoption in advanced technologies and therapeutic protocols.

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