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Review Article

Stem Cells in the Oral Cavity

Abstract

Stem cells have emerged in the health area as a promise for the healing of damaged tissues and replacement of organs. With their capacity of self-renewal and clonogenicity, as well as their ability to develop into many different cell types in the body, their potential seems to be unlimited, serving as a kind of cell stock for any cellular need in the human body. Nevertheless, their potential for odontology also seems to be promising for the simple possibility of tooth reconstruction and the reestablishment of shape and function. The aim of this review is to main sites in the oral cavity where these cells can be collected.

Introduction

It's common knowledge that many tissues in the human body have the potential to trigger undifferentiated cells in order to restore damages due to bacterial or viral diseases or to trauma in its different kinds. The production of tissues and organs in human beings may be too difficult to accomplish according to the technology available nowadays. Nevertheless it's a real possibility and finding a way to grow back tissues and produce organs in laboratories has been the aim of researchers for a long time, in order to enhance life, by offering the unique opportunity to replace a damaged organ and regain health. Stem cells have recently been featured as a possible path to reach this objective, by scrutinizing their functions, evolution, development and possibilities; which include the potential to develop into many kinds of different cells that have characteristics, shapes and specialized functions, such as heart, skin or nerve cells (2,3). Modern Odontology can contribute with this challenge by offering an opportunity to find and collect these precious cells in a cheap and available way, because the oral cavity has been shown to have a number of structures from which stem cells can be collected. Therefore, the aim of this review is to describe the main sites in the oral region where these stem cells can be found and to designate their terms and possible applications.

Stem cells in the oral region

The existence of stem cells in the oral cavity is a fact due to the number of articles describing them. They can be classified as Mesenchymal stem cells (MSCs) /Adult stem cells (ASCs) / Tissue stem cells (TSCs) [1].

Mesenchymal stem cells (MSCs) are regarded as a prospective source of adult stem cells. They show extraordinary plasticity with the characteristic of retaining their multilineage potential when expanded into groups of cells designated as colonies. They are able to differentiate into a number of different mesodermal cells such as chondrocytes, adipocytes or osteocytes and can also give rise to lineages of embryonic layers [2,3]. However, the first kind of these cells were named dental pulp stem cells (DPSCs) and, as the name

implies, were collected from the dental pulp. Thereafter, four other kinds were cultivated namely: Stem Cells from Exfoliated Deciduous Teeth - SHED [4], Periodontal Ligament Stem Cells (PDLSCs), Stem Cells from Apical Papilla –SCAP [5] and Stem cells from third molars. These have been identified because of their ability to generate clonogenic adherent cell clusters when plated under the same growth conditions as described for Bone Marrow Stromal Cells (BMSSCs) [6,7].

Dental pulp stem cells (DPSC)

DPSCs have three advantages over other stem cell sources widely researched. The first, and maybe more interesting advantage, is that they are possibly more prone to forming neurons than other stem cells, and neuron regeneration would be particularly interesting for Parkinson disease and spinal neuron regeneration. The second is that there are fewer ethical consideration than those which shroud other stem cells. Thirdly, they are more easily isolated than other stem cells, such as Mesenchymal Cells (MSCs).

The first time Dental Pulp Stem Cells (DPSCs) were isolated was in 2000 in a research accomplished by Gronthos et al. [8], opening new possibilities for the use of these cells in many other tissues in the human body. Their source is the dental pulp mesenchyme (neural crest mesenchyme). The access for collection is not only easy, as it is also cheap while producing very low morbidity. The extraction of stem cells from the pulp can be considered as a highly efficient procedure and easily accomplishable, for the fact that there is a great tooth loss in patients under orthodontic therapy whose premolars are usually requested for removal. DPSCs are even slow cycling and represent mature adult pulp stem cells which, *in vitro*, are able to differentiate into odontoblasts, osteoblasts, adipocytes and endothelial cells, under appropriate growth factors. They are multipotent stromal cells that can be cryopreserved and used in several models of scaffolds, which can proliferate extensively, and build *in vivo* an adult bone with Havers channels and adequate vascularization, but with no proof of being able to produce dentin [9-12], while their easy management makes them feasible for clinical trials in human patients.. Subsequent studies [13-15], were made to understand the differentiative capacity of DPSCs, especially compared with Bone Marrow Mesenchymal Stem Cells (BMMSCs); the latter used as gold pattern in field of stem cells. In 2002, again Gronthos et al. established their ability of self-duplication

in vivo, and went on in 2003 [16], by showing that BMMSC and DPSCs could be traced in the perivascular tissue of their respective origin tissue; which meant that such discovery could enhance tissue stem cells populations identification in other districts. In 2005 the work of Laino et al. [17] showed that DPSCs could still be found in over 30-year-old patients without substantial differences when compared to younger cells. This discovery opened the possibilities for collection since older patients could be potential donors. Inevitably, in 2008 and 2010, two main lines of research were developed: the therapeutic applications of DPSCs and bone regeneration comparing different types of scaffold when added with growth factors, such as BMP. The versatility of DPSCs made researchers use them for the treatment of myocardial infarction [18], neural regeneration [19], cerebral ischemia [20] and corneal regeneration [21,22].

Stem cells from human exfoliated deciduous teeth (SHED)

Their source is the coronal pulp of human exfoliated deciduous teeth. They are regarded as multipotent cells with very high proliferative potential and higher cell doublings. Deciduous teeth can be considered an ideal resource of stem cells to repair damaged tooth structures, induce bone regeneration and possibly treat neuronal tissue injury or degenerative diseases. *In vitro* they can differentiate odontogenically, osteogenically, adipogenically, chondrogenically, or neutrally, while *In vivo* they can form neurons, adipocytes, odontoblasts, and osteoinductive and endothelioid cells. Originally they can be subdivided in three main types of SHEDS namely:

Adipocytes; These cells have been successfully used to treat cardiovascular disease, spine and orthopedic conditions, as well as congestive heart failure and Crohn's disease, with promising uses in plastic surgery [19,23].

Chondrocytes and Osteoblasts: These cells have been successfully used to grow bone and cartilage suitable for transplants and more interestingly to grow intact teeth in animals [24,25].

Mesenchymal stem cells; these cells have the potential to treat neuronal degenerative disorders such as Alzheimer's and Parkinson's diseases and cerebral palsy. Mesenchymal stem cells seem to have more therapeutic potential than other type of adult stem cells [26,27].

Within the range of SHEDs, there is also the Immature Dental Pulp Stem Cells (IDPSC) which can be extracted from pulp of primary teeth. *In vitro*, these cells can be induced to undergo uniform differentiation into many kinds of different tissues, such as smooth and skeletal muscles, neurons, and bone under certain chemically defined culture conditions. Their applications need to be further explored.

Periodontal ligament stem cells (PDLSC)

The Periodontal Ligament (PDL) is a specialized connective tissue that connects cementum and alveolar bone to maintain and support teeth in situ and preserve tissue homeostasis. Stem cells have also been isolated from the periodontum and have been designated as Periodontal Ligament Stem Cells (PDLSCs) and can be extracted from periodontal ligament of the roots of the extracted teeth. They are the primary source for the treatment of periodontal diseases with

some peculiar characteristics: they are multi-potential, and *in vitro*, PDLSCs differentiate into osteoblasts, cementoblasts, and adipocytes, while *in vivo*, after transplantation into mice, and they can originate structures resembling bone-like tissue, Cementum-like tissue and cartilage. Although they contain multiple stem cells lineages, their utility is yet to be explored. The results of a study carried out by Kook et al. [28], suggest that PDL contains stem cells that have the potential to generate cementum/PDL-like tissue *in vivo*. Their research was enhanced by the fact that the transplantation of these cells can be easily accomplished and can also be expanded *ex vivo*, holding promise as a therapeutic approach for reconstruction of tissues destroyed by periodontal diseases.

Dental follicle stem cells (DFSC)

The dental follicle is an ectomesenchymal tissue surrounding the developing tooth germ. It is believed that this tissue contains stem cells and lineage committed progenitor cells or precursor cells (PCs) for cementoblasts, periodontal ligament cells and osteoblasts. The results of study of Morsczeck et al. [29,30], demonstrate that cultured PCs are unique undifferentiated lineage committed cells residing in the periodontium prior or during tooth eruption. Later on, they were designated as Dental Follicle Stem Cells (DFSC) and are extracted from dental follicle of the impacted teeth and possess multiple potentialities. They have lesser ability to form adipocytes and their potential is yet to be identified for forming odontoblasts, neural cells and other tissues.

Stem cells from apical papilla (SCAP)

They are taken from extraction sites of third molars or other teeth. They can be easily collected and *in vitro* can differentiate osteogenically, odontogenically, and adipogenically. *In vivo*, SCAPs seem to differentiate into odontoblasts and osteoblasts. The differentiation potential of apical papilla progenitor cells has not been established yet, and the nature of all embryonic dental papilla, mature dental pulp and apical papilla progenitor cell populations remain to be characterized further. Since SCAPs were discovered, a new clinical concept of therapeutic approaches have emerged. A clinical regenerative protocol has been proposed based on some research studies that showed the potential that these cells have to differentiate rapidly into other kind of cells, supported by many clinical case reports [31-35]. The reason for the establishment of this protocol is that SCAP in the apical papilla may be induced to regenerate damaged or lost pulp tissue in the canal space, opening new possibilities for endodontic reestablishment [36-38], especially as for what concerns the capacity of SCAP to regenerate pulp-dentin-like tissues *in vivo* in animal models. However, despite of all these possibilities, the understanding of the biology of SCAPs is still limited, and more studies are necessary before their application can be widely used in humans.

Bone marrow stromal cells (BMSC)

The term bone marrow stromal cells (BMSCs) was designated at first to indicate their residence in bone marrow stroma, their primary function to support hematopoiesis and their ability to generate heterotopic bone [39-41]. Bone marrow stromal cells are generally

used as a reference for the characterization of stem/progenitor cells that live within the orofacial connective tissues, being both of mesenchymal and/or mesodermal origins. Hematopoietic stem cells reside in bone marrow niches that are formed by stromal cells and osteoblasts [42-44]. Particularly as for what concerns the oral cavity, BMSCs are referred to as derived from the bone marrow of mandible/maxilla. They have lower odontogenic potential than DPSCs and are a secondary source for periodontal disease. Orofacial BMSCs seem to be less adipogenic than BMSCs from other sources in the human body. Collectable amount of cells from orofacial region is much less than from other sites so safe cell expansion techniques need to be used in order to establish a minimum amount that can be used for clinical experiments.

Epithelial stem cells (EpSC)

Epithelial stem cells can be located and collected mainly in the developing tooth germ, oral epithelium, and salivary gland. Connective tissue stem/progenitor cells (of mesenchyme/mesoderm origin) have also been isolated from calvarial bone, tooth pulp, dental papilla, the periodontal ligament, and marrow of alveolar bone. These stem cells are generally used and collected for laboratorial experiments from third molars of newborn or juvenile animals or from the cervical loop of rodent incisors. They possess clonogenicity and are unipotent. Stem cells from third molars are promising for tooth formation/ regeneration, especially for the fact that third molars are easily collectable because of their being impacted or for orthodontic therapy. Nevertheless, their clinical application is sometimes difficult as it requires tooth donation. Cells from cervical loop can only be used to study characterization of dental epithelial stem cells and analyses of dental epithelial tissue, while the cells from cervical loop of rodent incisor cannot be used for treatment as it would need introduction of rodent cells in mouth. There is a subdivision of epithelial stem cells, namely: Oral Epithelial Stem Cells, which are derived from the oral epithelial progenitor cells from basal layer of oral mucosa. They can be classified as unipotent stem cells and possess clonogenicity, and also form well organized grafts, but do not seem to differentiate into mesenchymal cell lineage.

Induced pluripotent stem cells (iPSC)

Induced Pluripotent Stem Cells can be described as adult cells which have been genetically reprogrammed until they reach an embryonic stem cell-like state by being forced to express genes and factors important for maintaining the defining properties of embryonic stem cells. They are in general immunologically more acceptable and an attractive alternative source since they can be manipulated and induced. A great amount of human postnatal cell types have been successfully reprogrammed to induced pluripotent stem cells (iPSCs) including skin fibroblasts, blood mononuclear cells (MNCs) [45,46], endothelial precursors cells (EPCs) derived from peripheral blood, exfoliated renal epithelial cells present in urine [47].

Nevertheless, the downside is that some of the transcription factors used is well known oncogenes. Viruses are currently used to introduce the reprogramming factors into adult cells in many experimental essays, and this process must be carefully controlled and tested; the technique can lead to useful and even disastrous

treatment for humans, the virus used to introduce the stem cell factors sometimes may cause cancers. In short, the technique involves intrinsic risks in regard to cell transformation.

Gingiva derived mscs (GMSCs)

These cells come from the lamina propria of gingival and show multipotent differentiation capacity along with clonogenicity, self-renewal and do proliferate faster than BMSCs, while displaying a more stable morphology after extended passages. They also exhibit adipogenic, osteogenic and chondrogenic potential, and seem to have immuno-modulatory effects on lymphocytes. Their applications further need to be explored.

Tooth germ progenitor cells (TGPCs)

They are the stem cells in the mesenchyme of the third molar tooth germ and possess very high proliferative activity. Mesenchymal cells in the developing E13.5 mouse tooth germ are multipotent and readily differentiate into nondental lineages including chondrocytes and osteoblasts, in addition to odontoblasts [48]. They can differentiate into lineages of three germ layers including osteoblasts, neural cells and hepatocytes. Their applications further need to be explored.

Salivary gland stem cells (SGSCs)

Salivary glands originate from the endoderm and are attractive candidates for the obtention of adult stem cells because they can be extracted from patients in a relative easy procedure. They are derived from the stromal tissue of salivary glands and are useful for regeneration of salivary gland damaged from irradiation and can be guided to osteogenic, chondrogenic and adipogenic differentiation. It is difficult to isolate salivary gland stem cells from the collection of stromal cells. However, such stem cells with the ability to differentiate into mesenchymal cells were isolated from human parotid glands [49-51]. The salivary gland stem cells (SGSCs) clearly showed the ability to differentiate into all 3 mesenchymal lineages *in vitro*. Interestingly, SGSCs expressed nestin, an intermediate filament expressed in the neural stem cells, and they differentiated into neural marker expressing cells. Thus, they seem to be a promising sort of cells that may be used for neuron formation.

Periosteum derived stem cells (PSCs)

Periosteum derived Stem Cells (PSCs) can be found in the inner membrane of periosteum and undergo preferential osteogenic differentiation while seem to possess mesenchymal multipotentiality. They can differentiate into osteoblasts, adipocytes and chondrocytes. Their potential, however, continue to be limited and more studies are necessary to better understand their mechanisms and future applications.

Conclusions

The oral cavity is a potential rich source of stem cells which can be collected with relative simple procedures. The stem cells from the oral cavity are promising but their usage and application need more works directed to their clinical applications.

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