REVIEW ARTICLE

Role of Dental Adult Stem Cells in Regenerative Medicine

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ABSTRACT

Statement of problem: Stem cell biology is today one of the most exciting field of research with promising possibilities in all spheres of medical and dental science. Erupting tooth and its allied structures have emerged as a valuable source of adult stem cells. A lot of research is going on around the world in the field of regenerative medicine with the help of adult dental stem cells, but a comprehensive review is missing.

Purpose: This article provides an overview of different types of adult stem cells that have been isolated from teeth, including dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHEDs), periodontal ligament stem cells (PDLSCs), dental follicle progenitor stem cells (DFPCs), and stem cells from apical papilla (SCAPs) with their use in regenerative medicine.

Materials and methods: The literature was acquired in a systematic search of the titles–DPSC, SHED, PDLSC, DFPC and SCAP on PubMed. Articles dealing with only regenerative medicine and in English language were selected for review.

Results: A total of 1,211 articles were found on PubMed. The articles were then shortlisted according to the set criteria and a total of 53 articles were selected and the review was prepared.

Conclusion: Dental adult stem cells have proved themselves to be of vast future use. Research has shown that these cells can differentiate into variety of cells, e.g. smooth muscle cells, adipocytes, chondrocytes, and neurons, etc. A cautious and systematic approach still needs to be adopted in embracing this technology.

Keywords: Dental pulp stem cells, Mesenchymal stem cells, Stem cells from human exfoliated deciduous teeth, Periodontal ligament stem cells, Dental follicle progenitor stem cells, Stem cells from apical papilla.

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INTRODUCTION

The most common treatment for congenital, acquired craniofacial and systemic problems is surgical approach and this field continues to make progress, but final functional and cosmetic outcomes can be varied, unpredictable and sometimes unsatisfactory. The science of tissue engineering and regenerative medicine has seen tremendous development especially in the field of stem cell research. Today stem cell biology is one of the most fascinating areas of science which brings in the hope for improved outcomes by replacing damaged or absent tissues with healthy regenerated tissue.[1]

The term stem cell was proposed for scientific use by Russian histologist Alexander Maksimov in 1909. He was the first to suggest the existence of hematopoietic stem cells (HSC) with the morphological appearance of a lymphocyte, capable of migrating throughout the blood to microecological niches that would allow them to proliferate and differentiate.[2] Based on their origin, there are two main types of stem cells: embryonic stem cells (ES cells) and postnatal or adult stem cells (AS cells).

Embryonic Stem Cells

ES cells are harvested from embryos, they are cells derived from the inner cell mass of the blastocyst (early stage embryo, 4-5 days old, consist of 50-150 cells) of earlier morula stage embryo. In other words these are the cells that form the three germ layers and are capable of developing more than 200 cell types. In 1998 the first human ES cell line was derived at University of Wisconsin-Madison.[3]

Stem cells can be classified according to their abilities to differentiate as totipotent, and pluripotent or multipotent. Totipotent stem cells are those that can be implanted in the uterus of a living animal and can give rise to a full organism. Pluripotent stem cells are those that can give rise to every cell of an organism except its extraembryonic tissues, such as the placenta. This limitation restricts pluripotent stem cells from developing into a full organism. ES cells and induced pluripotent stem (iPS) cells are pluripotent stem cells. Multipotent stem cells are AS cells which only generate specific lineages of cells.[4,5]

However, the application of ES cells for clinical purposes has been limited by ethical issues, dysregulated ES cell differentiation and immune rejection. In addition, the possibility of genomic instability and tumorigenesis still needs to be examined before any large-scale clinical experiments are planned.[1]

Adult Stem Cells

AS cells are of autologous origin and can be derived from areas like bone marrow, peripheral blood, umbilical cord blood (UCB), adult connective tissue, dental tissues, placenta and amniotic membrane. These cells are appealing, and practical source for cell-based regenerative therapies

that hold realistic clinical potential in the near future due to their accessibility, despite their reduced plasticity. Although limited in their capability to differentiate, they can still develop into a number of cell lineages. The possibility of harvesting postnatal stem cells for later use in the same patient eliminates immunological difficulties and the risk of pathogen transmission.[4] AS cells of dental origin present themselves to be the best contenders for this process. Some of the common sources are–dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHEDs), periodontal ligament stem cells (PDLSCs), dental follicle progenitor stem cells (DFPCs) and stem cells from apical papilla (SCAPs).

The purpose of this literature review is to present an overview of the current status of stem cell biology research in regenerative medicine with respect to tooth and its allied structures and discuss the future scopes of this promising new science.

MATERIALS AND METHODS

The literature was acquired in a systematic search of the titles–DPSCs, SHEDs, PDLSCs, DFPCs, and SCAPs on PubMed. Only those articles were selected that gave information on the use of these dental AS cells in various fields of regenerative medicine. During this process first, the articles were judged based on their titles, then on the abstracts, and finally on the entire text. Articles which contained no information on adult dental stem cells and regenerative medicine were excluded, as were doctoral theses, case reports and expert opinions. Articles published only in the English language were taken into consideration.

RESULTS

PubMed cited 681 articles for DPSCs, 65 for SHEDs, 382 for PDLSCs, 35 for DFPCs and 48 for SCAPs. A total of 1,211 articles were therefore found. Out of these articles 53 articles were selected based on the above given criteria.

DISCUSSION

Mesenchymal Stem Cells

Mesenchymal stem cells (MSC) are adult multipotent stem cells that have two unique properties. The first one is their capacity of self renewal beyond Hayflick's limit, a property shared by ES cells. The second is the ability of MSC to differentiate into mesenchymal and nonmesenchymal mature cell lines such as fat, bone, cartilage and neural cells. Until recently, postnatal stem cells have been isolated almost from all adult tissues (bone marrow, neural tissue, skin, retina, etc). Findings that MSC can be relatively easily isolated from various tissues and subsequently expanded render them a promising tool for regenerative medicine. These stem cells are thought to possess great therapeutic potential for repairing damaged tissues.[6]

Pioneering experiments of Tavassoli and Crosby (1968) revealed that the bone marrow includes an entity, unknown at the time, endowed with the capacity (potential) to generate histology-proven bone tissue.[7] In a series of seminal experiments thereafter, Friedenstein et al (1974) and Friedenstein (1980) assigned this osteogenic potential first to nonhematopoietic, adherent cells (i.e., to cells corresponding to something within the stroma of the bone marrow) and then to cells able to form single cell-derived colonies when grown in culture at low density (i.e., to clonogenic stromal cells).[8,9]

Friedenstein (1990) believed that clonogenic stromal cells could be a different class of bone marrow stem cells, distinct from the HSC. There observation was based on the fact that heterotopic transplants of these cell strains originating from a single clonogenic cell could generate a variety of tissues; that is, bone forming osteoblasts, cartilage-forming chondrocytes, adipocytes and fibroblasts. They proved that single clonogenic bone marrow stromal cells were multipotent in nature because of their ability to generate various kinds of tissues therefore, they are preferred to be called 'multipotent stromal cell'.[10]

These findings opened up an entirely new field of study with tremendous possibilities and uses. It was for the first time that stem cell could be used for making connective tissues, rather than just being confined to being hematopoietic in nature. Caplan used the term 'mesenchymal stem cell' to describe them and was based on the idea that stem cells is a common progenitors, not just of skeletal tissues, but of 'mesenchymal' tissues, meaning virtually all nonhematopoietic derivatives of mesoderm.[11] Later research found that although these were found in the bone marrow, they are not unique to the bone marrow.[12,13] MSC-like cells has been isolated from a variety of human tissues including muscle connective tissue, perichondrium, adipose tissue, peripheral blood, and also fetal tissues such as lung, liver, spleen as well as from amniotic fluid, placenta and UCB.[14-19]

These cell can also be harvested from various sites in and around the developing tooth germ, and are named accordingly such as–DPSCs, SHEDs, PDLSCs, dental follicle stem cells (DFSCs), and SCAPs; these cell are called as mesenchymal dental stem cells (MDSC).[20-24]

MDSCs are multipotent cells that proliferate extensively and can be safely cryopreserved, possess immuno-suppressive properties and express mesenchymal markers.

MSDSCs can be isolated using explant cultures or enzymatic digestion. In addition, the stem cells derived from teeth are large spindle-shaped cells with a large central nucleus abundant cytoplasm, and cytoplasmic extensions in culture. These adherent cells are morphologically identical to the MSCs obtained from bone marrow.[25]

Dental Pulp Stem Cells

DPSCs can be isolated from the dental pulp. Depending on specific signals from their environment, DPSCs can either regenerate new stem cells or undergo a differentiation process. In the dental pulp, there are different progenitor cell subpopulations, which differ in terms of self renewal ability, proliferation rate and differentiation potential (Gronthos et al 2002; Honda M et al, 2007; Sumita et al, 2009).[26-28] Dental pulp can be acquired from third molars or pulpectomized teeth left *in situ* (d'Aquino et al, 2008).[29] Even after temporary storage in liquid nitrogen, the DPSCs do not lose their multipotent ability to differentiate (Papaccio et al 2006; Zhang et al 2006; Woods et al 2009).[30-32] *In vitro*, DPSCs can differentiate to odontoblasts, osteoblasts, endotheliocytes, smooth muscle cells, adipocytes, chondrocytes and neurons. Carnevale G et al have recently found that human amniotic fluid stem cells and human DPSCs differentiate into insulin-producing cells, offering a nonpancreatic, low-invasive source of cells for islet regeneration.[33]

The developmental ability of DPSCs *in vitro* is limited. *In vivo*, more complex tissues can arise. For instance, DPSCs differentiate *in vitro* to osteoblast progenitor cells and mature into osteoblasts which produce living autologous fibrous bone tissue,[34] while DPSCs *in vivo* can form calcified bone tissue with Haversian canals and osteocytes[35-38] and dentin/pulp-like tissue complexes.[20,39] In addition, multilineage potential of DPSC has been used in the treatment of myocardial infarction as they were found to influence angiogenesis.[40]

Dentistry has long exploited the life-long regeneration potential of AS cells in human dental pulp which give rise to tertiary dentin, therapeutically employed for direct and indirect pulp capping after caries excavation near the pulp. The application of calcium hydroxide or calcium phosphate, among other substances, can induce pulpal progenitor cells to differentiate into odontoblasts. In the future, DPSCs could also be used to treat perforated furcations.[41]

Stem Cells from Human Exfoliated Deciduous Teeth

Human exfoliated deciduous teeth are a relatively easily accessible source of AS cells. SHEDs can be isolated from the coronal pulp of exfoliated deciduous teeth. It is assumed that in addition to their role in the eruption of permanent teeth, they also influence the osteogenesis associated with the same.[21] They can differentiate odontogenically, osteogenically, adipogenically, chondrogenically or neurally, depending on different conditions. Therefore, exfoliated deciduous tooth is said to be similar in some ways to an umbilical cord, containing stem cells that may offer a unique postnatal stem cell source for potential clinical applications.[42]

SHED are capable of extensive proliferation and multipotent differentiation, which makes them an important resource of stem cells for the regeneration and repair of craniofacial defects, tooth loss and bone regeneration. Given their ability to produce and secrete neurotrophic factors, SHED cells may also be beneficial for the treatment of neurodegenerative diseases and the repair of motor neurons following stroke or injury. Stem cells from third molars release chemicals that may allow the remaining nerves to survive the injury.[43]

Ma et al have suggested that cryopreservation of dental pulp tissues of deciduous teeth provide a suitable and desirable approach for stem cell-based immune therapy and tissue engineering in regenerative medicine.[44]

Periodontal Ligament Stem Cells

The periodontal ligament, which connects the alveolar bone to the root cementum and suspends the tooth in its alveolus, contains stem cells which have the potential to form periodontal structures such as cementum and ligament. It can be harvested from the roots of extracted teeth. *In vitro*, PDLSCs differentiate into osteoblasts, cementoblasts and adipocytes. *In vivo*, after transplantation into mice, structures resembling bone, cementum, cartilage and PDL have been found. In a study using pigs, PDLSCs were implemented to treat periodontal lesions.[45] Combined with SCAPs from impacted third molars; PDLSCs on a hydroxyapatite-tricalcium scaffold were transplanted into the alveoli of juvenile miniature pigs. A root and a periodontal complex were formed that were able to support a ceramic crown, thus fulfilling the function of a natural tooth.[24] The PDL contains multipotent stem cells that can be utilized as potential sources in tissue engineering applications.[46] The engraftment and differentiation properties of human PDL-derived cells in the adult brain indicate that they are a potential stem cell source to be used in neuroregenerative and/or neurotrophic medicine.[47] Recent study has revealed a previously unrecognized function of PDLSCs in regulating humoral immune responses, which may represent a novel therapeutic strategy for immune-related disorders.[48]

Dental Follicle Stem Cells

The dental follicle surrounds the developing tooth. It plays a major role in the genesis of cementum, periodontal ligament and alveolar bone. DFSCs can be isolated from the follicles of impacted third molars.[49] DFSCs cultivated *in vitro* exhibit characteristics of cementoblasts and osteoblasts and can differentiate neurally. *In vivo*, tissue similar to dental cementum and differentiation into PDL progenitor cells have been observed.

Stem Cells from the Dental Apical Papilla

SCAPs are stem cells from the apical part of the papilla, a precursor tissue of the dental pulp. Impacted third molars serve as a suitable source. *In vitro*, SCAPs can differentiate osteogenically, odontogenically and adipogenically. *In vivo*, SCAPs have been found to differentiate into odontoblasts and osteoblasts.

The different stem cells exhibit different potencies in tissue regeneration. Compared with DPSCs, SHEDs have a higher proliferation rate.[41] The potential of SCAPs to regenerate dentin is greater than that of DPSCs.[43] Further, MSCs of the dental papilla were shown to be more potent osteoblast progenitor cells than were DPSCs.[50] DFSCs can induce osteogenesis and dentin formations, but not–as opposed to DPSCs–a dentin-pulp complex.[21]

CONCLUSION

AS cells of dental origin appears to hold the key to various cell-based therapies in regenerative medicine, but most avenues are in experimental stages and many procedures are undergoing standardization and validation. Long-term preservation of SHED cells or DPSC is becoming a popular consideration, similar to the banking of UCB. It may still be necessary to explore the long-term (>15 years) effect of cryopreservation on the post-thaw yield of DPSC/ SHED in these cultures.[51]

The harvesting of these AS cells though having a set protocol is still a very tedious procedure requiring meticulous attention during identification, isolation, purification and growth of these cells in laboratory as these cells are required in large numbers to be therapeutically used. The oncogenic potential of these cells is still to be determined in long-term clinical studies. Moreover, till date the research is mainly confined to animal models and still human research trials are needed to document same results in humans. Immune rejection is also one of the issues which require a thorough consideration.

Though the stem cell research in the field of dentistry is reaching new heights, a cautious and systematic approach has to be adopted in embracing this technology. More research has to be carried out eradicate the gray areas before these stem cells are made fully operational in the field of regenerative dentistry and medicine.

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